



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

10 December 2020  
EMA/PRAC/698632/2020  
Human Medicines Division

## Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 31 August – 03 September 2020

Chair: Sabine Straus – Vice-Chair: Martin Huber

### Health and safety information

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

### Disclaimers

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

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

### Note on access to documents

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

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## **1. Introduction**

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

The Chairperson opened the 31 August – 03 September 2020 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 (Annex II – List of participants). No new or additional conflicts were declared.

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

The PRAC Chairperson welcomed Milou-Daniel Drici as a new independent scientific expert member nominated by the European Commission (EC) to PRAC. The Chair announced that Marcel Bruch, the member for Luxembourg, was to step down after the current plenary meeting.

### **1.2. Agenda of the meeting on 31 August - 03 September 2020**

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 06 - 09 July 2020**

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 06 - 09 July 2020 were published on the EMA website on 10 December 2020 ([EMA/PRAC/672654/2020](#)).

## **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

### 3.3.1. Ulipristal acetate<sup>1</sup> – ESMYA (CAP); NAP - EMEA/H/A-31/1496

Applicant(s): Gedeon Richter Plc.; various

PRAC Rapporteur: Annika Folin; PRAC Co-rapporteur: Menno van der Elst

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

#### Background

A referral procedure under Article 31 of Directive 2001/83/EC on medicinal products containing ulipristal acetate 5 mg is to be concluded. The procedure was initiated after a new case of serious liver injury leading to liver transplantation following exposure to Esmya (ulipristal acetate) was reported despite the implementation of risk minimisation measures (RMMs) in 2018 in line with the conclusions of a previous referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1460](#)) on Esmya (ulipristal acetate). In March 2020, the PRAC recommended the provisional suspension of the marketing authorisations of ulipristal acetate 5 mg-containing products. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes March 2020](#), [PRAC minutes June 2020](#) and [PRAC minutes July 2020](#).

#### Discussion

The PRAC discussed the conclusion reached by the Rapporteurs.

The PRAC reviewed the information available to the Committee on ulipristal acetate 5 mg and the risk of serious liver injury, including the data provided by the MAHs of ulipristal

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<sup>1</sup> 5 mg

acetate 5 mg in writing and in an oral explanation as well as the outcome of the consultation with the ad-hoc expert group (AHEG) convened in September 2020 in the context of this procedure.

The PRAC reviewed all cases of serious liver injury reported among women treated with ulipristal acetate 5 mg for the treatment of symptoms of uterine fibroids, including a new case of serious liver injury leading to liver transplantation reported although the risk minimisation measures (RMMs) agreed as an outcome of the 2018 referral procedure were followed. The PRAC concluded that the causal association of ulipristal acetate 5 mg with serious liver injury was highly probable and noted that a progression in the development of hepatic failure leading to liver transplantation could not be prevented.

The PRAC discussed further risk minimisation proposals but could not identify any additional measures that would ensure effective minimisation of the risk to an acceptable level. In view of the seriousness and idiosyncratic nature of the risk, the PRAC concluded that this risk outweighs the benefits of ulipristal acetate 5 mg in the treatment of symptoms of uterine fibroids. No sub-group of patients in which the benefits of ulipristal acetate 5 mg would outweigh the risks could be identified. Furthermore, the PRAC could not identify any condition, the fulfilment of which would demonstrate a positive benefit-risk balance of ulipristal acetate 5 mg medicinal products.

As a consequence, the PRAC considered that the benefit-risk balance of ulipristal acetate 5 mg medicinal products for the treatment of symptoms of uterine fibroids is not favourable and recommended the revocation of the marketing authorisations of all ulipristal acetate 5 mg medicinal products.

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

- The PRAC adopted, by majority, the revocation of the marketing authorisations for ulipristal acetate-containing medicines<sup>2</sup> and adopted a recommendation to be considered by CHMP for an opinion – see EMA Press Release entitled 'PRAC recommends revoking marketing authorisation of ulipristal acetate for uterine fibroids' ([EMA/455818/2020](https://www.ema.europa.eu/en/press-room/2020/09/wc-0000000000)).

Nineteen members voted in favour of the recommendation whilst fourteen members<sup>3</sup> had divergent views<sup>4</sup>. The Icelandic and Norwegian PRAC members agreed with the recommendation.

Post-meeting note: the press release 'Ulipristal acetate for uterine fibroids: EMA recommends restricting use' representing the opinion provided by the CHMP ([EMA/593162/2020](https://www.ema.europa.eu/en/press-room/2020/11/wc-0000000000)) was published on the EMA website on 13 November 2020.

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

None

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<sup>2</sup> 5mg

<sup>3</sup> Jan Neuhauser, Nikica Mirošević Skvrce, Eva Jirsová, Kirsti Villikka, Zane Neikena, John Joseph Borg, Menno van der Elst, Roxana Stefania Stroe, Michal Radik, Eva Segovia, Birgitta Grundmark, Milou-Daniel Drici, Hedvig Marie Egeland Nordeng, Raymond Anderson

<sup>4</sup> The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded

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

### 3.5. Others

None

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

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

See also Annex I 14.1.

#### 4.1.1. 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins): atorvastatin (NAP); fluvastatin (NAP); lovastatin (NAP); pitavastatin (NAP); pravastatin (NAP); rosuvastatin (NAP); simvastatin (NAP)

Applicant(s): various

PRAC Rapporteur: Adrien Inoubli

Scope: Signal of bullous pemphigoid

EPITT 19586 – New signal

Lead Member State(s): CZ, DE, ES, FI, FR, NL

#### Background

Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, also known as statins, are inhibitors of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase. They are indicated for the reduction of elevated level of total and low density lipoprotein (LDL)-cholesterol as an adjunct to diet and for the prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event subject to certain conditions.

The exposure for atorvastatin-containing medicines is estimated to have been more than 338 million patient-years worldwide, in the period from first authorisation in 1996 to 2017. The exposure for fluvastatin-containing medicines is estimated to have been more than 45.4 million patient-years worldwide, in the period from first authorisation in 1993 to 2017. The exposure for lovastatin-containing medicines is estimated to have been more than 3.86 million patient-years worldwide, in the period from first authorisation in 1987 to 2016. The exposure for pitavastatin-containing medicines is estimated to have been more than 20 million patient-years worldwide, in the period from first authorisation in 2003 to 2019. The exposure for pravastatin-containing medicinal products is estimated to have been more than 118 million patient-years worldwide, in the period from first authorisation in 1989 to 2017. The exposure for rosuvastatin-containing medicines is estimated to have been more than 170 million patient-years worldwide, in the period from first authorisation in 2002 to 2017. The exposure for simvastatin-containing medicines is estimated to have been more than 267.3 million patient-years worldwide, in the period from first authorisation in 1988 to 2017.

