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SCIENCE MEDICINES HEALTH

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Human Medicines Division

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes for the meeting on 06-09 April 2021

Chair: Sabine Straus – Vice-Chair: Martin Huber

### Disclaimers

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

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

### Note on access to documents

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

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<sup>1</sup> 17 March 2022. 7.3.1 dexamfetamine - EMEA/H/N/PSR/S/0028, page 41; 7.3.2. dexamfetamine - EMEA/H/N/PSR/S/0029, page 42: removal of background information relating to a different procedure



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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 remotely). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chair noted that Gabriela Jazbec was stepping down on 16 April 2021 from her position of member for Slovenia. The Chair thanked her for her contribution to the work of PRAC.

### 1.2. Agenda of the meeting on 06-09 April 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 08-11 March 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 08-11 March 2021 were published on the EMA website on 08 February 2021 ([EMA/PRAC/73527/2022](#)).

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

### 2.1. Newly triggered procedures

None

## **2.2. Ongoing procedures**

None

## **2.3. Procedures for finalisation**

None

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

### **3.1. Newly triggered procedures**

None

### **3.2. Ongoing procedures**

None

### **3.3. Procedures for finalisation**

None

### **3.4. Re-examination procedures<sup>2</sup>**

None

### **3.5. Others**

None

## **4. Signals assessment and prioritisation<sup>3</sup>**

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

#### **4.1.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S [recombinant]) - COVID-19 vaccine JANSSEN (CAP)**

Applicant(s): Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of embolic and thrombotic events

EPITT 19689 – New signal

Lead Member State(s): SE

<sup>2</sup> Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

<sup>3</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

## Background

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

During routine signal detection activities, a signal of embolic and thrombotic events was identified by EMA, based on 3 cases concerning events of thrombosis reported with thrombocytopenia retrieved from EudraVigilance including one case from study VAC31518COV.3001<sup>4</sup>. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

## Discussion

Having considered the available evidence from spontaneous reports and the relevant clinical trial data, as well as additional data provided by the MAH both in writing and in an oral explanation, PRAC agreed that the association between COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19-S [recombinant])) and the signal of embolic and thrombotic events deserves additional investigation. Therefore, further assessment of the signal is warranted.

## Summary of recommendation(s)

- The MAH for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVID-19-S [recombinant])) should submit to EMA, within 7 days, a detailed cumulative review of cases of embolic and thrombotic events with details on laboratory values from post-marketing sources and clinical trials. The MAH should include an observed/expected (O/E) analysis of cases of cerebral venous thrombosis and discuss a potential causal relationship between vaccination with Covid-19 vaccine Janssen (Ad26.COVID-19-S [recombinant]) and the events of thrombosis and thrombocytopenia, addressing possible pathophysiological mechanism, including potential for platelet activation. In addition, the MAH should discuss how, beyond the already-agreed studies in the RMP pharmacovigilance plan, the important potential risk venous thromboembolism, including the potential occurrence of the combination of thrombosis and thrombocytopenia, can be further studied. Ways of gaining further mechanistic data, both non-clinical and clinical, regarding potential interactions of the Covid-19 vaccine Janssen (Ad26.COVID-19-S [recombinant]) and the coagulation system should specifically be addressed. Finally, the MAH should propose to update the product information and/or RMP as warranted.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### 4.1.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (previously COVID-19 VACCINE ASTRAZENECA) (CAP)

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Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

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<sup>4</sup> A randomized, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COVID-19-S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older

Scope: Signal of capillary leak syndrome

EPITT 19672 – New signal

Lead Member State(s): BE

### **Background**

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

During routine signal detection activities, a signal of capillary leak syndrome was identified by Ireland, based on 2 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

### **Discussion**

Having considered the available evidence from case reports in EudraVigilance, PRAC agreed that the association of capillary leak syndrome following vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) deserves additional investigation. Therefore, further assessment of the signal is warranted.

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

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 30 days, a cumulative review of cases of capillary leak syndrome including data from post-marketing sources, clinical trials, pre-clinical data and relevant literature. The MAH should include a discussion on the plausibility of a causal association together with a proposal to update the product information and/or RMP as warranted.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### **4.1.3. Fluoroquinolones:** ciprofloxacin (NAP); delafloxacin - QUOFENIX (CAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

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Applicant(s): A. Menarini Industrie Farmaceutiche Riunite s.r.l.(Quofenix), Chiesi Farmaceutici S.p.A. (Quinsair), various

PRAC Rapporteur: Pernille Harg

Scope: Signal of acquired thrombotic thrombocytopenia purpura

EPITT 19669 – New signal

Lead Member State(s): DE, ES, HR, IT, NO, SI

### **Background**

Fluoroquinolones refer to a class of broad-spectrum antibiotics active against gram-negative and gram-positive bacteria including as individual substances: ciprofloxacin, delafloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and

rufloxacin. Fluoroquinolone-containing medicines for systemic and inhalation use are indicated for the treatment of bacterial infections subject to certain conditions.

Ciprofloxacin-containing medicinal products are estimated to have been used by more than 632 million patients worldwide, in the period from first authorisation in 1987 to 2018.

During routine signal detection activities, a signal of acquired thrombotic thrombocytopenia purpura was identified by EMA, based on 16 cases for ciprofloxacin retrieved from EudraVigilance. Norway as the Lead Member state (LMS) for ciprofloxacin confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

Having considered the available evidence from case reports in EudraVigilance and the literature for ciprofloxacin, moxifloxacin and levofloxacin, as well as the plausible pathophysiological mechanism, PRAC agreed on the need to broaden the scope of this signal from ciprofloxacin to all fluoroquinolones-containing medicines for systemic and inhalation use and to consider the signal as a class effect.

The PRAC appointed Pernille Harg as Rapporteur for the signal.

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

- The EMA will perform, within 120 days, a cumulative review of relevant cases in EudraVigilance of acquired thrombotic thrombocytopenia purpura associated with fluoroquinolones, together with a thorough literature review.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### **4.1.4. Pembrolizumab – KEYTRUDA (CAP)**

---

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of paraneoplastic neurological syndrome

EPITT 19671 – New signal

Lead Member State(s): NL

### **Background**

Pembrolizumab is a monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor indicated, as Keytruda, for the treatment of advanced (unresectable or metastatic) melanoma, for adjuvant treatment of adult patients with stage III melanoma and lymph node involvement who have undergone complete resection, first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) with a  $\geq 50\%$  tumour proportion score (TPS) or metastatic non-squamous NSCLC in adults whose tumours have no endothelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations. It is also indicated for the treatment of relapsed or refractory classical Hodgkin lymphoma (cHL), locally advanced or metastatic urothelial carcinoma and recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a  $\geq 50\%$  TPS, subject to certain conditions.

The exposure for Keytruda (pembrolizumab) is estimated to have been more than 370,740 patient-years worldwide, in the period from first authorisation in 2015 to 2020.

During routine signal detection activities, a signal of paraneoplastic neurological syndrome was identified by EMA, based on 5 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

### **Discussion**

Having considered the available evidence from case reports in EudraVigilance and in the literature, PRAC considered that there is a potential underlying mechanism between pembrolizumab and the occurrence of paraneoplastic neurological syndrome. Taking also into account the seriousness of the event and that paraneoplastic neurological syndrome can cover a broader range of adverse events, PRAC agreed that further evaluation of the signal on paraneoplastic neurological syndrome is warranted.

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

- In the next PSUR<sup>5</sup>, the MAH for Keytruda (pembrolizumab) should submit to EMA a cumulative review of cases of paraneoplastic neurological syndrome, including data from spontaneous reports, clinical trials and the literature, and discuss whether an update of the product information and/or RMP is warranted.

#### **4.1.5. Piperacillin (NAP); piperacillin, tazobactam (NAP)**

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Applicant(s): various

PRAC Rapporteur: Marek Juračka

Scope: Signal of hemophagocytic lymphohistiocytosis (HLH)

EPITT 19676 – New signal

Lead Member State(s): IT, SK

### **Background**

Piperacillin is a beta-lactam antibiotic and tazobactam a beta-lactamase inhibitor. In combination, piperacillin/tazobactam is indicated for serious infections, such as severe pneumonia, complicated urinary tract infections or complicated intra-abdominal infections.

During routine signal detection activities, a signal of hemophagocytic lymphohistiocytosis (HLH) was identified by France, based on cases retrieved from the French pharmacovigilance database and EudraVigilance as well as published cases. Slovakia as the Lead Member State (LMS) for piperacillin/tazobactam combination and Italy for piperacillin mono-component confirmed that the signal needed initial analysis and prioritisation by PRAC.

### **Discussion**

Having considered the available evidence from case reports in EudraVigilance and the literature, PRAC agreed that the role of piperacillin and/or piperacillin/tazobactam in the development of HLH cannot be ruled out. The PRAC agreed that further evaluation of the signal on HLH is warranted.

The PRAC appointed Marek Juračka as Rapporteur for the signal.

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<sup>5</sup> Data lock point (DLP): 03 September 2021



### Summary of recommendation(s)

- The MAHs Fresenius Kabi, Mylan, Novartis, Pfizer, and Teva for piperacillin and/or piperacillin/tazobactam-containing product(s) should submit to EMA, within 60 days, a cumulative review of cases of HLH associated with the use of piperacillin/tazobactam combination.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

## 4.2. New signals detected from other sources

None

## 4.3. Signals follow-up and prioritisation

### 4.3.1. Azathioprine (NAP)

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Applicant(s): various

PRAC Rapporteur: Anette Kristine Stark

Scope: Signal of erythema nodosum

EPITT 19623 – Follow-up to December 2020

#### Background

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

The originator/brand leader MAHs (Aspen, Teva, Novartis) for azathioprine-containing products replied to the request for information on the signal of erythema nodosum and the responses were assessed by the Rapporteur.

#### Discussion

Having considered the available evidence from the literature and EudraVigilance, and the cumulative review provided by the MAHs, PRAC considered that there is sufficient evidence to establish a causal relationship between azathioprine and erythema nodosum. Therefore, PRAC agreed that an update of the product information is warranted to add erythema nodosum as an undesirable effect to the list of immune system disorders.

#### Summary of recommendation(s)

- The MAHs for azathioprine-containing products should submit to EMA, within 60 days, a variation in order to amend<sup>7</sup> the product information.
- In the next PSUR<sup>8</sup>, the MAH(s) for mercaptopurine-containing products should provide a cumulative review on erythema nodosum.

For the full PRAC recommendation, see [EMA/PRAC/199751/2021](#) published on 03 May 2021 on the EMA website.

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<sup>6</sup> Held 23-26 November 2020

<sup>7</sup> Update of SmPC section 4.8. The package leaflet is to be updated accordingly

<sup>8</sup> Data lock point (DLP): 01 September 2021

#### 4.3.2. Coronavirus (COVID-19) vaccine (Ad26.COVS2-S [recombinant]) - COVID-19 vaccine JANSSEN (CAP)

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Applicant(s): Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of embolic and thrombotic events

EPITT 19689 – Follow-up to April 2021<sup>9</sup>

##### **Background**

For background information, see Coronavirus (COVID-19) vaccine (Ad26.COVS2-S [recombinant]) - COVID-19 vaccine JANSSEN (CAP)4.3.2.

Based on responses to the request for information on the signal of embolic and thrombotic events, specifically on cases of unusual thrombosis in combination with thrombocytopenia provided by the MAH for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVS2-S [recombinant])) and further data and analyses from EudraVigilance, the Rapporteur prepared a further assessment.

At an extraordinary meeting convened remotely on 20 April 2021, the PRAC further reviewed the signal. The PRAC heard the MAH in the context of an oral explanation. The PRAC is responsible for adopting a recommendation.

The evaluation of the data revealed eight reports of interest, which included severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age. PRAC agreed that there is sufficient evidence to conclude, with a reasonable possibility, that thrombosis in combination with thrombocytopenia can be considered as a very rare undesirable effect of COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVS2-S [recombinant])).

- The MAH for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVS2-S [recombinant])) should submit to EMA, within 1 day, a variation to amend<sup>10</sup> the product information.
- The PRAC agreed on the content of a further direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.
- The MAH for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVS2-S [recombinant])) should submit to EMA, within 2 days<sup>11</sup>, further responses to a request for supplementary information (RSI). In particular, the MAH should ensure that laboratory results from clinical studies and post-marketing data are provided. In addition, the MAH should include further data and analyse whether thrombocytopenia without thrombosis or bleeding may be caused by COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COVS2-S [recombinant])). The MAH should also provide an updated observed/expected (O/E) analysis. The MAH should also propose to update the product information and/or RMP as warranted.