<sup>6</sup> Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

During routine signal detection activities, a signal of bullous pemphigoid was identified by France, based on cases retrieved from the French pharmacovigilance database as well as published cases. France as the lead Member state (LMS) for pravastatin, the Netherlands as the LMS for rosuvastatin and pitavastatin and Germany as the LMS for atorvastatin confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the available evidence from individual case study reports and the literature regarding the risk of bullous pemphigoid in patients treated with statins and agreed that the signal required further investigation. The PRAC agreed to request a cumulative review of cases of bullous pemphigoid from the MAHs of originator single-ingredient statins-containing medicinal products.

The PRAC appointed Adrien Inoubli as Rapporteur for the signal.

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

- The MAHs for originator atorvastatin-, fluvastatin-, lovastatin-, pitavastatin-, pravastatin-, rosuvastatin- and simvastatin-containing products should submit to EMA, within 60 days, a cumulative review of the signal, including an analysis of all case reports of bullous pemphigoid and related terms, and a proposal for amending the product information, as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of vasculitis

EPITT 19578 – New signal

Lead Member State(s): NL

### **Background**

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor. Keytruda (pembrolizumab) is a centrally authorised product 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 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.

The exposure for Keytruda (pembrolizumab) is estimated to have been more than 99,000 patient-years worldwide, in the period from first authorisation in 2015 to 2018.

During routine signal detection activities, a signal of vasculitis was identified by EMA, based on 40 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the available evidence from case reports in EudraVigilance and in the literature on cases of vasculitis and agreed that the causal association of pembrolizumab with vasculitis is possible and should be reflected in the product information. Therefore, the PRAC agreed to request comments from the MAH on the proposed wording for the product information.

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

- The MAH for Keytruda (pembrolizumab) should submit to EMA, within 60 days, comments on the proposed wording for the product information as agreed by the PRAC and an estimate of the frequency of vasculitis based on clinical trials.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

See Annex I 14.2.

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

### **4.3.1. Abiraterone – ZYTIGA (CAP) - EMEA/H/C/002321/SDA/023**

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Applicant(s): Janssen-Cilag International NV

PRAC Rapporteur: Eva Segovia

Scope: Signal of anaphylactic reaction

EPITT 19535 – Follow-up to April 2020

### **Background**

For background information, see [PRAC minutes April 2020](#).

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

### **Discussion**

Having considered the available evidence in EudraVigilance, the literature and the data provided by the MAH, the PRAC agreed that there is sufficient evidence to establish an association between abiraterone and anaphylactic reactions. Therefore, the PRAC agreed that the product information should be updated to add anaphylactic reactions as an undesirable effect with a frequency 'not known'.

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

- The MAH for Zytiga (abiraterone) should submit to EMA, within 60 days, a variation to

amend<sup>7</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/458924/2020](https://www.ema.europa.eu/en/press/news/2020/09/2020-09-28-prac-recommends-chloroquine-and-hydroxychloroquine-should-be-used-to-treat-covid-19) published on 28 September 2020 on the EMA website.

#### 4.3.2. Chloroquine (NAP); hydroxychloroquine (NAP)

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Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of psychiatric disorders

EPITT 19572 – Follow-up to June 2020

##### **Background**

For background information, see [PRAC minutes June 2020](#).

The MAHs, Sanofi and ACE Pharma, as MAHs for the originator chloroquine- and hydroxychloroquine-containing products, replied to the request for information on the signal of psychiatric disorders and the responses were assessed by the Rapporteur.

##### **Discussion**

Having considered the cumulative reviews submitted by the MAHs, the PRAC considered that more detailed information on certain aspects is required before reaching a final recommendation on the signal. Therefore, the PRAC agreed to request additional information from the MAHs.

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

- The MAHs for the originator chloroquine- and hydroxychloroquine-containing products should submit to EMA, within 30 days, an updated cumulative review of the signal, including an analysis of all case reports of cases of coronavirus (COVID-19) disease from clinical trials, post-marketing use and the literature together with a proposal for amending the product information, as appropriate.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### 4.3.3. Fluoroquinolones: ciprofloxacin (NAP); delafloxacin – QUOFENIX (CAP) - EMEA/H/C/004860/SDA/003; levofloxacin – QUINSAIR (CAP) - EMEA/H/C/002789/SDA/005, 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 (Quofenix), Chiesi Farmaceutici S.p.A. (Quinsair), various

PRAC Rapporteur: Martin Huber

Scope: Signal of heart valve regurgitation, cervical artery dissection, and aortic aneurysm and dissection

EPITT 19522 – Follow-up to May 2020

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

## Background

For background information, see [PRAC minutes May 2020](#).

The MAHs replied to the request for comments on the proposed updates to the product information relating to the signal of heart valve regurgitation, cervical artery dissection, and aortic aneurysm and dissection and the responses were assessed by the Rapporteur.

## Discussion

Having considered the available evidence including the responses from the MAHs, the PRAC concluded that there is sufficient evidence for an association between fluoroquinolone treatment and the development of heart valve regurgitation, cervical artery dissection, and aortic aneurysm and dissection and that the product information of systemic and inhaled fluoroquinolones formulations should be updated accordingly.

## Summary of recommendation(s)

- The MAHs for ciprofloxacin-, delafloxacin-, levofloxacin-, lomefloxacin-, moxifloxacin-, norfloxacin-, ofloxacin-, pefloxacin-, prulifloxacin- and rifloxacin-containing products (systemic and inhaled formulations) should submit to EMA or to the National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend<sup>8</sup> the product information.
- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.

For the full PRAC recommendation, see [EMA/PRAC/458924/2020](#) published on 28 September 2020 on the EMA website.

4.3.4. [Interferon alfa-2a \(NAP\); interferon alfa-2b - INTRONA \(CAP\) - EMEA/H/C/000281/SDA/054; peginterferon alfa-2a - PEGASYS \(CAP\) - EMEA/H/C/000395/SDA/056; peginterferon alfa-2b - PEGINTRON \(CAP\) - EMEA/H/C/000280/SDA/087, VIRAFERONPEG \(CAP\) - EMEA/H/C/000329/SDA/084](#)

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Applicant(s): Merck Sharp & Dohme B.V. (IntronA, PegIntron, ViraferonPeg); Roche Registration GmbH (Pegasys), various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of neuromyelitis optica spectrum disorder

EPITT 19532 – Follow-up to March 2020

## Background

For background information, see [PRAC minutes March 2020](#).

The MAHs, Merck Sharp & Dohme B.V. and Roche, replied to the request for information on the signal of neuromyelitis optica spectrum disorder and the responses were assessed by the Rapporteur.

## Discussion

Having considered the available evidence in EudraVigilance, literature and data obtained from the MAHs, the PRAC agreed that there is sufficient evidence for an association between

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<sup>8</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

interferon alfa-containing products and the development of neuromyelitis optica spectrum disorder. The PRAC concluded that the product information for interferon alfa-2a-containing product(s) and Pegasys (peginterferon alfa-2a) should be updated accordingly. The product information for Introna (interferon alfa-2b), PegINTRON and ViraferonPEG (peginterferon alfa-2b) already reflect the relevant level of evidence.

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

- The MAH for interferon alfa-2a-containing product(s) and Pegasys (peginterferon alfa-2a) should submit to EMA or to the national Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend<sup>9</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/458924/2020](#) published on 28 September 2020 on the EMA website.

#### **4.3.5. Paclitaxel – ABRAXANE (CAP) - EMEA/H/C/000778/SDA/030, APEALEA (CAP) - EMEA/H/C/004154/SDA/002, PAZENIR (CAP) - EMEA/H/C/004441/SDA/002; NAP**

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Applicant(s): Celgene Europe BV (Abraxane), Oasmia Pharmaceutical AB (Apealea), ratiopharm GmbH (Pazenir), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19553 – Follow-up to April 2020

#### **Background**

For background information, see [PRAC minutes April 2020](#).

The MAHs, Aurobindo, Mylan, Teva, Novartis, Oasmia, AgVida, Bristol-Myers Squibb, Cipla, Intrapharm, Hikma, Celgene and Pfizer, replied to the request for information on the signal of progressive multifocal leukoencephalopathy (PML) and the responses were assessed by the Rapporteur.

#### **Discussion**

Having considered the available evidence from the literature, EudraVigilance and the cumulative reviews provided by the MAHs, the PRAC concluded that there is insufficient evidence at this stage to establish an association between treatment with paclitaxel and the development of progressive multifocal leukoencephalopathy (PML). Therefore, the PRAC agreed that no further regulatory action is warranted at this stage.

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

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

#### **4.3.6. Pomalidomide – IMNOVID (CAP) - EMEA/H/C/002682/SDA/014**

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Applicant(s): Celgene Europe BV

PRAC Rapporteur: Eva Segovia

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<sup>9</sup> Update of SmPC section 4.8. The package leaflet is to be updated accordingly

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19546 – Follow-up to April 2020

### **Background**

For background information, see [PRAC minutes April 2020](#).

The MAH replied to the request for information on the signal of progressive multifocal leukoencephalopathy (PML) and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence in EudraVigilance, in the literature and the data provided by the MAH, the PRAC concluded that there is sufficient evidence for an association between Imnovid (pomalidomide) and the development of PML. Therefore, the PRAC agreed that the product information should be updated accordingly.

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

- The MAH for Imnovid (pomalidomide) should submit to EMA, within 60 days, a variation to amend<sup>10</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/458924/2020](#) published on 28 September 2020 on the EMA website.

## **4.3.7. Vedolizumab – ENTYVIO (CAP) - EMEA/H/C/002782/SDA/005**

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Applicant(s): Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylowski

Scope: Signal of Evans' syndrome, autoimmune haemolytic anaemia, immune thrombocytopenic purpura

EPITT 19547 – Follow-up to April 2020

### **Background**

For background information, see [PRAC minutes April 2020](#).

The MAH replied to the request for information on the signal of Evans' syndrome, autoimmune haemolytic anaemia, immune thrombocytopenic purpura and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence from the literature, EudraVigilance and the cumulative review provided by the MAH, the PRAC concluded that there is insufficient evidence at present for an association between the treatment with vedolizumab and the development of Evans' syndrome, autoimmune haemolytic anaemia or immune thrombocytopenic purpura. The PRAC agreed that no further regulatory action is warranted at this stage.

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

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<sup>10</sup> Update of SmPC section 4.4. The package leaflet is to be updated accordingly

- The MAH for Entyvio (vedolizumab) should continue to monitor cases of Evans' syndrome, autoimmune haemolytic anaemia, and immune thrombocytopenic purpura as part of routine safety surveillance.

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

None

## 5. Risk management plans (RMPs)

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

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

Please refer to the CHMP pages for upcoming information

(<http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights>).

#### 5.1.1. Baloxavir marboxil - EMEA/H/C/004974

Scope: Treatment of influenza in patients aged 12 and above, including patients at high risk of developing influenza-related complications and for post-exposure prophylaxis of influenza in individuals aged 12

#### 5.1.2. Duvelisib - EMEA/H/C/005381, Orphan

Applicant: Verastem Europe GmbH

Scope: Treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and relapsed or refractory follicular lymphoma (FL)

#### 5.1.3. Glucagon – EMEA/H/C/005391

Scope: Treatment of severe hypoglycaemia in adults, adolescents and children aged 2 years and over with diabetes mellitus

#### 5.1.4. Icosapent ethyl - EMEA/H/C/005398

Scope: Reduction of cardiovascular risk as an adjunct to statin therapy

#### 5.1.5. Idecabtagene vicleucel - EMEA/H/C/004662, Orphan

Applicant: Celgene Europe BV, ATMP<sup>13</sup>

Scope (accelerated assessment): Treatment of multiple myeloma

<sup>13</sup> Advanced therapy medicinal product

#### 5.1.6. Inclisiran – EMEA/H/C/005333

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Scope: Treatment of primary hypercholesterolaemia or mixed dyslipidaemia

#### 5.1.7. Netarsudil, latanoprost - EMEA/H/C/005107

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Scope: Reduction of elevated intraocular pressure

#### 5.1.8. Pemigatinib - EMEA/H/C/005266, Orphan

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Applicant: Incyte Biosciences Distribution B.V.

Scope: Treatment of locally advanced or metastatic cholangiocarcinoma

#### 5.1.9. Trastuzumab deruxtecan - EMEA/H/C/005124

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Scope (accelerated assessment): Treatment of unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer

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

See also Annex I 15.2.

#### 5.2.1. Ioflupane (<sup>123</sup>I) - DATSCAN (CAP) - EMEA/H/C/000266/II/0060

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Applicant: GE Healthcare B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the first RMP (version 0.1) following the introduction of a signification change to the marketing authorisation(s)

##### **Background**

Ioflupane (<sup>123</sup>I) is a diagnostic radiopharmaceutical indicated, as Datscan, for detecting loss of functional dopaminergic neuron terminals in the striatum in adult patients with clinically uncertain Parkinsonian syndromes in order to help differentiate essential tremor from parkinsonian syndromes related to idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. The medicinal product is unable to discriminate between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. It is also indicated in adult patients to help differentiate probable dementia with Lewy bodies from Alzheimer's disease. The medicinal product is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.