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<sup>9</sup> Held 06-09 April 2021

<sup>10</sup> Update of SmPC sections 4.4 and 4.8. Annex II and the package leaflet are to be updated accordingly

<sup>11</sup> See also 4.1.1.

See EMA Press Release entitled [COVID-19 Vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets](#).

For the full PRAC recommendation, see [EMA/PRAC/199751/2021](#) published on 03 May 2021 on the EMA website.

#### 4.3.3. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (previously COVID-19 VACCINE ASTRAZENECA) (CAP) - EMEA/H/C/005675/SDA/035

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Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of embolic and thrombotic events

EPITT 19683 – Follow-up to March 2021

##### **Background**

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

Based on additional data analysis from EudraVigilance with individual case review, an observed/expected (O/E) analysis, available literature and the outcome of the ad hoc expert group (AHEG) held on 29 March 2021, the Rapporteur prepared a further assessment.

##### **Discussion**

The PRAC received an oral feedback from the AHEG. The PRAC also heard the MAH of Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) in the context of an oral explanation.

Considering the available evidence including the input from the AHEG and experts, PRAC considered that an atypical heparin induced thrombocytopenia (aHIT) like disorder is the most plausible hypothesis for the events of thrombosis in combination with thrombocytopenia given the similarities observed in both the serological profile and clinical presentation of affected patients. PRAC also considered that the syndrome which resembles aHIT concerns a severe autoantibody against platelet factor 4 (PF4) which exhibits a high binding affinity. Hence, PRAC is of the view that a causal relationship between the vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) and the adverse events is at least a reasonable possibility. Therefore, PRAC agreed that the product information should be updated to revise the warning on thrombocytopenia and coagulation disorders and to add thrombocytopenia and thrombosis in combination with thrombocytopenia as undesirable effects with a frequency common and very rare respectively. Moreover, PRAC supported requesting additional studies as obligations to the marketing authorisation(s) (MA) to identify the exact pathophysiological mechanism for the occurrence of these thrombotic events and define the precise magnitude of the risk.

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

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 1 day, a variation to amend<sup>12</sup> the product information.

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<sup>12</sup> Update of SmPC sections 4.4 and 4.8. Annex II and the package leaflet are to be updated accordingly

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 14 day, a variation to update the RMP.
- The PRAC agreed on the content of a further direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.
- In the next monthly summary safety report (MSSR), the MAH should discuss possible implications regarding the second dose and commit to timely and closely monitor this issue. In addition, the MAH should comment if the observed thromboembolic adverse reactions could be potentially related to a dosing issue. Furthermore, the MAH should comment on the findings in a non-clinical study in monkeys in relation to rare thrombosis and thrombocytopenia in humans following vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])).

See EMA Press Release entitled [AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets](#).

For the full PRAC recommendation, see [EMA/PRAC/199751/2021](#) published on 03 May 2021 on the EMA website.

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

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

See also Annex I 15.1.

#### 5.1.1. Bimekizumab - EMEA/H/C/005316

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Scope : Treatment of plaque psoriasis

#### 5.1.2. Vosoritide – EMEA/H/C/005475, Orphan

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Applicant: BioMarin International Limited

Scope: Treatment of achondroplasia

#### 5.1.3. Zanubrutinib - EMEA/H/C/004978, Orphan

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Applicant: BeiGene Ireland Ltd

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

See Annex I 15.2.

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

See also Annex I 15.3.

### 5.3.1. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/II/0005/G

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC in order to add hyperglycaemic hyperosmolar non-ketotic syndrome to the list of adverse drug reactions (ADRs) with frequency 'unknown' and to update the warning on hyperglycaemia and ketoacidosis based on a review of the safety database. The package leaflet and Annex II are updated accordingly. The RMP (version 3.0) is updated accordingly; 2) update of sections 4.2 and 4.8 of the SmPC to modify the management of hyperglycaemia, rash and diarrhoea and add information about osteonecrosis of the jaw based on pivotal trial SOLAR-1: a phase 3 randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment. The MAH also took the opportunity to make minor editorial changes to the SmPC

#### Background

Alpelisib is an antineoplastic agent indicated, as Piqray, in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.

The CHMP is evaluating grouped variations for Piqray, a centrally authorised product containing alpelisib, consisting of adding hyperglycaemic hyperosmolar non-ketotic syndrome to the product information and update the warning on hyperglycaemia and ketoacidosis as well as of modifying the management of hyperglycaemia, rash and diarrhoea and add information about osteonecrosis of the jaw. These include an update of the key elements of educational material on hyperglycaemia. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support these grouped variations.

#### Summary of advice

- The RMP version 3.0 for Piqray (alpelisib) in the context of the grouped variations under evaluation by CHMP is considered acceptable.
- PRAC supported the proposed update of the prescribers' guide relating to hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS) and ketoacidosis.

### 5.3.2. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0010

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH). 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 2.1) are updated in accordance. In addition, Annex II is updated to reflect the addition of a PNH parent guide

### **Background**

Ravulizumab is a monoclonal antibody immunoglobulin G2 (IgG2)/4K indicated, as Ultomiris, for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH), under certain conditions. It is also indicated in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

The CHMP is evaluating an extension of the therapeutic indication for Ultomiris, a centrally authorised product containing ravulizumab, to include the treatment of paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH). The PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation.

### **Summary of advice**

- The RMP version 2.1 for Ultomiris (ravulizumab) in the context of the variation procedure under evaluation by the CHMP is considered acceptable.
- PRAC supported the addition of a PNH parent guide as an additional risk minimisation measure to address the risks of meningococcal infection and serious infections in infants and children.

### **5.3.3. 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

### **Background**

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties indicated, as Aubagio, for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

CHMP is evaluating grouped variations for Aubagio, a centrally authorised product containing teriflunomide, consisting of the extension of indication to include treatment of paediatric patients aged 10 years and older with relapsing remitting MS (RRMS) and of the addition of a new strength for use in paediatric patients from 10 years of age and older. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support

these grouped variations. For further background, see [PRAC minutes September 2020](#) and [PRAC minutes February 2021](#).

### **Summary of advice**

- The RMP for Aubagio (teriflunomide) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 6.2 is submitted.
- The MAH should review its proposed new format for specific adverse reaction follow-up questionnaires (FUQ) in accordance with PRAC requested amendments. In addition, the MAH should review the proposed additional key messages to be included in the educational material, particularly in the patient card. In particular, the MAH should ensure that the card is also to be given to patient caregivers, that reference to pancreatitis is removed as this risk is adequately addressed in the product information, and that key messages for female patients are revised.
- In the next PSUR, the MAH should discuss the need for and usefulness of the existing FUQ and how these are distributed.

## **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. Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/202009 (with RMP)**

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### **Background**

Alemtuzumab is a recombinant deoxyribonucleic acid (DNA)-derived humanised monoclonal antibody indicated, as Lemtrada, for the treatment of relapsing remitting multiple sclerosis (RRMS) as a single disease modifying therapy (DMT) in adult patients with highly active disease despite a full and adequate course of treatment with at least one DMT as well as in adult patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

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

- Nevertheless, the product information should be updated to add thrombotic thrombocytopenic purpura (TTP) as a warning and as an undesirable effect with a frequency 'rare'. In addition, the information regarding pneumonitis as an undesirable effect should be amended. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>13</sup>.
- In the next PSUR, the MAH should include detailed reviews of new cases of cardiomyopathy and of hypersensitivity vasculitis, including a discussion on whether any action is needed.

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

### 6.1.2. Dulaglutide - TRULICITY (CAP) - PSUSA/00010311/202009

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

#### **Background**

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Trulicity, a centrally authorised medicine containing dulaglutide, 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 Trulicity (dulaglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the information regarding pancreatitis and acute pancreatitis in order to reflect data from the post-marketing setting. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>14</sup>.
- In the next PSUR, the MAH should submit a cumulative review of cases of hepatic disorders and of cases of acute kidney injury, chronic kidney disease, renal failure and renal impairment. These reviews should include data from clinical trials, post-marketing and literature as well as a discussion whether an update of the product information is 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>13</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

<sup>14</sup> Update of SmPC section 4.8. The PRAC AR and the PRAC recommendation are transmitted to CHMP for adoption of an opinion



### 6.1.3. Emtricitabine, rilpivirine, tenofovir disoproxil - EVIPLERA (CAP) - PSUSA/00009142/202008

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

#### **Background**

Emtricitabine is a nucleoside reverse transcriptase inhibitor, rilpivirine is a nonnucleoside reverse transcriptase inhibitor and tenofovir is a nucleotide reverse transcriptase inhibitor. In combination, emtricitabine/rilpivirine/tenofovir disoproxil is indicated, as Eviplera, for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with a viral load  $\leq 100,000$  HIV-1 ribonucleic acid (RNA) copies/mL.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Eviplera, a centrally authorised medicine containing emtricitabine/rilpivirine/tenofovir disoproxil, 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 Eviplera (emtricitabine/rilpivirine/tenofovir disoproxil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing information on bone effects due to tenofovir disoproxil-induced proximal renal tubulopathy and the role tenofovir disoproxil may have on bone mineral density (BMD). Therefore, the current terms of the marketing authorisation(s) should be varied<sup>15</sup>.

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

### 6.1.4. Enzalutamide - XTANDI (CAP) - PSUSA/00010095/202008

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### **Background**

Enzalutamide is an androgen receptor signalling inhibitor indicated, as Xtandi, for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) and for the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. It is also indicated for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

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<sup>15</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and the PRAC recommendation are transmitted to CHMP for adoption of an opinion

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xtandi, a centrally authorised medicine containing enzalutamide, 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 Xtandi (enzalutamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add dysgeusia as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>16</sup>.
- In the next PSUR, the MAH should provide cumulative reviews of cases of hepatic enzyme elevation, of depression and of suicidal ideation/suicide including data from the literature and clinical trials, as well as a discussion on possible biological mechanisms. The MAH should also provide a cumulative review of cases of interstitial lung disease (ILD).

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. Isatuximab - SARCLISA (CAP) - PSUSA/00010851/202009**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### **Background**

Isatuximab is an immunoglobulin G1 (IgG1)-derived monoclonal antibody indicated, as Sarclisa, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy. It is also indicated in combination with carfilzomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Sarclisa, a centrally authorised medicine containing isatuximab, 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 Sarclisa (isatuximab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on infusion reaction and to add anaphylactic reaction as an undesirable effect with a

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<sup>16</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and the PRAC recommendation are transmitted to CHMP for adoption of an opinion

frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>17</sup>.

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

#### 6.1.6. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/202009

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Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

##### **Background**

Naltrexone is a mu-opioid antagonist and bupropion an inhibitor of neuronal dopamine and norepinephrine reuptake. In combination, naltrexone/bupropion is indicated, as Mysimba, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients with an initial body mass index (BMI) of  $\geq 30 \text{ kg/m}^2$ , or  $\geq 27 \text{ kg/m}^2$  to  $< 30 \text{ kg/m}^2$  in the presence of one or more weight-related co-morbidities.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mysimba, a centrally authorised medicine containing naltrexone/bupropion 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 Mysimba (naltrexone/bupropion) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include serotonin syndrome as a warning and as an undesirable effect with a frequency 'not known' as well as an overdose symptom. Also, the existing information on interaction with other medicinal products should be amended. In addition, the product information should be updated to amend the existing warning on elevation of blood pressure to add hypertensive crisis to reflect data from the post-marketing setting during the initial titration phase and to amend the existing undesirable effect of hypertension to reflect that cases of hypertensive crisis have been reported during the initial titration phase. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>18</sup>.
- In the next PSUR, the MAH should provide cumulative reviews of cases of hepatic and renal impairments in order to evaluate whether risk minimisation measures (RMM) were adhered to. Also, the MAH should provide a cumulative review of cases of anaphylactic reaction and of acute generalised exanthematous pustulosis (AGEP), along with a causality assessment. In addition, the MAH should provide a cumulative review of cases reporting concomitant use with opioids/opiate agonists and discuss whether further RMM are warranted. The MAH should also provide a cumulative review of cases of pulmonary hypertension and cardiac valve disorders, including data on bupropion as a single agent and as bupropion/naltrexone fixed dose combination. Furthermore, the MAH should

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<sup>17</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and the PRAC recommendation are transmitted to CHMP for adoption of an opinion

<sup>18</sup> Update of SmPC sections 4.4, 4.5, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and the PRAC recommendation are transmitted to CHMP for adoption of an opinion

provide a cumulative review of cases of panic attacks, including clinical trials and literature data, together with a discussion on the potential biological mechanism and a discussion on the need to update the product information as warranted. Finally, the MAH should include proposals to increase compliance to the recommended posology, particularly regarding the gradual dose adaptation at treatment initiation.