The PRAC is evaluating a type II variation procedure for Datscan, a centrally authorised medicine containing ioflupane (<sup>123</sup>I), setting up the first RMP for the medicinal product. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

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

- The RMP for Datscan (ioflupane (<sup>123</sup>I)) in the context of the variation procedure under evaluation could be considered acceptable provided that an update to RMP version 0.1

and satisfactory responses to the request for supplementary information (RSI) are submitted.

- The MAH should discuss the risk of potential uptake of ioflupane (<sup>123</sup>I) by the thyroid gland as it is a known risk and risk minimisation messages are provided in the product information. In addition, in line with revision 2 of GVP module V on 'Risk management systems', it is expected that as a product matures, the classification as missing information might not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to the areas of missing information. Therefore, the PRAC agreed that missing information of 'increased risk of radiation exposure in patients with renal and hepatic impairment' is not relevant for inclusion in the RMP. Finally, the PRAC agreed that routine pharmacovigilance is sufficient to identify and characterise the risks of the medicinal product at present. The PRAC also agreed that routine risk minimisation measures are sufficient to minimise the risks of the medicinal product in the proposed indication(s) in light of the current knowledge.

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

See also Annex I 15.3.

#### 5.3.1. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/X/0074/G

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Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form, granules for oral suspension, 1 mg/mL; 2) extension of indication to include treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18 years following initiation of standard anticoagulation treatment for Xarelto (rivaroxaban) 15 mg and 20 mg tablets. As a consequence, sections 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 12.1) are updated accordingly. In addition, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated for all other dose strengths (2.5/10 mg and 15/20 mg initiation packs). Furthermore, the MAH took the opportunity to update the product information with regards 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'

#### Background

Rivaroxaban is a direct factor Xa inhibitor. It is indicated, as Xarelto, under certain conditions for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers and 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.

The CHMP is evaluating grouped type II variations for Xarelto, a centrally authorised product containing rivaroxaban, consisting of an extension application to introduce a new pharmaceutical form, granules for oral suspension and an extension of indication to include treatment of VTE and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18 years following initiation of standard anticoagulation treatment with Xarelto (rivaroxaban) 15 mg and 20 mg tablets. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see [PRAC minutes April 2020](#) and [PRAC minutes July 2020](#).

### Summary of advice

- The RMP for Xarelto (rivaroxaban) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 12.2 is submitted.
- The MAH should include medication errors related to reconstitution of and dosing with oral suspension in the list of safety concerns as an important potential risk. In addition, the MAH should discuss whether there are any European paediatric registries that encompass children treated with anticoagulant therapy and which could be used for post-authorisation safety assessment of use of rivaroxaban in children. Furthermore, a training video should be implemented as an additional risk minimisation measure (aRMM) as part of the educational material for oral suspension, both for healthcare professionals (HCPs) and patients/caregivers. The MAH should consider a separate patient alert card for the oral suspension presentation. Finally, the MAH discuss how effectiveness of aRMM will be evaluated.

## 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. Abatacept - ORENCIA (CAP) - PSUSA/00000013/201912

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

### Background

Abatacept is an immunosuppressant fusion protein indicated, as Orencia, for the treatment of rheumatoid arthritis, psoriatic arthritis, and polyarticular juvenile idiopathic arthritis, alone or in combination with methotrexate (MTX), under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Orenzia, a centrally authorised medicine containing abatacept 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 Orenzia (abatacept) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a review of the reasons for the most frequent medication errors, device malfunction events and needle issues, together with a proposal for risk minimisation measures, as appropriate.
- The MAH should submit to EMA, within 60 days, a cumulative review of cases of pancreatitis with a proposal for updating the product information, as appropriate.

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

#### **6.1.2. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/202002**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### **Background**

Baricitinib is a selective inhibitor of Janus kinase indicated, as Olumiant, alone or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Olumiant, a centrally authorised medicine containing baricitinib 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 Olumiant (baricitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on hepatic transaminase elevations to indicate that this effect is dose-dependent and to update the undesirable effect wording on 'hepatic transaminase elevations' accordingly. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>18</sup>.
- In the next PSUR, the MAH should provide complete information on blood transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) activity elevations during extended baricitinib use, separately in doses used in rheumatoid

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<sup>18</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

arthritis (RA), in atopic dermatitis (AD) and together in RA and AD clinical trials in comparison to placebo.

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

#### 6.1.3. **Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - PSUSA/00010695/202002**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

##### **Background**

Bictegravir is an integrase strand transfer inhibitor and emtricitabine and tenofovir alafenamide are nucleoside reverse transcriptase inhibitors. In combination bictegravir/emtricitabine/tenofovir alafenamide is indicated, as Biktarvy, for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Biktarvy, a centrally authorised medicine containing bictegravir/emtricitabine/tenofovir alafenamide 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 Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to re-word the listed undesirable effect of 'suicidal behaviour' into 'suicidal ideation and suicide attempt' with a frequency remaining 'uncommon' and to specify that such undesirable effects have been particularly reported in patients with a pre-existing history of depression or psychiatric illness. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>19</sup>.
- In the next PSUR, the MAH should provide a discussion on case(s) of hepatotoxicity.

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. **Brivaracetam - BRIVIACT (CAP) - PSUSA/00010447/202001**

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

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

Scope: Evaluation of a PSUSA procedure

### Background

Brivaracetam is an antiepileptic indicated, as Briviact, for the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy, as an adjunctive therapy.

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

### Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Briviact (brivaracetam) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on the possible interaction between brivaracetam and cannabidiol during co-administration. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>20</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.

#### 6.1.5. [Dolutegravir - TIVICAY \(CAP\); dolutegravir, lamivudine - DOVATO \(CAP\); dolutegravir, abacavir, lamivudine - TRIUMEQ \(CAP\) - PSUSA/00010075/202001](#)

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Applicant(s): ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

### Background

Dolutegravir is a human immunodeficiency virus (HIV) integrase inhibitor indicated, as Tivicay, for the treatment of HIV infection in adults, under certain conditions. It is also indicated in combination with lamivudine, a nucleoside reverse transcriptase inhibitor, as Dovato, for the treatment of HIV infection in adults, under certain conditions. In addition, it is indicated in combination with abacavir and lamivudine, nucleoside reverse transcriptase inhibitors, as Triumeq, for the treatment of HIV infection in adults, under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Tivicay, Dovato and Triumeq, centrally authorised medicines containing dolutegravir, dolutegravir/lamivudine, dolutegravir/abacavir/lamivudine respectively and issued a recommendation on their marketing authorisations.

### Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tivicay (dolutegravir), Dovato (dolutegravir/lamivudine) and Triumeq (dolutegravir/abacavir/lamivudine) in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to include new data regarding the transfer of dolutegravir into breast milk. 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 cutaneous vasculitis, erythema multiforme, Stevens-Johnson syndrome (SJS), thrombocytopenia, myocarditis, gastroschisis/omphalocele and of cases with midline defects of holoprosencephaly. The MAH should also further evaluate the signals of hyperglycaemia and diabetes mellitus.

The PRAC considered that the transfer of dolutegravir into breast milk is also relevant for inclusion in the product information of other medicinal product(s) containing dolutegravir. Therefore, the MAH for Juluca (dolutegravir/rilpivirine) should update the product information by submitting to EMA the relevant regulatory procedure.

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

#### 6.1.6. Ivacaftor - KALYDECO (CAP) - PSUSA/00009204/202001 (with RMP)

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

##### **Background**

Ivacaftor is a potentiator of the cystic fibrosis transmembrane conductance regulator (CFTR) protein indicated, as Kalydeco, for the treatment of adults, adolescents, and children with cystic fibrosis, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Kalydeco, a centrally authorised medicine containing ivacaftor 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 Kalydeco (ivacaftor) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a cumulative review of cases of acute pancreatitis and a plausible mechanism to explain this safety concern with a proposal for updating the product information, as appropriate.
- In the next PSUR, the MAH should continue to closely monitor cases of blood creatine phosphokinase (CPK) increased and cases related to hypoglycaemia. The MAH should also monitor cases of depression, providing data on dose and type of therapy, and cases

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<sup>21</sup> Update of SmPC section 4.6. The package leaflet for Tivicay (dolutegravir) is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

of withdrawal effects. The MAH should also provide a detailed discussion of the undesirable effects related to the use in children less than 6 years of age in order to better characterise the safety profile of this population.

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. Lenvatinib - KISPLYX (CAP); LENVIMA (CAP) - PSUSA/00010380/202002

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Applicant(s): Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

##### **Background**

Lenvatinib is a multikinase inhibitor indicated, as Kisplyx and Lenvima, for the treatment of adult patients with differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), hepatocellular carcinoma (HCC), and advanced renal cell carcinoma (RCC), under certain conditions.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Kisplyx and Lenvima (lenvatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include osteonecrosis of the jaw as an undesirable effect with a frequency 'uncommon' and a warning on this undesirable effect. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>22</sup>.
- In the next PSUR, the MAH should further monitor cases of radiation sensitisation and radiation recall symptoms and provide a causality assessment. In addition, the MAH should further monitor cases of severe cutaneous adverse reactions (SCARs).

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. Nilotinib - TASIGNA (CAP) - PSUSA/00002162/202001

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

##### **Background**

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<sup>22</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

Nilotinib is a protein kinase inhibitor indicated, as Tasigna, for the treatment of adult and paediatric patients with Philadelphia chromosome positive chronic myelogenous leukaemia (CML), under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tasigna, a centrally authorised medicine containing nilotinib 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 Tasigna (nilotinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on myopathy, including rhabdomyolysis caused by drug-drug interaction with statins and to amend the frequencies of the undesirable effects of cardiac failure, pneumonia, and renal failure to 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>23</sup>.
- In the next PSUR, the MAH should provide a cumulative review of cases of anaphylactic and anaphylactoid reactions. The MAH should also provide a detailed cumulative review of cases of pneumonia with a proposal for updating the product information, as appropriate. In addition, the MAH should provide detailed cumulative reviews of cases of renal failure in adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CMLCP) and of cases of periodontitis with respective discussions on the plausible causality mechanism together with a proposal for updating the product information, as appropriate.

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

#### **6.1.9. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/202002**

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Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### **Background**

Patisiran is a double-stranded small interfering ribonucleic acid (siRNA) indicated, as Onpattro, for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

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

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

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<sup>23</sup> Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Onpattro (patisiran) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the list of infusion-related reactions to add pruritis. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>24</sup>.
- In the next PSUR, the MAH should provide a detailed cumulative review of cases of hypersensitivity with a proposal for updating the product information, as appropriate. The MAH should provide a further review of cases of sudden death and sudden cardiac deaths including cases coded to these preferred terms, as well as cases not coded to these preferred terms but adjudicated as such. In addition, the MAH should provide a discussion on infusion-related reactions including falls.

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.

#### 6.1.10. **Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) - PREVENAR 13 (CAP) - PSUSA/00009263/202001**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

##### **Background**

Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) is a pneumococcal vaccine indicated, as Prevenar 13, for the active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants, children and adolescents from 6 weeks to 17 years of age. It is also indicated for the active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in adults  $\geq 18$  years of age and the elderly.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prevenar 13, a centrally authorised medicine containing pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) 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 Prevenar 13 (pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include anaphylaxis as an undesirable effect with a frequency 'not known' in the age group of children > 5 years

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<sup>24</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

and adults. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>25</sup>.

- In the next PSUR, the MAH should provide an updated review regarding literature reports of cases of vitamin A deficiency and the impact on vaccine effect.

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

#### 6.1.11. Sarilumab - KEVZARA (CAP) - PSUSA/00010609/202001

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

##### **Background**

Sarilumab is a immunoglobulin G1 (IgG1) indicated, as Kevzara, for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs), in combination with methotrexate (MTX). It can be indicated as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Kevzara, a centrally authorised medicine containing sarilumab 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 Kevzara (sarilumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include gastrointestinal perforation as an undesirable effect with a frequency 'rare' and to add that gastrointestinal perforation has been reported in association with Kevzara (sarilumab) in patients with and without diverticulitis. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>26</sup>.
- In the next PSUR, the MAH should provide a cumulative review of cases of leukopenia and agranulocytosis with a plausible causality mechanism and a proposal for updating the product information, as appropriate. The MAH should also provide a cumulative review of cases of diverticulitis with a plausible causality mechanism and a proposal for updating the product information, as appropriate.

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

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<sup>25</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

<sup>26</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

#### 6.1.12. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/202001

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Applicant: CO.DON AG, ATMP<sup>27</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

##### **Background**

Spheroids of human autologous matrix-associated chondrocytes are an ex vivo expanded human autologous chondrocytes and self-synthesised extracellular matrix indicated, as Spherox, for the repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm<sup>2</sup> in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Spherox, a centrally authorised medicine containing spheroids of human autologous matrix-associated chondrocytes 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 Spherox (spheroids of human autologous matrix-associated chondrocytes) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include arthritis infective and arthrofibrosis related to the medicinal product as undesirable effects with a frequency 'rare' and 'not known' respectively. In addition, pneumonia and pulmonary embolism should be added as surgery-related undesirable effects with a frequency 'not known' and 'uncommon' respectively. In addition, cellulitis and osteomyelitis should be added as medicinal product- and surgery related-undesirable effects with a frequency 'rare'. The frequencies of several undesirable effects are also amended. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>28</sup>.
- In the next PSUR, the MAH should provide a review of cases of closure of the epiphyseal growth plate.