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

#### 6.1.7. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/202009

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

##### **Background**

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor. Keytruda (pembrolizumab) is indicated for the treatment of advanced (unresectable or metastatic) melanoma, stage III melanoma and lymph node involvement in patients who have undergone complete resection, first-line treatment of metastatic non-small-cell lung carcinoma (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) with a  $\geq 50\%$  tumour proportion score (TPS) or metastatic non-squamous NSCLC in adults whose tumours have no endothelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations, subject to certain conditions. It is also indicated for the treatment of relapsed or refractory classical Hodgkin lymphoma (cHL), locally advanced or metastatic urothelial carcinoma and recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a  $\geq 50\%$  TPS, subject to certain conditions and for the first-line treatment of advanced renal cell carcinoma in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Keytruda, a centrally authorised medicine containing pembrolizumab 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 Keytruda (pembrolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add cholangitis sclerosing and gastritis to the existing warning on other immune-related adverse reactions and as undesirable effects with a frequency 'rare' for cholangitis sclerosing and a frequency 'uncommon' for gastritis in monotherapy and 'common' for gastritis in combination with chemotherapy. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>19</sup>.
- In the next PSUR, the MAH should provide cumulative reviews of cases of Aspergillus infection and of myocarditis, together with a discussion on the need to update the

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<sup>19</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and the PRAC recommendation are transmitted to CHMP for adoption of an opinion

product information as warranted. In addition, the MAH should include a detailed review of cases of cardiac failure and late cardiac adverse reactions, including data from clinical trials, post-marketing and literature data. Furthermore, the MAH should provide a review of the new data available on risk factors and risk groups associated with immune-mediated pneumonitis, including data from clinical trials, post-marketing and literature and provide a discussion on the need to update the product information as warranted.

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

#### 6.1.8. Raltegravir - ISENTRESS (CAP) - PSUSA/00010373/202009

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

##### **Background**

Raltegravir is an integrase strand transfer inhibitor active against human immunodeficiency virus 1 (HIV-1) indicated, as Isentress, in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infection.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Isentress, a centrally authorised medicine containing raltegravir 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 Isentress (raltegravir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the potential interaction of raltegravir with iron salts. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>20</sup>.
- In the next PSUR, the MAH should provide a review of cases of medication error reported with paediatric formulations.

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

#### 6.1.9. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/202009

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Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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<sup>20</sup> Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and the PRAC recommendation are transmitted to CHMP for adoption of an opinion

## Background

Rivaroxaban is a factor Xa inhibitor indicated, as Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, and co-administered with ASA, for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. It is also indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. In addition, it is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors under certain conditions.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Xarelto, a centrally authorised medicine containing rivaroxaban, 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 Xarelto (rivaroxaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing information on the risk of bleeding in case of overdose. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>21</sup>.
- In the next PSUR, the MAH should provide cumulative reviews of cases of alopecia, arthralgia and myalgia, pancreatitis and of tubulointerstitial nephropathy confirmed by renal biopsy together with a discussion whether an update of the product information is warranted.

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

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

See Annex I 16.2.

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

See also Annex I 16.3.

### 6.3.1. Oxcarbazepine (NAP) - PSUSA/00002235/202008

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Applicant(s): various

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<sup>21</sup> Update of SmPC section 4.9. The PRAC AR and the PRAC recommendation are transmitted to CHMP for adoption of an opinion

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

### **Background**

Oxcarbazepine is an anticonvulsant indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing oxcarbazepine 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 oxcarbazepine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a thorough review of cases of congenital malformations, including post-marketing, clinical trials and literature data. In particular, the MAHs should carefully review data from the metaPreg database<sup>22</sup>. In addition, the MAHs should provide a discussion on a possible biological mechanism regarding the occurrence of congenital malformations and consider whether additional risk minimisation measures (RMMs) are needed with regards to this risk. Finally, MAHs should include a cumulative review on breast milk transfer and safety in breast fed infants, including literature data, case reports and clinical trials, as well as a discussion on the need to update the product information as warranted.

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

## **6.3.2. Permethrin (NAP) - PSUSA/00002355/202008**

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

### **Background**

Permethrin is an anti-parasitic agent indicated for the treatment of head lice (*Pediculus capitis*), scabies (caused by *Sarcoptes scabiei*) and crab lice (caused by *Pthirus pubis*).

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

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

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<sup>22</sup> Database of studies evaluating drug use during pregnancy

- Based on the review of the data on safety and efficacy, the benefit-risk balance of permethrin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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

### 6.3.3. Phenytoin (NAP) - PSUSA/00002392/202008

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Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

#### **Background**

Phenytoin is an antiepileptic indicated for the treatment of tonic-clonic seizures, partial seizures, for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury as well as for the treatment of cardiac arrhythmias and trigeminal neuralgia under certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing phenytoin 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 phenytoin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning to highlight important information on the risks associated with use during pregnancy and the need for effective contraception in women of childbearing potential and the potential for interaction with hormonal contraception potentially leading to lack of efficacy. In addition, a warning should be added on the increased risk of severe cutaneous adverse reactions (SCARs) in carriers of the CYP2C9<sup>23</sup>\*3 allele and the risk of increased toxicity in intermediate or poor metabolisers of CYP2C9 substrates. Furthermore, the product information should be updated to reflect the potential for interaction between phenytoin and direct oral anticoagulants (DOACs), lacosamide, ticagrelor and valproate. Finally, the product information should be updated to add pure red cell aplasia as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>24</sup>.
- In the next PSUR, the MAHs should provide cumulative reviews of cases of hypothyroidism evaluating the impact of phenytoin on laboratory tests and the evidence in support of an association with symptomatic hypothyroidism. In addition, MAHs should

<sup>23</sup> Cytochrome P450 family 2 subfamily C member 9

<sup>24</sup> Update of SmPC sections 4.4, 4.5, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and the PRAC recommendation are transmitted to CMDh for adoption of a position



include cumulative reviews of the potential impact of phenytoin on lipid profiles and on cardiovascular risk and of the association between alleles of the HLA<sup>25</sup> gene and phenytoin-induced severe cutaneous adverse reactions (SCARs), together with a discussion on the need to update the product information updates. MAH Pfizer should also provide a cumulative review of data from spontaneous and literature reports on signs and symptoms which may occur as a consequence of an overdose and discuss the need for an update of the product information as warranted.

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

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

See also Annex I 16.4.

### 6.4.1. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/LEG 054

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Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Detailed review of cases reporting suicidal action, behaviour or ideation as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002511/202001) adopted in September 2020

#### Background

Pregabalin is an anti-epileptic indicated, as Lyrica, a centrally authorised product, for the treatment of adults with partial seizures with or without secondary generalisation, as an adjunctive therapy for the treatment of peripheral and central neuropathic pain in adults as well as for the treatment of generalised anxiety disorder (GAD).

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the PRAC requested the MAH to submit a detailed review of cases reporting suicidal action/behaviour/ideation. For background, see [PRAC minutes September 2020](#). The responses were assessed by the Rapporteur for further PRAC advice.

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

- Based on the available data and the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to support a causal association between pregabalin and suicidal ideation and behaviour. Therefore, PRAC supported to update the product information to amend the existing warning on suicidal ideation and behaviour and to add these as undesirable effects.
- The MAH should submit to EMA, within 60 days, a variation to update<sup>26</sup> the product information accordingly.

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<sup>25</sup> Human leukocyte antigen

<sup>26</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

- In the next PSUR, the MAH should provide a cumulative review of cases of suicidal action/behaviour/ideation, following discontinuation/withdrawal/dose reduction of pregabalin, with or without the occurrence of other withdrawal symptoms.

#### 6.4.2. Pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/LEG 007

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Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Detailed review of cases reporting suicidal action, behaviour or ideation as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002511/202001) adopted in September 2020

##### **Background**

Pregabalin is an anti-epileptic indicated, as Pregabalin Pfizer, a centrally authorised product, for the treatment of adults with partial seizures with or without secondary generalisation, as an adjunctive therapy for the treatment of peripheral and central neuropathic pain in adults as well as for the treatment of generalised anxiety disorder (GAD).

Following the evaluation of the most recently submitted PSURs for the above-mentioned medicine(s), the PRAC requested the MAH to submit a detailed review of cases reporting suicidal action/behaviour/ideation. For background, see [PRAC minutes September 2020](#). The responses were assessed by the Rapporteur for further PRAC advice.

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

- Based on the available data and the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to support a causal association between pregabalin and suicidal ideation and behaviour. Therefore, PRAC supported to update the product information to amend the existing warning on suicidal ideation and behaviour and to add these as undesirable effects.
- The MAH should submit to EMA, within 60 days, a variation to update<sup>27</sup> the product information accordingly.
- In the next PSUR, the MAH should provide a cumulative review of cases of suicidal action/behaviour/ideation, following discontinuation/withdrawal/dose reduction of pregabalin, with or without the occurrence of other withdrawal symptoms.

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

See also Annex I 16.5.

##### 6.5.1. Coronavirus (COVID-19) mRNA<sup>28</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/II/0016/G

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variation consisting of: 1) update of section 4.8 SmPC to add 'diarrhoea'

<sup>27</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

<sup>28</sup> Messenger ribonucleic acid

and 'vomiting' as adverse drug reactions (ADRs) with frequencies and update the ADR 'pain in extremity' in order to fulfil MEA 002.1 concluded in February 2021; 2) update of section 4.8 SmPC to update the ADR 'hypersensitivity reactions' in more detail with the relevant frequency categories in order to fulfil LEG 022.1. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to perform editorial changes in section 6.6 of the SmPC

### **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.

Following the evaluation of the monthly summary safety reviews (MSSR) for the above-mentioned medicine(s) (MEA 002.1 and MEA 002.2) and of a review on anaphylaxis and hypersensitivity reactions (LEG 022.1), the PRAC requested the MAH to submit further analyses and proposals to update the product information, this includes the response to the request for supplementary information (RSI) adopted in March 2021. For background information, see [PRAC minutes February 2021](#) and [PRAC minutes March 2021](#). PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

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

- Based on the available data and the Rapporteur's assessment including the MAH's response to the RSI, PRAC supported the proposed update of the product information to add rash, pruritus as undesirable effects with a frequency 'uncommon' as well as urticaria and angioedema with a frequency 'rare'. In addition, diarrhoea and vomiting are added as undesirable effects with a frequency 'very common' and 'common' respectively.

## **6.6. Expedited summary safety reviews<sup>29</sup>**

### **6.6.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (previously COVID-19 VACCINE ASTRAZENECA) (CAP) - EMEA/H/C/005675/LEG 036**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Cumulative review of cases of hypersensitivity as per the conclusions of the signal procedure (EPITT 19668) adopted in March 2021

### **Background**

Coronavirus (COVID-19) (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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<sup>29</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

indicated, as Vaxzevria, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

The PRAC assessed a thorough analysis of cases of hypersensitivity including anaphylaxis as requested in the recommendation adopted in March 2021 in the context of the signal of anaphylactic reactions (EPITT 19668). For further background, see [PRAC minutes March 2021](#).

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

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 15 days, a further detailed analysis of cases hypersensitivity/anaphylaxis including data such as time to onset, treatability and outcome. The review should also include a proposal to update the product information as warranted. The MAH should also discuss cases with persons who experienced a hypersensitivity (non-anaphylactic) reaction following receipt of their first dose should still receive their second dose with the vaccine. Finally, the MAH should further discuss cases of angioedema and propose to update the product information as warranted.

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

See also Annex I 17.1.