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

#### 6.1.13. Voretigene neparvovec - LUXTURNA (CAP) - PSUSA/00010742/202001

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Applicant: Novartis Europharm Limited, ATMP<sup>29</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

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<sup>27</sup> Advanced therapy medicinal product

<sup>28</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CAT/CHMP for adoption of an opinion

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

Scope: Evaluation of a PSUSA procedure

### **Background**

Voretigene neparvovec is a gene transfer vector indicated, as Luxturna, for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65<sup>30</sup> mutations and who have sufficient viable retinal cells.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Luxturna, a centrally authorised medicine containing voretigene neparvovec 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 Luxturna (voretigene neparvovec) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include vitreous opacities as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>31</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.

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

### **6.2.1. Abacavir - ZIAGEN (CAP); NAP - PSUSA/00000010/201912**

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Applicant(s): ViiV Healthcare B.V. (Ziagen), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

### **Background**

Abacavir is a nucleoside reverse transcriptase inhibitor indicated for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children, in antiretroviral combination therapy.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of abacavir-containing medicinal products in the approved indication(s) remains unchanged.

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<sup>30</sup> Retinal pigment epithelium 65 (isomerase)

<sup>31</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CAT/CHMP for adoption of an opinion

- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should present a detailed review of cases of abacavir related-hypersensitivity reaction.

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

#### 6.2.2. Abacavir, lamivudine - KIVEXA (CAP); NAP - PSUSA/00000011/201912

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Applicant(s): ViiV Healthcare B.V. (Kivexa), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

##### **Background**

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors indicated in antiretroviral combination therapy for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing at least 25 kg.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of abacavir/lamivudine-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should present a detailed review of cases of abacavir related-hypersensitivity reaction.

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

#### 6.2.3. Abacavir, lamivudine, zidovudine - TRIZIVIR (CAP); NAP - PSUSA/00003144/201912

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Applicant(s): ViiV Healthcare B.V. (Trizivir), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

##### **Background**

Abacavir, lamivudine and zidovudine are nucleoside reverse transcriptase inhibitors indicated for the treatment of human immunodeficiency virus (HIV) infection in adults, under certain conditions.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of abacavir/lamivudine/zidovudine-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should present a detailed review of cases of abacavir related-hypersensitivity reaction.

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

#### **6.2.4. Pregabalin - LYRICA (CAP); PREGABALIN PFIZER (CAP); NAP - PSUSA/00002511/202001**

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Applicant(s): Upjohn EESV (Lyrica, Pregabalin Pfizer), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

#### **Background**

Pregabalin is an anti-epileptic indicated for the treatment of adults with partial seizures with or without secondary generalisation, as adjunctive therapy.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of pregabalin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include respiratory depression as an undesirable effect with a frequency 'not known' and to add a warning on respiratory depression related to pregabalin use. As patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system (CNS) depressants and elderly may be at higher risk of experiencing this severe adverse reaction, dose adjustment may be necessary. Therefore, the current terms of the marketing authorisations should be varied<sup>32</sup>.

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<sup>32</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

- The MAH for Lyrica/Pregabalin Pfizer (pregabalin) should submit to EMA, within 120 days, a detailed review of cases reporting suicidal action/behaviour/ideation.
- In the next PSUR, the MAHs should provide a further review of cases of abuse and dependence with a proposal for updating the product information, as appropriate. The MAHs should also provide a discussion on the usefulness of the targeted questionnaire (TQ) on abuse compared to a standard TQ. In addition, the MAHs should provide a further cumulative review of cases of pregnancy outcomes and congenital malformations. Finally, the MAHs should provide a detailed cumulative review of cases of Parkinson-like events with a proposal for updating the product information, as appropriate.

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

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

See also Annex I 16.3.

#### **6.3.1. Bendamustine hydrochloride (NAP) - PSUSA/00003162/202001**

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

##### **Background**

Bendamustine hydrochloride is an alkylating anti-tumour agent indicated for the first-line treatment of chronic lymphocytic leukaemia, indolent non-Hodgkin's lymphomas and front-line treatment of multiple myeloma under certain conditions.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of bendamustine hydrochloride-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on progressive multifocal encephalopathy (PML) following the use of bendamustine mainly in combination with rituximab or obinutuzumab. In addition, a warning on non-melanoma skin cancer should be also added. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>33</sup>.

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<sup>33</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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. Codeine camphosulphonate, sodium benzoate (NAP); codeine camphosulphonate, sulfogaiacol, grindelia<sup>34</sup> (NAP) - PSUSA/00010542/201912

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Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

#### Background

Codeine camphosulphonate is an opioid analgesic and sodium benzoate is an expectorant indicated, in combination, for the symptomatic treatment of irritative non-productive coughs in adults, while syrup can be used in children over 12 years. Codeine camphosulphonate is also indicated in combination with sulfogaiacol, an expectorant, and grindelia, an antitussive, for the symptomatic treatment of irritative non-productive coughs in adults, while syrup can be used in children over 12 years.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing codeine camphosulphonate/sodium benzoate and codeine camphosulphonate/sulfogaiacol/grindelia respectively and issued a recommendation on their marketing authorisations.

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of codeine camphosulphonate/sodium benzoate- and codeine camphosulphonate/sulfogaiacol/grindelia-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the potential risk of dependence, abuse and misuse due to codeine. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>35</sup>.
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of codeine exposure during pregnancy and of cases of medication errors with a proposal for updating the product information, as appropriate.

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

### 6.3.3. Iopamidol (NAP) - PSUSA/00001771/201912

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Applicant(s): various

PRAC Lead: Ronan Grimes

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<sup>34</sup> Soft extract

<sup>35</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Scope: Evaluation of a PSUSA procedure

### **Background**

Iopamidol is an iodinated contrast agent indicated for contrast enhancement in diagnostic procedures, such as excretory urography, angiography, computed tomography and myelography, for the solution for injection, and for diagnostic procedures of the digestive tract either by oral or rectal route (enema), for the oral/rectal solution formulations.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of iopamidol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include hemiplegia, Kounis syndrome, and acute generalised exanthematous pustulosis (AGEP) as undesirable effects with a frequency 'not known'. In addition, a warning on severe cutaneous adverse reactions (SCARs) should be added. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>36</sup>.

The PRAC considered that the risks of contrast-induced encephalopathy, drug reaction with eosinophilia and systemic symptoms (DRESS), and persistence of iopamidol in the foetus/neonate secondary to transplacental passage of non-ionic, iodinated contrast media need to be further assessed. Further consideration is to be given at CMDh.