### **7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>30</sup>**

#### **7.1.1. Cabotegravir - VOCABRIA (CAP); rilpivirine - REKAMBYS (CAP) - EMEA/H/C/PSP/J/0092**

Applicant(s): Janssen-Cilag International N.V. (Rekambys), ViiV Healthcare B.V. (Vocabria)

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for a joint drug utilisation study (DUS) to assess adherence, effectiveness and resistance: a prospective observational cohort study in people living with human immunodeficiency virus (HIV) (PLWH) initiating antiretroviral (ARV) regimen of cabotegravir (CAB) + rilpivirine (RPV) long-acting (LA) in collaboration with EuroSIDA<sup>31</sup>

#### **Background**

Cabotegravir is a human immunodeficiency virus (HIV) integrase inhibitor indicated, as Vocabria, in combination with rilpivirine, for the treatment of HIV-1 infection in adults under certain conditions. Rilpivirine is diarylpyrimidine non-nucleoside reverse-transcriptase inhibitor (NNRTI) of HIV-1 indicated, as Rekambys, in combination with cabotegravir, for the treatment of HIV-1 infection in adults under certain conditions.

In order to fulfil a specific obligation to conduct a PASS ([Annex II-D](#) for Vocabria and [Annex II-D](#) for Rekambys) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAHs Janssen-Cilag International N.V. for Rekambys (rilpivirine) and ViiV Healthcare B.V. for Vocabria (cabotegravir) submitted to EMA a joint protocol 1.0 version for a study entitled: 'drug utilisation, adherence, effectiveness and resistance: a prospective observational cohort study in people living with HIV (PLWH) initiating antiretroviral (ARV) regimen of cabotegravir

<sup>30</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>31</sup> Prospective observational pan-European cohort study

(CAB) + rilpivirine (RPV) long-acting (LA) in collaboration with EuroSIDA' for review by PRAC. PRAC is responsible for evaluating the PASS protocol.

### **Endorsement/Refusal of the protocol**

- 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). PRAC agreed that the PASS is non-interventional, but the study design does not fulfil the study objectives at this stage.
- PRAC considered that the MAHs should provide a combined analysis for different inappropriate regimens and describe patient characteristics that are non-adherent with the dosing regimen. In addition, the MAHs should add the evaluation of the effectiveness of routine risk minimisation measures (RMM) to the study objectives and describe how the effectiveness of the RMM will be measured. Finally, the MAHs should include further details on viral resistance as well as an estimation of the study size.
- The MAH should submit a revised PASS protocol within 30 days to EMA. A 30 day-assessment timetable will be followed.

## **7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>32</sup>**

See also Annex I 17.2.

### **7.2.1. Coronavirus (COVID-19) mRNA<sup>33</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017**

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study vACCine Covid-19 monitoring readinESS (ACCESS)/Vaccine monitoring Collaboration for Europe (VAC4EU): an assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine [final clinical study report (CSR): expected in January 2024] (from initial opinion/marketing authorisation)

#### **Background**

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Comirnaty, 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 16 years and older.

As stated in the [RMP](#) of Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)), the MAH is requested to conduct a study assessing the occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine. The MAH BioNTech Manufacturing GmbH submitted to EMA a protocol for study ACCESS/VAC4EU (C4591021) entitled: 'a post-approval active surveillance safety study using secondary data to monitor real-world safety of the Pfizer-BioNTech COVID-19 vaccine in the EU' which was

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<sup>32</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

<sup>33</sup> Messenger ribonucleic acid

assessed by the Rapporteur. 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 1.0 and the assessment from the Rapporteur, the PRAC considered the protocol for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) could be acceptable provided that an updated protocol is submitted to EMA. The MAH should provide further data and clarifications.
- In particular, the MAH should provide additional details regarding the matching process and confirm that proposed censoring (after 6 weeks) will be applied for sensitivity analysis only and not for the main analysis. The MAH should also discuss the need and feasibility to use a historical comparator cohort in the proposed study, estimate the number of vaccinated persons in the databases during the study period and provide a discussion on the availability of information on pregnancy, pregnancy outcomes and mother-baby linkage in the chosen electronic health record (eHR) databases.

## 7.3. Results of PASS imposed in the marketing authorisation(s)<sup>34</sup>

See also Annex I 17.3.

### 7.3.1. Dexamfetamine (NAP) - EMEA/H/N/PSR/S/0028

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Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Results of a PASS to evaluate the long-term safety of dexamfetamine to assess the incidence proportion and incidence rate for cardiovascular, psychiatric, growth and sexual maturity related adverse events in children with a diagnosis of attention deficit hyperactivity disorder (ADHD) who have been treated with dexamfetamine, methylphenidate or lisdexamfetamine as recorded in healthcare databases of three countries. The study also compares the risk of long-term cardiovascular, psychiatric, growth and sexual maturity-related adverse events of dexamfetamine versus methylphenidate or lisdexamfetamine in each database

#### Background

Dexamfetamine is an amphetamine derivative indicated for the treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD) in children between 6 to 17 years of age who respond insufficiently to methylphenidate.

In line with the conclusions reached in 2014 of the referral procedure under Article 29(4) of Directive 2001/83/EC ([EMEA/H/A-29/1375](#)) conducted by PRAC for dexamfetamine-containing medicines (Amfexa/Dexamed and associated names), the MAH was required as a condition to the marketing authorisation(s) ([Annex IV](#)) to conduct a PASS to evaluate the long-term safety of dexamfetamine. For further background, see [PRAC minutes April 2013](#), [PRAC minutes March 2015](#), [PRAC minutes May 2015](#), [PRAC minutes September 2015](#), [PRAC minutes February 2016](#) and [PRAC minutes June 2016](#).

The MAH submitted to EMA a final study for the PASS on a 5-year retrospective long-term safety study for dexamfetamine in children with ADHD evaluating cardiovascular events,

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<sup>34</sup> In accordance with Article 107p-q of Directive 2001/83/EC

growth and psychiatric related adverse events. This was assessed by the Rapporteur, PRAC discussed the final study results and adopted a recommendation.

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

- Based on the review of the final report of the non-interventional PASS and the assessment from the Rapporteur, PRAC considered that a request for supplementary information (RSI) was necessary before a final recommendation could be issued.
- The MAH should provide further clarifications in particular on differences in incidences between the European and the United States' (US) databases; and on implications of the results on the benefit/risk of dexamfetamine namely whether a clinically significant difference can be excluded when comparing dexamfetamine with methylphenidate. The MAH should propose to update the product information as warranted.
- The MAH should submit responses to the RSI within 60 days to EMA. A 60 day-assessment timetable will be followed.

### **7.3.2. Dexamfetamine (NAP) - EMEA/H/N/PSR/S/0029**

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Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Results of a drug utilisation study (DUS) to collect data on abuse, misuse, overdose, diversion and dependence related to dexamfetamine in five European countries

#### **Background**

Dexamfetamine is an amphetamine derivative indicated for the treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD) in children between 6 to 17 years of age who respond insufficiently to methylphenidate.

In line with the conclusions reached in 2014 of the referral procedure under Article 29(4) of Directive 2001/83/EC ([EMEA/H/A-29/1375](#)) conducted by PRAC for dexamfetamine-containing medicines (Amfexa/Dexamed and associated names), the MAH was required as a condition to the marketing authorisation(s) ([Annex IV](#)) to conduct a drug utilisation study (DUS) to follow the use of prescribed dexamfetamine in European countries. For further background, see [PRAC minutes April 2013](#), [PRAC minutes March 2015](#), [PRAC minutes May 2015](#) and [PRAC minutes September 2015](#).

The MAH submitted to EMA a final study for the DUS for assessment by the Rapporteur. The PRAC discussed the final study results and adopted a recommendation.

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

- Based on the review of the final report of the DUS and the assessment from the Rapporteur, PRAC considered that a request for supplementary information (RSI) was necessary before a final recommendation could be issued.
- The MAH should provide further clarifications. Considering the off-label use, the MAH should comment in particular on the implications of this medicine being used so often and, in some countries, almost exclusively in adult patients. In addition, the MAH should comment on the need for risk minimisation measures (RMM) to decrease the use of doses above the recommended intervals.
- The MAH should submit responses to the RSI within 60 days to EMA. A 60 day-

assessment timetable will be followed.

## 7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>35</sup>

See also Annex I 17.4.

### 7.4.1. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/II/0053

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Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on intestinal perforation and to add gastrointestinal perforation to the list of adverse drug reactions (ADRs) with frequency rare based on the Truven MarketScan<sup>36</sup> study and as requested by PRAC in the conclusions of LEG 15.1 adopted in December 2020 [as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010025/201908) adopted in March 2020]. The MAH took the opportunity to update the list of local representatives in the package leaflet

#### Background

Linaclotide is a guanylate cyclase-C receptor agonist (GCCA) indicated, as Constella, for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

As requested in the most recent PSUR single assessment (PSUSA) procedure PSUSA and further post-authorisation measure procedures, the MAH of Constella (linaclotide) conducted an analysis of cases of gastrointestinal perforation reported in the Truven MarketScan database study together with further analysis of cases reported in the post-marketing setting. The Rapporteur assessed the MAH's final report. For further background, see [PRAC minutes March 2020](#), [PRAC minutes July 2020](#) and [PRAC minutes December 2020](#)<sup>37</sup>.

#### Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- The PRAC further confirmed the need to include a warning to the product information on the occurrence of intestinal perforation and to add gastrointestinal perforation as an undesirable effect. PRAC agreed on some wording amendments<sup>38</sup> to the proposed product information changes.

## 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>35</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

<sup>36</sup> Truven MarketScan claims database used to assess the potential association between linaclotide and gastrointestinal (GI) perforation

<sup>37</sup> Held 23-26 November 2020

<sup>38</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly



## **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**

None

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

See Annex I 18.2.

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

See Annex I 18.3.

# **9. Product related pharmacovigilance inspections**

## **9.1. List of planned pharmacovigilance inspections**

None

## **9.2. Ongoing or concluded pharmacovigilance inspections**

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

## **9.3. Others**

None

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

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

None

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

None

### 10.3. Other requests

None

### 10.4. Scientific Advice

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

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

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

None

### 11.2. Other requests

#### 11.2.1. Dinoprostone (NAP) - SE/H/PSUFU/00001104/201909

Applicant(s): Ferring (Propess), Pfizer (Minoprostin, Prepidil, Prostaglandin E2 Pfizer, Prostin E2)

PRAC Lead: Annika Folin

Scope: Second PRAC consultation on a PSUR follow-up (PSU FU) procedure on risk minimisation measures to further minimise the risk of uterine hyperstimulation, including serious complications as uterine rupture, foetal and neonatal death and uterine haemorrhage, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00001104/201909) concluded in May 2020, and following advice from PRAC adopted in December 2020, on request of Sweden

#### **Background**

Dinoprostone is a prostaglandin of the E series (PGE2) indicated for the induction of labour, as an oral formulation. As endocervical and intravaginal formulations, it is indicated for the ripening of an unfavourable cervix when there is a medical or obstetrical need for labour induction, and for induction of labour, for the termination of pregnancy from the twelfth through the twentieth gestational week and evaluation of the uterine contents in the management of missed abortion or intrauterine foetal death up to 28 weeks of gestational

age as well as for management of non-metastatic gestational trophoblastic disease. Finally, as a sterile solution for intravenous (IV) or for extra-amniotic use, it is indicated for the induction of labour and for therapeutic termination of pregnancy, missed abortion and hydatidiform mole.

Following the initial evaluation and PRAC advice of a PSUR follow-up (PSU FU) procedure on a review of the risk minimisation measures in place and ways to further minimise the risk of uterine hyperstimulation and uterine rupture as requested in the assessment of the last PSUR single assessment (PSUSA) procedure, Sweden as the Lead Member State (LMS) requested a further PRAC advice on its assessment. For further background, see [PRAC minutes May 2020](#) and [PRAC minutes December 2020](#)<sup>39</sup>.

### Summary of advice

- Based on the review of the available information and the further LMS assessment, PRAC supported the proposed changes to the product information<sup>40</sup>. These changes include information regarding uterine hyperstimulation and uterine rupture and its serious complications, a restriction of usage of dinoprostone to qualified healthcare professionals (HCPs) and hospitals/clinics with specialised obstetric units with facilities for continuous monitoring as well as a strengthened warning regarding the maximum recommended dose/dosing interval. Considering the existing differences in nationally approved product information, PRAC supported the dissemination of a direct healthcare professional communication (DHPC) at national level to inform HCPs of the updates of the product information. To this end, PRAC endorsed key messages for inclusion in DHPC to be agreed at national level as appropriate.

### 11.2.2. Phenobarbital (NAP) - EE/H/PSUFU/00002370/202001

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Applicant(s): Accord UK Limited (Phenobarbital Accord), Bausch Health Companies (Sevenaletta), Bayer (Phenobarbital), Bial (Bialminal), Desitin Arzneimittel GmbH (Luminal, Phenaemaletten, Phenaemal), Dompe Farmaceutici S.p.A. (Luminale), Kern Pharma S.L. (Luminal), Sanofi, Stada, Takeda (Fenemal), Teva

PRAC Lead: Maia Uusküla

Scope: PRAC consultation on a PSUR follow-up (PSU FU) procedure on a review of recent studies on major congenital malformations following exposure to phenobarbital in utero, on neurodevelopmental disorders, on the use of phenobarbital during pregnancy and on the need for additional risk minimisation measures, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00002370/202001) concluded in October 2020, on request of Estonia

#### Background

Phenobarbital is a barbiturate indicated for the treatment of epilepsy, prophylaxis of convulsions and for the short-term treatment of insomnia. The solution for injection formulation is also indicated as a co-adjuvant in anaesthesia.

In the context of the evaluation of a PSUR follow-up (PSU FU) procedure on a review of recent studies on major congenital malformations following exposure to phenobarbital in utero, on neurodevelopmental disorders, on the use of phenobarbital during pregnancy and

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<sup>39</sup> Held 23-26 November 2020

<sup>40</sup> SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8 for MAH Pfizer and SmPC sections 4.2, 4.3, 4.4 and 4.8 for MAH Ferring. The package leaflet is to be updated accordingly

on the need for additional risk minimisation measures as requested in the assessment of the last PSUR single assessment (PSUSA) procedure, Estonia as the Lead Member State (LMS) requested a further PRAC advice on its assessment. For further background, see [PRAC minutes October 2020](#)<sup>41</sup>.

### Summary of advice

- Based on the review of the available information and the LMS assessment, PRAC supported the proposed updates to the product information<sup>42</sup> on major congenital malformations together with consistent information of appropriate measures to be taken in women of childbearing potential (WCBP) and women who plan on becoming or become pregnant. With regards to neurodevelopmental disorders (NDD), PRAC acknowledged the small sample sizes and methodological limitations of available studies and agreed that, at present, there is insufficient evidence to draw firm conclusions on a causal association between adverse neurodevelopmental outcomes and phenobarbital monotherapy administration during pregnancy. However, PRAC considered there is sufficient evidence to suggest an increased risk of NDD in children exposed to phenobarbital monotherapy during pregnancy, compared to those unexposed or exposed to other antiepileptic drugs. Therefore, PRAC supported to update the product information<sup>43</sup> accordingly. Finally, PRAC was of the view that, at present, no contraindication in WCBP is appropriate as there may be patients where alternative safer treatment options are not available.

## 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 – Q1 2021

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see [PRAC minutes May 2016](#) and [PRAC minutes June 2018](#)) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see [PRAC minutes June 2016](#) and [PRAC minutes June 2018](#)), the EMA secretariat informed PRAC about the quantitative measures collected for Q1 2021 of PRAC meetings. For previous update, see [PRAC minutes February 2021](#).

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

None

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

None

<sup>41</sup> Held 28 September – 01 October 2020

<sup>42</sup> SmPC sections 4.4, 4.6 and 5.3. The package leaflet is to be updated accordingly

<sup>43</sup> SmPC sections 4.4, 4.6 and 5.3. The package leaflet is to be updated accordingly

## 12.4. Cooperation within the EU regulatory network

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

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

### 12.4.2. Heads of Medicines Agencies (HMA)-EMA joint big data – Big data steering group: data standards strategy initiative - call for expressions of interest

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On behalf of the Big Data steering group, the EMA Secretariat presented to PRAC an initiative to develop a data standards strategy to enable the European regulatory network to more effectively leverage data to deliver evidence in support of benefit-risk decision-making on the development, authorisation and use of medicines. This initiative addresses the Data Task force recommendation on the need to engage in international initiatives related to data standardisation. The first consultation phase is planned in writing via an online survey to collect feedback on needs and priorities from different stakeholders' perspectives. All input and use cases received will be integrated into a draft data standards strategy document, that will outline a roadmap for the development and implementation of data standards with estimated timelines. PRAC members were informed that a virtual workshop on data standardisation is scheduled on 18 May 2021.

### 12.4.3. Joint advisory board (JAB) for COVID-19 vaccines studies - call for expressions of interest

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The EMA Secretariat provided PRAC with an update on the Joint ECDC<sup>44</sup>/EMA COVID-19 vaccine monitoring platform (VMP) for European Commission (EC)-funded safety and effectiveness/impact studies procured by EMA and ECDC through their respective framework contracts. The VMP is jointly managed by a virtual ECDC/EMA secretariat, and a joint advisory board (JAB) is set up to advise on design, implementation and interpretation of the studies, to facilitate dialogue between experts from national regulatory agencies, national public health bodies, and other relevant experts and to advise on rapid dissemination of evidence to relevant EU decision-makers. A call for interest from PRAC members was launched to join the JAB for COVID-19 vaccines studies. PRAC was also informed that calls for PRAC interest to review upcoming proposals from contractors and deliverables of upcoming studies will be made in the course of time. Further updates to PRAC will be planned in due course.

Post-meeting note: Daniel Morales was appointed member of the JAB as PRAC representative.

### 12.4.4. PRAC strategic review and learning meeting (SRLM) under the Portuguese presidency of the European Union (EU) Council – Remote meeting, 23 April 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 refined agenda for the 'PRAC strategic review and learning

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<sup>44</sup> European Centre for Disease Prevention and Control

meeting (SRLM)' under the Portuguese presidency of the Council of the European Union (EU). The meeting will be held remotely on 23 April 2021. For further background, see [PRAC minutes February 2021](#).

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

None

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

None

## **12.7. PRAC work plan**

None

## **12.8. Planning and reporting**

### **12.8.1. Marketing authorisation applications (MAA) forecast for 2021 – planning update dated Q1 2021**

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The EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications (MAA) planned for submission (the business 'pipeline').

### **12.8.2. PRAC workload statistics – Q1 2021**

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The EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the workload of PRAC for Q1 2021, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see [PRAC minutes February 2021](#).

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

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

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None

### **12.9.2. Pharmacovigilance inspections**

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None

### **12.9.3. Pharmacovigilance audits**

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None

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

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

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None

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

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None

### **12.10.3. PSURs repository**

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None

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

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

Post-meeting note: following the PRAC meeting of April 2021, the updated EURD list was adopted by CHMP and CMDh at their April 2021 meetings and published on the EMA website on 28 April 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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None

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

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

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None

### **12.12.2. Additional monitoring**

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None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 28 April 2021, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

## **12.13. EudraVigilance database**

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

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None

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

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

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None

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

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None

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

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

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None

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

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None

## **12.16. Community procedures**

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

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None

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

None

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

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

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None

### **12.18.2. Safety communication**

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None



## **12.19. Continuous pharmacovigilance**

### **12.19.1. Incident management**

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None

## **12.20. Others**

### **12.20.1. Real world data (RWE) use in marketing authorisation applications and extensions of indications – EMA study preliminary results**

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The EMA Secretariat presented to PRAC preliminary results of an EMA study on the use of real-world data (RWD) to support centralised marketing authorisation applications (MAA) and extensions of indication submitted in 2018 and 2019. The primary objective of this study is to characterise RWD/real world evidence (RWE) and its contribution to benefit-risk decision-making. Further discussion is planned at the upcoming PRAC strategic review and learning meeting (SRLM) on 23 April 2021. See under 12.4.4.

### **12.20.2. Video conferencing tool - WebEx rollout plan for PRAC**

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The topic was postponed until May 2021.

## **13. Any other business**

None

## **14. Annex I – Signals assessment and prioritisation<sup>45</sup>**

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

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

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

None

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<sup>45</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>46</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

## 15. Annex I – Risk management plans

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

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

#### 15.1.1. Eladocagene exuparvovec - EMEA/H/C/005352, Orphan

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Applicant: PTC Therapeutics International Limited, ATMP<sup>47</sup>

Scope: Treatment of aromatic L-amino acid decarboxylase (AADC) deficiency

#### 15.1.2. Imatinib - EMEA/H/C/005595

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Scope: Treatment of Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML), Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL), myelodysplastic/myeloproliferative diseases (MDS/MPD), hypereosinophilic syndrome (HES), eosinophilic leukaemia (CEL), Kit (CD 117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) and unresectable dermatofibrosarcoma protuberans (DFSP)

#### 15.1.3. Lisocabtagene maraleucel - EMEA/H/C/004731, Orphan

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Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP<sup>48</sup>

Scope: Treatment of large B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B)

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

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

#### 15.2.1. Cetrotirelix - CETROTIDE (CAP) - EMEA/H/C/000233/II/0075

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 5.2) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' including the consequential removal of a number of important identified risks and important potential risk of congenital anomalies, as well as the removal of missing information on infertile premenopausal women. The MAH also revised the RMP based on the most recent data and post-marketing

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<sup>47</sup> Advanced therapy medicinal product

<sup>48</sup> Advanced therapy medicinal product

exposure

#### 15.2.2. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/II/0034, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 5.0) in order to update the safety specifications and the pharmacovigilance plan, and to add healthcare provider educational materials and process indicator to evaluate the distribution of the educational materials. The RMP is also brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

#### 15.2.3. Ibritumomab tiuxetan - ZEVALIN (CAP) - EMEA/H/C/000547/II/0053

Applicant: Ceft Biopharma s.r.o.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 5.0) in line with revision 2 of GVP module V on 'Risk management systems'

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

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

#### 15.2.5. Rasagiline - AZILECT (CAP) - EMEA/H/C/000574/WS2011/0087; RASAGILINE RATIOPHARM (CAP) - EMEA/H/C/003957/WS2011/0019

Applicant: Teva B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 3.0) following the completion of study TV1030-CNS-50024 (listed as a category 3 study in the RMP): a non-interventional retrospective cohort study which was conducted using the United States Medicare research database to assess the potential risk of melanoma associated with the use of rasagiline mesylate in patients with Parkinson's disease (as assessed and concluded in procedure WS/1749 finalised in September 2020). The MAH took the opportunity to introduce a minor update to the targeted follow-up questionnaire for the important potential risk of malignant melanoma and to revise the list of safety concerns in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

#### 15.2.6. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/II/0029

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 14.4) to include dehydration and the pregnancy prevention programme as additional risk minimisation measures (aRMM) in order to align the RMP with Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'

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

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

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

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Applicant: Kite Pharma EU B.V., ATMP<sup>49</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

#### 15.3.2. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0070

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the use of belatacept in conversion from a calcineurin inhibitor-based regimen to a belatacept-based regimen post transplantation. 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 18.0) are updated in accordance. Furthermore, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1) and to update it with regard to sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

#### 15.3.3. Budesonide, formoterol - BIRESP SPIROMAX (CAP) - EMEA/H/C/003890/II/0033/G

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Applicant: Teva Pharma B.V.