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

#### **6.3.4. Levonorgestrel, ethinylestradiol; ethinylestradiol<sup>37</sup> (NAP) - PSUSA/00010442/202001**

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Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

### **Background**

Levonorgestrel is a synthetic progestogen and ethinylestradiol is a synthetic oestrogen indicated, as a combination pack of levonorgestrel/ethinylestradiol and ethinylestradiol tablets, as an oral contraceptive.

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

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<sup>36</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>37</sup> Combination pack only

### Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of levonorgestrel/ethinylestradiol and ethinylestradiol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a revised warning and a revised contraindication regarding co-administration with direct-acting antivirals (DAA). In addition, a warning on angioedema should be added. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>38</sup>.
- In the next PSUR, the MAH(s) should closely monitor the safety concerns and signals of meningioma and focal nodular hyperplasia. The MAH(s) should also provide a cumulative review of cases of off-label use and medication errors.

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

#### 6.3.5. Phenylephrine<sup>39</sup> (NAP) - PSUSA/00010402/202001

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Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

### Background

Phenylephrine is a direct-acting sympathomimetic amine indicated in ophthalmic use for the treatment of conjunctival irritation for diagnostic and/or therapeutic and preoperative purposes depending on the strength of the formulation used.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing phenylephrine 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 phenylephrine<sup>40</sup>-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of medicinal product(s) containing 10% phenylephrine (ophthalmic formulation) should be updated to include information not recommending the use in children aged 12 to 18 years and to clarify the age specification of the contraindication in children below 12 years. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>41</sup>.

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<sup>38</sup> Update of SmPC sections 4.3, 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>39</sup> Ophthalmic formulation(s) only

<sup>40</sup> Ophthalmic formulation(s) only

<sup>41</sup> Update of SmPC sections 4.2, 4.3 and 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- In the next PSUR, the MAH, Antibiotic-Razgrad AD, should include cardiovascular reactions as an important identified risk and necrotising enterocolitis as an important potential risk. The MAHs, Europhta Laboratories and Antibiotic-Razgrad AD, should provide a discussion of data related to special populations, off-label use, overdose, abuse or misuse.

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

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

See Annex I 16.4.

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

### 6.5.1. Vismodegib - ERIVEDGE (CAP) - EMEA/H/C/002602/II/0046

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Submission of an update of the educational materials as part of the pregnancy prevention programme in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010140/201901) finalised in September 2019. Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 14.0) are updated accordingly. Furthermore, section 4.4 of the SmPC is updated to remove the warning on cutaneous squamous cell carcinoma. Finally, the MAH took the opportunity to update the package leaflet to implement the statement on 'sodium' content in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

#### Background

Vismodegib is an orally available small-molecule inhibitor of the Hedgehog pathway. It is indicated, as Erivedge, for the treatment of adult patients with symptomatic metastatic basal cell carcinoma and for the treatment of adult patients with locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the PRAC requested the MAH to submit a variation to update the educational materials as part of the pregnancy prevention programme. For background information, see [PRAC minutes September 2019](#) and [PRAC minutes June 2020](#). The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

#### Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed on the content of the healthcare professional (HCP) reminder card, replacing the previous HCP brochure. The PRAC agreed that the HCP brochure did not provide additional information to enhance the understanding and awareness of the risk of teratogenicity and necessary treatment precautions beyond the information provided in the product information. In

addition, the PRAC agreed with keeping the patient brochure and concluded that the patient alert card was not necessary any longer as it is not considered to further contribute to risk minimisation over that provided in the patient brochure and the package leaflet. Furthermore, the PRAC further confirmed the removal of the warning on cutaneous squamous cell carcinoma in the product information<sup>42</sup> as agreed in June 2020.

## 6.6. Expedited summary safety reviews<sup>43</sup>

See also Annex I 16.6.

### 6.6.1. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/MEA 017.1

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Fourth expedited monthly summary safety report for remdesivir for August 2020 including spontaneously reported data and data from compassionate use and expanded access programmes for the duration of the coronavirus disease (COVID-19) pandemic

#### Background

Remdesivir is an antiviral medicine indicated, as Veklury, for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents from 12 years of age and weighing at least 40 kilograms with pneumonia requiring supplemental oxygen.

The PRAC assessed the fourth expedited summary safety report for Veklury (remdesivir) for the safety monitoring of remdesivir.

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

- The PRAC agreed that the data presented in the summary safety report was consistent with the known safety profile of remdesivir, and no new signal was identified.
- The MAH should provide, in the next pandemic report, or in the first PSUR, information regarding the follow-up information of reported cases as well as follow-up information for cases reported with a fatal outcome, for which little information was available in the initial notification.

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

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>44</sup>

See also Annex I 17.1.

#### 7.1.1. Hydroxyethyl starch (HES) (NAP) - EMEA/H/N/PSA/J/0056

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Applicant(s): Fresenius Kabi (Volulyte, Voluven), B. Braun Melsungen AG (Tetraspan,

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<sup>42</sup> Update of SmPC section 4.4 and Annex II-D. The package leaflet is updated accordingly

<sup>43</sup> Requirement to the compassionate use opinion to submit expedited summary safety reports for review accompanied by a summary of remdesivir distribution, in addition to the 6-monthly or annual PSURs falling within the pandemic period

<sup>44</sup> In accordance with Article 107n of Directive 2001/83/EC

Venofundin)

PRAC Rapporteur: Adrien Inoubli

Scope: Amendment to a joint protocol previously agreed in June 2019 for a retrospective, multinational, drug utilisation study (DUS) to assess the non-adherence of physicians in hydroxyethyl starch (HES) accredited hospitals to the approved European product information regarding indication for use, contraindications and posology (dosage) for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures, as required in the outcome of the referral procedure under Article 107i of Directive 2001/83/EC for HES completed in 2018 (EMA/H/A-107i/1457)

## Background

Hydroxyethyl starch (HES) containing products derive from potato or corn with different molecular weights and substitution ratios (e.g. 200/0.5; 130/0.4). HES is approved for intravenous use for infusion and is indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

Further to the conclusions of the referral procedures under Article 31 of Directive 2001/83/EC ([EMA/H/A-31/1348](#)) and Article 107i of Directive 2001/83/EC ([EMA/H/A-107i/1376](#)) in 2013 for HES-containing medicines as well as a further referral procedure under Article 107i of Directive 2001/83/EC ([EMA/H/A-107i/1457](#)) concluded in 2018, MAHs were required as a condition of the marketing authorisations ([Annex IV](#)) to implement additional risk minimisation measures.

The MAHs Fresenius Kabi Deutschland GmbH and B. Braun Melsungen AG submitted to the EMA a protocol for a joint study entitled: 'a retrospective, multinational, drug utilisation study (DUS) to investigate the routine use of HES-containing infusion solutions in HES-accredited European (EU) hospitals after implementation of a set of risk minimisation measures' for review by the PRAC. For further information, see [PRAC minutes January 2019](#) and [PRAC minutes June 2019](#). The amended draft protocol for a joint non-interventional (PASS) version 3.0 was presented for review by the PRAC.