PRAC Rapporteur: Anette Kirstine Stark

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<sup>49</sup> Advanced therapy medicinal product

Scope: Grouped variation consisting of: 1) extension of indication to include adolescents of 12 years and older for the regular treatment of asthma, where the use in combination of an inhaled corticosteroid and long-acting  $\beta_2$  adrenoceptor agonist is appropriate, either in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting  $\beta_2$  adrenoceptor agonists, or in patients already adequately controlled on both inhaled corticosteroids and long-acting  $\beta_2$  adrenoceptor agonists. The extension to the indication is based upon data from literature. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to make an administrative update to the Greek, Icelandic, Irish and Maltese local representatives. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1); 2) update of sections 4.2, 5.1 and 5.2 of the SmPC to update the information on paediatric data and section 4.4 of the SmPC to remove the warning regarding the risk of growth retardation in children and the guidance on how to address this risk as agreed during the assessment of the initial application for Budesonide/Formoterol Teva Pharma B.V finalised in January 2020

#### 15.3.4. [Budesonide, formoterol - DUORESP SPIROMAX \(CAP\) - EMEA/H/C/002348/II/0033/G](#)

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Applicant: Teva Pharma B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped variation consisting of: 1) extension of indication to include adolescents of 12 years and older for the regular treatment of asthma, where the use in combination of an inhaled corticosteroid and long-acting  $\beta_2$  adrenoceptor agonist is appropriate, either in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting  $\beta_2$  adrenoceptor agonists, or in patients already adequately controlled on both inhaled corticosteroids and long-acting  $\beta_2$  adrenoceptor agonists. The extension to the indication is based upon data from literature. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to make an administrative update to the Greek, Icelandic, Irish and Maltese local representatives. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1); 2) update of sections 4.2, 5.1 and 5.2 of the SmPC to update the information on paediatric data and section 4.4 of the SmPC to remove the warning regarding the risk of growth retardation in children and the guidance on how to address this risk as agreed during the assessment of the initial application for Budesonide/Formoterol Teva Pharma B.V finalised in January 2020

#### 15.3.5. [Burosumab - CRYSVITA \(CAP\) - EMEA/H/C/004275/II/0023, Orphan](#)

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of fibroblast growth factor 23 (FGF23)-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged 1 year and over, based on data from two ongoing open-label clinical studies, namely: 1) study UX023T-CL201: a phase 2 open-label trial to assess the efficacy and

safety of burosumab in subjects with TIO or epidermal nevus syndrome (ENS)-associated osteomalacia, 2) study KRN23-002: a phase 2 Open-label trial to assess the efficacy and safety of burosumab in patients with TIO or ENS (144-week data and 88-week data respectively). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly. The MAH also applied for one additional year of market protection

#### 15.3.6. Clopidogrel - ISCOVER (CAP) - EMEA/H/C/000175/WS1820/0142; PLAVIX (CAP) - EMEA/H/C/000174/WS1820/0140

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of section 4.2 of the SmPC in order to add 600 mg as an alternative loading dose to the existing 300 mg to be used at initiation of treatment in the indication of secondary prevention of atherothrombotic events in adult patients suffering from acute coronary syndrome. This update is based on a bibliographic review of published studies. The package leaflet and the RMP (version 2.0) are updated accordingly

#### 15.3.7. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) – VAXZEVRIA (previously COVID-19 VACCINE ASTRAZENECA) (CAP) - EMEA/H/C/005675/II/0002

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.8 of the SmPC in order to update the safety profile and to add the adverse drug reactions: abdominal pain and urticaria with frequency uncommon and pain in extremity and influenza-like illness with frequency common based on the primary analysis from the pooled pivotal studies (listed as a specific obligation in the Annex II) namely: 1) study COV001: a phase 1/2 study to determine efficacy, safety and immunogenicity of the candidate coronavirus disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers; 2) study COV002: a single-blind, randomised, controlled, phase 2/3 trial assessing the safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults conducted in the UK; 3) study COV003: a single-blinded, multicentre, randomised, controlled phase 3 trial assessing the safety, efficacy, and immunogenicity of AZD1222 in participants in Brazil; 4) study COV005: a blinded, multicentre, randomised, controlled phase 1/2 trial assessing the safety, efficacy, and immunogenicity of AZD1222 in participants in South Africa. The MAH took the opportunity to introduce some editorial changes throughout the product information. The package leaflet, labelling and the RMP (version 2.1) are updated accordingly

#### 15.3.8. COVID-19 mRNA<sup>50</sup> vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/II/0019

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Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Proposal to replace post-authorisation effectiveness epidemiology study C4591014

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<sup>50</sup> Messenger ribonucleic acid

currently included in the RMP (listed as a category 3 study in the RMP): a test-negative design to evaluate the effectiveness of Comirnaty (BNT162b2 – COVID-19 vaccine) against acute respiratory illness due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among adults ≥18 years of age as a milestone with three other studies to pursue the same objective. The RMP (version 1.1) is updated accordingly

#### **15.3.9. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1952/0042; FORXIGA (CAP) - EMEA/H/C/002322/WS1952/0060**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication for Forxiga and Edistride (dapagliflozin) to include treatment of children aged 10 years and adolescents with type 2 diabetes mellitus (T2DM) based on the results from studies: 1) study MB10209/D1690C000016: a randomised, multicentre, parallel, single-dose study to explore the pharmacokinetics and pharmacodynamics of dapagliflozin in children 10 to less than 18 years of age with T2DM receiving one of three dose levels of dapagliflozin: 2.5, 5 or 10 mg; 2) study MB102-138/D1690C000017: a randomised, double-blind, placebo-controlled, 24-week efficacy and safety study of dapagliflozin 10 mg as compared to placebo with a 28-week open label safety extension phase, in patients aged from 10 to less than 18 years (and young adults from 18 to less than 25 years) with T2DM who have inadequate glycaemic control on diet and exercise with: either metformin only, or insulin only or with metformin and insulin. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 21.0) are updated in accordance

#### **15.3.10. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0055**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of adult patients with heart failure and reduced ejection fraction. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9 and 5.1 of the SmPC are updated based on final results from study EMPEROR-Reduced: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo in patients with chronic heart failure with reduced ejection fraction (HFrEF). The package leaflet, labelling and the RMP (version 15.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

#### **15.3.11. 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

#### **15.3.12. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/II/0003**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of sections 4.5 and 5.2 of the SmPC to update the wording on the inhibition of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) by the primary metabolite of filgotinib (GS-829845) based upon results from an in vitro study AD-417-2028 which assessed in vitro inhibition of human P-gp and BCRP by filgotinib. The package leaflet and the RMP (version 1.2) are updated accordingly

#### **15.3.13. Filgrastim - ACCOFIL (CAP) - EMEA/H/C/003956/II/0046/G**

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of: 1) introduction of a new presentation Accofil 12 MU/0.2 mL solution for injection or infusion in pre-filled syringe; 2) introduction of a new presentation, Accofil 70 MU/0.73 mL solution for injection or infusion in pre-filled syringe. The product information and the RMP (version 5) are updated accordingly

#### **15.3.14. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/II/0046**

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Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an alternative study: an evaluation of the effect of lomitapide treatment on major adverse cardiovascular events (MACE) in patients with homozygous familial hypercholesterolemia (LILITH) to the currently agreed protocol for study on the effects of lomitapide on carotid and aortic atherosclerosis in patients treated with lomitapide in usual care (CAPTURE) in order to propose an evaluation of the effect of lomitapide treatment on MACE in patients with homozygous familial hypercholesterolemia. As a consequence, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 6.4) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.2)

#### **15.3.15. Paliperidone - PALIPERIDONE JANSSEN-CILAG INTERNATIONAL (CAP) - EMEA/H/C/005486/X/0002/G**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to introduce two new strengths of 700 mg and 1000 mg prolonged-release suspension for injection. The RMP (version 10.1) is updated accordingly; 2) change of the (invented) name of the medicinal product from Paliperidone Janssen-Cilag International to Byannli; 3) deletion of the 25 mg,



50 mg, 75 mg, 100 mg and 150 mg/100 mg strengths from the Paliperidone Janssen-Cilag marketing authorisation (EU/1/20/1453/001-006)

#### **15.3.16. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/II/0054**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study MO28047 (PERUSE) (listed as an obligation in Annex II): a multicentre, open-label, single-arm study of pertuzumab in combination with trastuzumab and taxane in first line treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive advanced (metastatic or locally recurrent) breast cancer. The RMP (version 13.0) is updated accordingly

#### **15.3.17. Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/II/0069**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to include the treatment of unclassifiable interstitial lung disease (UIILD). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 11.0) are updated in accordance

#### **15.3.18. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/II/0023/G, Orphan**

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Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of an update of sections 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC based on new clinical data from: 1) study P09-10 (HARMONY III): an open-label naturalistic pragmatic study to assess the long-term safety of pitolisant in the treatment of excessive daytime sleepiness (EDS) (with or without cataplexy) in narcolepsy; 2) study P16-02: a randomised, double-blind, active- and placebo-controlled, single-dummy, 4-way crossover study to determine the abuse potential of pitolisant compared to phentermine and placebo, in healthy, non-dependent recreational stimulant users. The proposed update also includes results of a post approval network meta-analysis which compares efficacy and safety of multiple treatments, multi-arm studies, and multi-criteria treatment decisions. The package leaflet and the RMP (version 6.0) are updated accordingly

#### **15.3.19. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0093**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Update of section 4.6 of the SmPC in order to update safety information following pregnancy outcome data for raltegravir 400 mg film-coated tablet from prospective reports of pregnancy data with known outcome and time of raltegravir exposure. The RMP (version 15.1) is updated accordingly. In addition, the MAH took the opportunity to introduce some minor changes agreed in previous procedures in the product information and to update the list of local representatives for Germany. Finally, the product information

is brought in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.20. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/004195/X/0018

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add a new strength of 3000 IU for rurioctocog alfa pegol powder and solvent for solution for injection, for intravenous use. The RMP (version 2.1) is updated in accordance. Furthermore, the MAH took opportunity to include editorial changes throughout the product information

#### 15.3.21. Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0026

Applicant: Eurocept International B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (350 mg/mL oral solution). The RMP (version 0.1) is updated in accordance

#### 15.3.22. Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0028

Applicant: Eurocept International B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (500 mg film-coated tablets). The RMP (version 0.1) is updated in accordance

#### 15.3.23. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0030

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of the final report from study GS-US-320-4018 (listed as a category 3 study in the RMP): a phase 3, randomized, double blind study to evaluate the efficacy and safety of switching from tenofovir disoproxil fumarate 300 mg once daily to tenofovir alafenamide 25 mg once daily in subjects with chronic hepatitis B who are virologically suppressed. The RMP (version 6.1) is updated accordingly

#### 15.3.24. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0030

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication in combination with hypomethylating agents (HMAs) or low dose cytarabine (LDAC) for the treatment of adult patients with newly-diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. As a consequence, sections 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and RMP (version 6.1) are updated accordingly

## 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. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/202009

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### 16.1.2. Azilsartan medoxomil - EDARBI (CAP) - PSUSA/00000280/202008

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.3. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/202009

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.4. Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/202008

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Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.1.5. Cholic acid<sup>51</sup> - ORPHACOL (CAP) - PSUSA/00010208/202009

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Applicant: Laboratoires CTRS

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<sup>51</sup> Treatment of inborn errors in primary bile acid synthesis due to 3 $\beta$ -hydroxy- $\Delta$ 5-C27-steroid oxidoreductase deficiency or  $\Delta$ 4-3-oxosteroid-5 $\beta$ -reductase indication(s) only

PRAC Rapporteur: Sofia Trantza  
Scope: Evaluation of a PSUSA procedure

**16.1.6. [Ciclosporin<sup>52</sup> - IKERVIS \(CAP\); VERKAZIA \(CAP\) - PSUSA/00010362/202009](#)**

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

**16.1.7. [Damoctocog alfa pegol - JIVI \(CAP\) - PSUSA/00010732/202008](#)**

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Applicant: Bayer AG  
PRAC Rapporteur: Menno van der Elst  
Scope: Evaluation of a PSUSA procedure

**16.1.8. [Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA \(CAP\) - PSUSA/00010646/202009](#)**

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Applicant: Janssen-Cilag International N.V.  
PRAC Rapporteur: Ana Sofia Diniz Martins  
Scope: Evaluation of a PSUSA procedure

**16.1.9. [Darvadstrocel - ALOFISEL \(CAP\) - PSUSA/00010676/202009](#)**

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Applicant: Takeda Pharma A/S, ATMP<sup>53</sup>  
PRAC Rapporteur: Brigitte Keller-Stanislawski  
Scope: Evaluation of a PSUSA procedure

**16.1.10. [Doravirine - PIFELTRO \(CAP\) - PSUSA/00010729/202008](#)**

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Applicant: Merck Sharp & Dohme B.V.  
PRAC Rapporteur: Ana Sofia Diniz Martins  
Scope: Evaluation of a PSUSA procedure

**16.1.11. [Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO \(CAP\) - PSUSA/00010731/202008](#)**

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Applicant: Merck Sharp & Dohme B.V.  
PRAC Rapporteur: Ana Sofia Diniz Martins  
Scope: Evaluation of a PSUSA procedure

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<sup>52</sup> Topical use only

<sup>53</sup> Advanced therapy medicinal product

#### 16.1.12. Eluxadoline - TRUBERZI<sup>54</sup> - PSUSA/00010528/202009

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### 16.1.13. Esketamine<sup>55</sup> - SPRAVATO (CAP) - PSUSA/00010825/202009

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.1.14. Fremanezumab - AJOVY (CAP) - PSUSA/00010758/202009

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.1.15. Gilteritinib - XOSPATA (CAP) - PSUSA/00010832/202009

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### 16.1.16. Ibalizumab - TROGARZO (CAP) - PSUSA/00010797/202009

Applicant: Theratechnologies Europe Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

#### 16.1.17. Idebenone<sup>56</sup> - RAXONE (CAP) - PSUSA/00010412/202009

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

#### 16.1.18. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - PSUSA/00001742/202008

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

<sup>54</sup> European Commission (EC) decision on the marketing authorisation (MA) withdrawal of Truberzi dated 18 December 2020

<sup>55</sup> Centrally authorised product(s) only

<sup>56</sup> Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

#### 16.1.19. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/202009

Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### 16.1.20. Linaclotide - CONSTELLA (CAP) - PSUSA/00010025/202008

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### 16.1.21. Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/202009

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

#### 16.1.22. Mecasermin - INCRELEX (CAP) - PSUSA/00001942/202008

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.1.23. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/202009

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.24. Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/202008

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

#### 16.1.25. Moroctocog alfa - REFACTO AF (CAP) - PSUSA/00002089/202008

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### 16.1.26. Naldemedine - RIZMOIC (CAP) - PSUSA/00010753/202009

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Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.27. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/202009

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.28. Pandemic influenza vaccine (H5N1) (whole virion, vero cell derived, inactivated) - PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP) - PSUSA/00002282/202008

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Applicant: Ology Bioservices Ireland Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.29. Risankizumab - SKYRIZI (CAP) - PSUSA/00010765/202009

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

#### 16.1.30. Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/202008

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.31. Siponimod - MAYZENT (CAP) - PSUSA/00010818/202009

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

#### 16.1.32. Sodium zirconium cyclosilicate - LOKELMA (CAP) - PSUSA/00010675/202009

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Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.1.33. Solriamfetol - SUNOSI (CAP) - PSUSA/00010831/202009

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

#### 16.1.34. Tasonermin - BEROMUN (CAP) - PSUSA/00002850/202008

Applicant: Belpharma s.a.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### 16.1.35. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/202008

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### 16.1.36. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/202009

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### 16.1.37. Tobramycin<sup>57 58</sup> - VANTOBRA (CAP) - PSUSA/00010370/202009

Applicant: PARI Pharma GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.38. Trabectedin - YONDELIS (CAP) - PSUSA/00003001/202009

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### 16.1.39. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202009

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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<sup>57</sup> Nebuliser solution

<sup>58</sup> Centrally authorised product(s) only



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

### **16.2.1. Anagrelide - ANAGRELIDE MYLAN (CAP); XAGRID (CAP); NAP - PSUSA/00000208/202009**

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Applicants: Mylan S.A.S (Anagrelide Mylan), Shire Pharmaceuticals Ireland Limited (Xagrid), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

### **16.2.2. Glycopyrronium<sup>59</sup> - SIALANAR (CAP); NAP - PSUSA/00010529/202009**

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Applicants: Proveca Pharma Limited (Sialanar), various

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

### **16.2.3. Trientine - CUFENCE (CAP); CUPRIOR (CAP); NAP - PSUSA/00010637/202009**

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Applicants: Orphalan (Cuprior), Univar Solutions BV (Cufence), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

### **16.2.4. Zoledronic acid<sup>60</sup> - ZOLEDRONIC ACID HOSPIRA (CAP); ZOLEDRONIC ACID MEDAC (CAP); ZOMETA (CAP); NAP - PSUSA/00003149/202008**

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Applicants: Medac Gesellschaft für klinische Spezialpräparate mbH (Zoledronic acid medac), Novartis Europharm Limited (Zometa), Pfizer Europe MA EEIG (Zoledronic acid Hospira), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

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

### **16.3.1. Bromazepam (NAP) - PSUSA/00000435/202008**

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Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

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<sup>59</sup> Treatment of severe sialorrhoea (chronic pathological drooling) indication(s) only

<sup>60</sup> Treatment of cancer and fractures indication(s) only

#### 16.3.2. Dalteparin sodium (NAP) - PSUSA/00000922/202008

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Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

#### 16.3.3. Dermatophagoides pteronyssinus, dermatophagoides farina<sup>61 62 63</sup> (NAP) - PSUSA/00010582/202009

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Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

#### 16.3.4. Dexamfetamine (NAP) - PSUSA/00000986/202009

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Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.3.5. Dexibuprofen (NAP) - PSUSA/00000996/202008

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.3.6. Hexoprenaline sulfate (NAP) - PSUSA/00003170/202008

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Applicant(s): various

PRAC Lead: Roxana Dondera

Scope: Evaluation of a PSUSA procedure

#### 16.3.7. Metronidazole, neomycin, nystatin (NAP) - PSUSA/00010508/202009

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Applicant(s): various

PRAC Lead: Roxana Dondera

Scope: Evaluation of a PSUSA procedure

#### 16.3.8. Modafinil (NAP) - PSUSA/00010242/202008

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Applicant(s): various

PRAC Lead: Martin Huber

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<sup>61</sup> Allergen for therapy

<sup>62</sup> For oromucosal use only

<sup>63</sup> Medicinal product(s) authorised via mutually recognition procedure and decentralised procedure only

Scope: Evaluation of a PSUSA procedure

#### **16.3.9. Nifedipine (NAP) - PSUSA/00002156/202008**

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **16.3.10. Pefloxacin (NAP) - PSUSA/00002322/202008**

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Applicant(s): various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

#### **16.3.11. Poractant alfa (NAP) - PSUSA/00002478/202008**

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Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### **16.3.12. Suxamethonium (NAP) - PSUSA/00002834/202008**

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Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

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

#### **16.4.1. Docetaxel - TAXOTERE (CAP) - EMEA/H/C/000073/LEG 039**

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Applicant: Sanofi Mature IP

PRAC Rapporteur: Tiphaine Vaillant

Scope: Detailed review on the potential risk for decreased efficacy of docetaxel when used along with any selective cyclooxygenase-2 (Cox-2) inhibitors as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001152/201911) adopted in July 2020

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

#### **16.5.1. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0024**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.4 of the SmPC to amend the wording on progressive multifocal leukoencephalopathy (PML) as requested in the conclusions of the latest periodic safety

update report single assessment (PSUSA) procedure (PSUSA/00010662/202003) adopted in November 2020

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

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

### 17.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>64</sup>

#### 17.1.1. Direct acting antivirals (DAAV): Dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir - ZEPATIER (CAP); glecaprevir, pibrentasvir - MAVIRET (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, periteprevir, ritonavir - VIEKIRAX (CAP); sofosbuvir - SOVALDI (CAP); sofosbuvir, velpatasvir - EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/PSA/J/0068

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Applicant(s): Gilead Science International (on behalf of a consortium)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Substantial amendment for a joint protocol previously agreed in June 2020 (PSA/J/0028.1) for a non-interventional imposed PASS on early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAAV) therapy in order to estimate the risk of early HCC recurrence associated with DAAV therapy exposure relative to no DAAV therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

#### 17.1.2. Pitolisant - WAKIX (CAP) - EMEA/H/C/PSA/S/0060.1

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Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to PSA/S/0060 [substantial amendment to a protocol previously agreed in September 2016 for a 5-year multicentre, observational PASS to document the utilisation of Wakix (pitolisant) in the treatment of narcolepsy with or without cataplexy and to collect information on its long-term safety when used in routine medical practice] as per the request for supplementary information (RSI) adopted in December 2020

#### 17.1.3. Sotagliflozin – ZYNQUISTA (CAP) - EMEA/H/C/PSP/S/0084.4

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Applicant: Guidehouse Germany GmbH

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<sup>64</sup> In accordance with Article 107n of Directive 2001/83/EC

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0084.3 [protocol for an observational retrospective cohort study using existing data sources on the incidence of diabetic ketoacidosis (DKA) in adult patients with type 1 diabetes mellitus (T1DM) treated with sotagliflozin as an adjunct to insulin versus insulin alone, as required in the outcome of the initial opinion/marketing authorisation (EMA/H/C/004889) finalised in February 2019] as per the request for supplementary information (RSI) adopted in December 2020

## **17.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>65</sup>**

### **17.2.1. Cabotegravir - VOCABRIA (CAP) - EMA/H/C/004976/MEA 004**

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Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study 215162 (listed as a category 3 study in the RMP): a prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir-containing antiretroviral regimen. Summary objectives [final clinical study report (CSR): expected in March 2027]

### **17.2.2. Cabotegravir - VOCABRIA (CAP) - EMA/H/C/004976/MEA 005**

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Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study 215163: a study on pregnancy and neonatal outcomes following prenatal exposure to cabotegravir long acting (CAB LA) – data from the European Pregnancy and Paediatric human immunodeficiency virus (HIV) Cohort Collaboration (EPPICC)

### **17.2.3. Cabotegravir - VOCABRIA (CAP) - EMA/H/C/004976/MEA 006**

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Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study 215325: a study on pregnancy and neonatal outcomes following prenatal exposure to cabotegravir - data from the Antiretroviral Pregnancy Registry (APR)

### **17.2.4. Darbepoetin alfa - ARANESP (CAP) - EMA/H/C/000332/MEA 092.2**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 092.1 [protocol for study 20190404: a retrospective cohort study to assess the use of erythropoiesis stimulating agents (ESAs) in subjects receiving myelosuppressive chemotherapy in Europe] as per the request for supplementary information (RSI) adopted in November 2020

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<sup>65</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

#### 17.2.5. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 007.2

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Amendment to a protocol previously agreed in October 2020 to study 109MS401 (ESTEEM): a multicentre, global, observational study to collect information on safety and to document the drug utilisation of Tecfidera (dimethyl fumarate) when used in routine medical practice in the treatment of relapsing multiple sclerosis

#### 17.2.6. Fenofibrate, pravastatin sodium - PRAVAFENIX (CAP) - EMEA/H/C/001243/MEA 007.6

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Adrien Inoubli

Scope: Amendment to a protocol previously agreed in 2014 for study POSE (Pravafenix Observational Study in Europe) (EUPAS13661): a European, observational, three-year cohort comparative study on the safety of the fixed dose combination pravastatin 40 mg/fenofibrate 160 mg (Pravafenix) versus statin alone in real clinical practice

#### 17.2.7. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.5

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Amendment to a protocol previously agreed in September 2020 for study TEG4001: a prospective, non-interventional, long-term, multinational cohort safety study of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN)

#### 17.2.8. Sotagliflozin - ZYNQUISTA (CAP) - EMEA/H/C/004889/MEA 004.3

Applicant: Guidehouse Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 004.2 [protocol for a nested, case-control study to evaluate the risk of malignancies (bladder, renal, breast, Leydig cell, pancreatic, thyroid and prostate cancers) in adult patients with type 1 diabetes mellitus (T1DM) using sotagliflozin in existing healthcare databases in Europe and in the United States [final clinical study report (CSR) expected in April 2030]] as per the request for supplementary information (RSI) adopted in October 2020

#### 17.2.9. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 015.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Amendment to a protocol previously agreed in November 2020 for study A3921334 (listed as a category 3 study in the RMP): a non-interventional PASS to evaluate the effectiveness of additional risk minimisation measures (aRMM) materials for Xeljanz (tofacitinib) in Europe via a survey of healthcare professionals (HCPs), 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

### **17.3. Results of PASS imposed in the marketing authorisation(s)<sup>66</sup>**

#### **17.3.1. Aprotinin (NAP) - EMA/H/N/PSR/S/0030**

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Applicant: Nordic Group BV (Trasylol)

PRAC Rapporteur: Laurence de Fays

Scope: Results for a Nordic aprotinin patient registry to record utilisation information on patients at cardiac surgery centres

### **17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>67</sup>**

#### **17.4.1. Dapagliflozin - EDISTRIDE (CAP) - EMA/H/C/004161/WS2009/0045/G; FORXIGA (CAP) - EMA/H/C/002322/WS2009/0064/G**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from studies MB102103, MB102104 and MB102110 listed as a category 3 study in the RMP. These are observational studies comparing the risk of severe complications of UTI, acute liver injury and acute kidney injury respectively, between type 2 diabetes patients exposed to dapagliflozin and those exposed to other antidiabetic treatments. The RMP version 23.1 for Forxiga and Edistride has also been submitted

#### **17.4.2. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP) - EMA/H/C/000703/II/0091**

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Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study V501-070 (listed as a category 3 study in the RMP): a post-licensure observational study of the safety of Gardasil (human papillomavirus vaccine) in males. The RMP (version 14.1) is updated accordingly. The MAH took the opportunity to update the RMP with the synopsis for the study protocol for an observational study combining health-registries in Sweden on the 2-dose effectiveness of Gardasil (human papillomavirus vaccine) as agreed in MEA 82.6 by the CHMP in June 2020

#### **17.4.3. Insulin detemir - LEVEMIR (CAP) - EMA/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

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<sup>66</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>67</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

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

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

### **17.5.1. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/MEA 001.2**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First interim report for study 20160264 (ABP 501) - British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR): an observational study to evaluate long term safety of Amgevita (adalimumab) in patients with rheumatoid arthritis [final report: expected in Q3 2027]

### **17.5.2. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.12**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Seventh annual interim report for study C1CL670E2422: an observational, multicentre cohort study to evaluate the long-term exposure and safety of deferasirox in the treatment of paediatric non-transfusion dependent thalassaemia patients over 10 years-old for whom deferoxamine is contraindicated or inadequate

### **17.5.3. Fenofibrate, pravastatin sodium - PRAVAFENIX (CAP) - EMEA/H/C/001243/MEA 007.7**

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Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Adrien Inoubli

Scope: Interim results for study POSE (Pravafenix Observational Study in Europe) (EUPAS13661): a European, observational, three-year cohort comparative study on the safety of the fixed dose combination pravastatin 40 mg/ fenofibrate 160 mg (Pravafenix) versus statin alone in real clinical practice

### **17.5.4. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 033.5**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third annual interim report for study MK-8259-050 (version 2.0) (listed as a category 3 study in the RMP): an observational PASS for golimumab in the treatment of poly-articular juvenile idiopathic arthritis (pJIA) using the German Biologics JIA registry (BiKeR)



#### 17.5.5. **Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 114.11**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for study C0168Z03 (PSOLAR: PSoriasis Longitudinal Assessment and Registry): a multicentre, open study of patients with plaque psoriasis who are candidates for systemic therapy including biologics [final clinical study report (CSR) for PSOLAR expected in June 2023]

### 17.6. **Others**

#### 17.6.1. **Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study D8220C00008 (listed as a category 3 study in the RMP): a phase 3b, multicentre, open-label, single-arm study in subjects with chronic lymphocytic leukaemia (ASSURE) to address missing information around moderate to severe cardiac impaired patients in subjects treated with Calquence (acalabrutinib)

#### 17.6.2. **Melatonin - SLENYTO (CAP) - EMEA/H/C/004425/REC 002.1**

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Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Second annual French 'recommandation temporaire d'utilisation (RTU)' report on special temporary recommendation of use for Circadin (melatonin) 2-6 mg in the autism spectrum disorder (ASD) and neurogenetic 6-18 year-old population for the period from October 2015 to July 2019

### 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 listed-below medicines and the CHMP Rapporteur's assessment report, PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the listed-below medicines 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**

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

#### **18.2.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0061 (without RMP)**

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Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

#### **18.2.2. Belantamab mafodotin - BLENREP (CAP) - EMEA/H/C/004935/R/0003 (without RMP)**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

#### **18.2.3. Bulevirtide - HEPCLUDEX (CAP) - EMEA/H/C/004854/R/0003 (without RMP)**

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Applicant: MYR GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Conditional renewal of the marketing authorisation

#### **18.2.4. Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/R/0002 (without RMP)**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

#### **18.2.5. Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/R/0003 (without RMP)**

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Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

#### 18.2.6. Pretomanid - DOVPRELA (CAP) - EMEA/H/C/005167/R/0005 (without RMP)

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

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

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

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

#### 18.3.2. Enoxaparin sodium - INHIXA (CAP) - EMEA/H/C/004264/R/0076 (with RMP)

Applicant: Techdow Pharma Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

#### 18.3.3. Glycopyrronium - SIALANAR (CAP) - EMEA/H/C/003883/R/0018 (without RMP)

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Zane Neikena

Scope: 5-year renewal of the marketing authorisation

#### 18.3.4. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/R/0043 (without RMP)

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: 5-year renewal of the marketing authorisation

#### 18.3.5. 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

#### 18.3.6. Sildenafil - MYSILDECARD (CAP) - EMEA/H/C/004186/R/0009 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

### 18.3.7. Vismodegib - ERIVEDGE (CAP) - EMEA/H/C/002602/R/0050 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

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 06-09 April 2021 meeting (marked as 'a'), and for the 20 April 2021 extraordinary meeting (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
Sonja Hrabcik <sup>a, b</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
Julian Eftimov <sup>a</sup>	Alternate	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce <sup>a, b</sup>	Member	Croatia	No interests declared	Full involvement
Christina Sylvia Chrysostomou <sup>a, b</sup>	Alternate	Cyprus	No interests declared	Full involvement
Panagiotis Psaras <sup>a</sup>	Member	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 Kirstine Stark <sup>a, b</sup>	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted <sup>a, b</sup>	Alternate	Denmark	No participation in discussion,	16.1.23 Mepolizumab - NUCALA (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			final deliberations and voting on:	PSUSA/000104 56/202009
Maia Uusküla <sup>a, b</sup>	Member	Estonia	No interests declared	Full involvement
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, b</sup>	Alternate	Germany	No interests declared	Full involvement
Agni Kapou <sup>a, b</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, b</sup>	Alternate	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir <sup>a</sup>	Member	Iceland	No participation in discussion, final deliberations and voting on:	6.1.4. Enzalutamide - XTANDI (CAP) - PSUSA/000100 95/202008 6.1.15. Gilteritinib - XOSPATA (CAP) - PSUSA/000108 32/202009 17.2.4. Darbepoetin alfa - ARANESP (CAP) - MEA 092.2

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				17.5.1. Adalimumab - AMGEVITA (CAP) - MEA 001.2
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, b</sup>	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
Anne-Cécile Vuillemin <sup>b</sup>	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg <sup>a, b</sup>	Member (CHMP member)	Malta	No interests declared	Full involvement
Benjamin Micallef <sup>a, b</sup>	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst <sup>a, b</sup>	Member	The Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan <sup>a, b</sup>	Alternate	The Netherlands	No interests declared	Full involvement
David Olsen <sup>a, b</sup>	Member	Norway	No participation in final deliberations and voting on:	4.1.3. Fluoroquinolones: ciprofloxacin (NAP); delafloxacin - QUOFENIX (CAP); levofloxacin - QUINSAIR (CAP), NAP; lomefloxacin

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) 6.1.9. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/202009 11.2.2. Phenobarbital (NAP) - EE/H/PSUFU/0002370/202001 16.1.7. Damoctocog alfa pegol - JIVI (CAP) - PSUSA/00010732/202008 16.3.9. Nifedipine (NAP) - PSUSA/00002156/202008
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>a, 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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Roxana Dondera <sup>a, b</sup>	Member	Romania	No interests declared	Full involvement
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 <sup>68</sup>	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, b</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, b</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng <sup>a</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente <sup>a, b</sup>	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Milou Daniel Drici <sup>a, b</sup>	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stefan Weiler <sup>a, b</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

<sup>68</sup> Until 16 April 2021



Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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
Andrea Laslop <sup>a</sup>	Expert - via telephone*	Austria	No interests declared	Full involvement
Els Beghein <sup>a</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Christelle Bizimungu <sup>b</sup>	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Ingrid Bourges <sup>b</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Inne Crèvecoeur <sup>a</sup>	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Gaelle De Meyer <sup>a</sup>	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Christophe Focke <sup>a</sup>	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Edwige Haelterman Brenneisen <sup>a</sup>	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani <sup>a, b</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Flora Musuamba Tshinanu <sup>a</sup>	Expert - via telephone*	Belgium	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
Martine Sabbe <sup>a</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Charlotte Selvais <sup>a</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume <sup>a</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Margareta Bego <sup>a</sup>	Expert - via telephone*	Croatia	No interests declared	Full involvement
Ivana Ljubičić <sup>a, b</sup>	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Petra Kaftanová <sup>a, b</sup>	Expert - via telephone*	Czechia	No interests declared	Full involvement
Sinan Bardakci Sarac <sup>a</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Kirstine Moll Harboe <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
Kroot Aab <sup>a, b</sup>	Expert - via telephone*	Estonia	No interests declared	Full involvement
Johanna Lähteenvuo <sup>a</sup>	Expert - via telephone*	Finland	No restrictions applicable to this meeting	Full involvement
Outi Mäki-Ikola <sup>a</sup>	Expert - via telephone*	Finland	No restrictions applicable to this meeting	Full involvement
Pierre Demolis <sup>a, b</sup>	Expert - via telephone*	France	No interests declared	Full involvement
Stephanie Hueber <sup>a</sup>	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Alexis Jacquet <sup>a</sup>	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Isabelle Parent du Chatelet <sup>a</sup>	Expert - via telephone*	France	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jean-Michel Race <sup>a</sup>	Expert - via telephone*	France	No interests declared	Full involvement
Harald Enzmann <sup>a</sup>	Expert - via telephone*	Germany	No interests declared	Full involvement
Dennis Lex <sup>a</sup>	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Jan Mueller-Berghaus <sup>a</sup>	Expert - via telephone*	Germany	No interests declared	Full involvement
Konstantinos Markopoulos <sup>a</sup>	Expert - via telephone*	Greece	No interests declared	Full involvement
Agnes Gyurasics <sup>a</sup>	Expert - via telephone*	Hungary	No restrictions applicable to this meeting	Full involvement
Jayne Crowe <sup>a</sup>	Expert - via telephone*	Ireland	No interests declared	Full involvement
Grainne Kirwan <sup>a</sup>	Expert - via telephone*	Ireland	No interests declared	Full involvement
Sara Galluzzo <sup>b</sup>	Expert - via telephone*	Italy	No interests declared	Full involvement
Elita Poplavska <sup>a</sup>	Expert - via telephone*	Latvia	No restrictions applicable to this meeting	Full involvement
Martine Trauffler <sup>a</sup>	Expert - via telephone*	Luxemburg	No interests declared	Full involvement
Helen Vella <sup>a</sup>	Expert - via telephone*	Malta	No interests declared	Full involvement
Frederikus Klok <sup>a</sup>	Expert - via telephone*	The Netherlands	No restrictions applicable to this meeting	Full involvement
Paula van Hennik <sup>a</sup>	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Bjorg Bolstad <sup>a</sup>	Expert - via telephone*	Norway	No restrictions applicable to this meeting	Full involvement
Ingrid Wang <sup>a</sup>	Expert - via telephone*	Norway	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Ewa Balkowiec Iskra <sup>a</sup>	Expert - via telephone*	Poland	No restrictions applicable to this meeting	Full involvement
Patrícia Catalão <sup>b</sup>	Expert - via telephone*	Portugal	No interests declared	Full involvement
Carla Torre <sup>a</sup>	Expert - via telephone*	Portugal	No restrictions applicable to this meeting	Full involvement
Bruno Sepodes <sup>a</sup>	Expert - via telephone*	Portugal	No restrictions applicable to this meeting	Full involvement
Fatima Ventura <sup>a</sup>	Expert - via telephone*	Portugal	No participation in final deliberations and voting on:	4.1.5. COVID-19 vaccine (ChAdOx1-S [recombinant]) - COVID-19 VACCINE ASTRAZENECA (CAP)
Simona Badoi <sup>a</sup>	Expert - via telephone*	Romania	No interests declared	Full involvement
Dana Marin <sup>a</sup>	Expert - via telephone*	Romania	No interests declared	Full involvement
Roxana Stroe <sup>a, b</sup>	Expert - via telephone*	Romania	No interests declared	Full involvement
Maria Chamorro Somoza <sup>a, b</sup>	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Silvia De Orbe Izquierdo <sup>a</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Ana Fernandez Dueñas <sup>a</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Blanca García-Ochoa <sup>a</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Monica Martinez Redondo <sup>a</sup>	Expert - via telephone*	Spain	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Consuelo Mejias Pavón <sup>a</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Dolores Montero Corominas <sup>a</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Milena Peraita Ezcurra <sup>a</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Alicia Pérez <sup>b</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Augustin Portela Moreira <sup>a</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Sol Ruiz <sup>a</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Ana Sagredo <sup>a, b</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Helena Back <sup>a, 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
Sofia Bosdotter Enroth <sup>a, b</sup>	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson <sup>a</sup>	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jessica Mwinyi <sup>b</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 evaluated against the agenda topics or activities they participated in.

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

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

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

## 21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

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

### **Signals assessment and prioritisation**

(Item 4 of the PRAC minutes)

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

The presence of a safety signal does not mean that a medicine has caused the reported adverse event.

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

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

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

(Item 5 of the PRAC minutes)

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

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

(Item 6 of the PRAC minutes)

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

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

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

(Item 7 of the PRAC minutes)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

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

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

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