## Endorsement/Refusal of the protocol

- Having considered the amended protocol version 3.0 in accordance with Article 107o of Directive 2001/83/EC, the PRAC objected to the draft protocol as the Committee considered that the design of the study did not fulfil the study objectives at this stage.
- The PRAC considered that some clarifications and complementary information are needed before drawing final conclusions on the amended protocol. The PRAC also recommended that the MAHs take all the necessary measures to avoid further delay in the data collection.
- The MAHs should submit a revised PASS protocol within 30 days to the EMA. A 30 day-assessment timetable will be followed.

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>45</sup>

See also Annex I 17.2.

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<sup>45</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

### 7.2.1. Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/MEA 007

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Applicant: GW Pharma (International) B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Protocol for study GWEP19022 (listed as a category 3 study in the RMP): a long-term safety study to assess the potential for chronic liver injury in patients treated with Epidyolex (cannabidiol oral solution)

#### **Background**

Cannabidiol is an anticonvulsant indicated, as Epidyolex a centrally authorised product, for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.

As part of the RMP for Epidyolex (cannabidiol), the MAH was required to conduct a category 3 post-marketing cohort study to evaluate the long term safety profile of Epidyolex (cannabidiol) and further characterise the safety concerns of Epidyolex (cannabidiol) when used under conditions of routine clinical care. The MAH submitted a protocol dated 15 June 2020 for study GWEP19022: a long-term safety study to assess the potential for chronic liver injury in participants treated with Epidyolex (cannabidiol) oral solution which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

#### **Summary of advice**

- Based on the review of the protocol and the assessment from the Rapporteur, the PRAC agreed that the study protocol was not satisfactory as the proposed study is (low) interventional falling under the scope of Directive 2001/20/EC.
- Acknowledging the challenges to the requested observational study, aiming at addressing a total of 12 safety concerns, the PRAC considered that the study protocol for Epidyolex (cannabidiol) as a (low) interventional study could be acceptable provided that an updated protocol is submitted to EMA within 60 days to consider conducting the study also in the EU (or if not deemed feasible to clarify extrapolation of the US data to a different EU population) and the inclusion of other endpoints particularly related to the evaluation of cannabidiol consequences on neurological development and behaviour. Moreover, the MAH should provide the study limitations, the description of the study sample size, the basis for recruitment and the description of the study variables.

### 7.2.2. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 002.2

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Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002.1 [protocol for study PUMA-NER-6202: a randomised study to characterise the incidence and severity of diarrhoea in patients with early stage epidermal growth factor receptor 2 + (HER2+) breast cancer treated with neratinib and intensive loperamide prophylaxis versus neratinib and intensive loperamide prophylaxis plus a bile acid sequestrant in the first month of treatment [final study results expected in December 2021]] as per the request for supplementary information (RSI) adopted in March 2020

## Background

Neratinib is an irreversible pan-erythroblastic leukaemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (TKI) indicated, as Nerlynx a centrally authorised product, for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

As part of the RMP of Nerlynx (neratinib), the MAH is requested to conduct a randomised study to characterise the incidence and severity of diarrhoea in patients with early stage HER2+ breast cancer treated with neratinib. The MAH was requested to submit a revised protocol (version 2.0 dated June 2020) for study PUMA-NER-6202 for the evaluation of the risk of diarrhoea which was assessed by the Rapporteur. The PRAC is requested to provide advice to CHMP on the protocol submitted by the MAH. For further background, see [PRAC minutes July 2019](#) and [PRAC minutes March 2020](#).

## Summary of advice

- Based on the review of PASS protocol version 2.0 dated June 2020 and the assessment from the Rapporteur, the MAH should submit to EMA, within 60 days, a revised protocol investigating both colesevelam and dose escalation of neratinib versus loperamide prophylaxis. In addition, the MAH should provide a rationale to choose one of the dose escalation schemes or alternatively both dose escalation schemes should be investigated. Moreover, the MAH should provide clarifications and motivations over the choice for the primary analysis when considering missing data, confirmation that adverse events of special interests (AESIs) will be collected and a discussion on the possibility of adding a quality of life (QoL) questionnaire dedicated to gastro-intestinal symptoms. Finally, the MAH is requested to collect descriptive and supportive data showing that the prevention of premature discontinuation by the prophylactic method does not affect the efficacy.

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

None

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

See also Annex I 17.4.

#### 7.4.1. Rasagiline - AZILECT (CAP) - EMEA/H/C/000574/WS1749/0084; RASAGILINE RATIOPHARM (CAP) - EMEA/H/C/003957/WS1749/0016

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Applicant: Teva B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from 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

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

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

melanoma associated with the use of rasagiline mesylate in patients with Parkinson's disease

## **Background**

Rasagiline is an irreversible monoamine oxidase B (MAO-B) selective inhibitor indicated, as Azilect and Rasagiline ratiopharm centrally authorised medicines, in adults for the treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations.

As stated in the RMP of Azilect and Rasagiline ratiopharm (rasagiline), the MAH conducted a non-imposed non-interventional study TV1030-CNS-50024: a non-interventional retrospective cohort study to assess the potential risk of melanoma associated with the use of rasagiline in patients with PD. The Rapporteur assessed the MAH's final study report together with the MAH's responses to the requests for supplementary information (RSI). For further background, see [PRAC minutes February 2020](#) and [PRAC minutes July 2020](#).

## **Summary of advice**

- Based on the available data, the MAH's responses to the second RSI including a proposal for updating the product information and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report could be recommended for approval including some adjustments to the proposed product information to amend<sup>48</sup> the information on the risk of melanoma associated with the use of rasagiline.

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

See Annex I 17.5.

## **7.6. Others**

See Annex I 17.6.

## **7.7. New Scientific Advice**

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

## **7.8. Ongoing Scientific Advice**

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

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

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

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<sup>48</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly

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

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

See Annex I 18.1.

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

See Annex I 18.2.

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

See also Annex I 18.3.

#### **8.3.1. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/R/0033 (with RMP)**

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

#### **Background**

Susoctocog alfa is a recombinant, B-domain deleted, porcine sequence factor VIII indicated, as Obizur, for the treatment of bleeding episodes in adult patients with acquired haemophilia caused by antibodies to factor VIII.

Obizur, a centrally authorised medicine containing susoctocog alfa, was authorised in 2015.

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

#### **Summary of advice**

- Based on the review of the available pharmacovigilance data for Obizur (susoctocog alfa) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds that include a limited post-marketing experience and the need to take into account the future results of the EU-PASS<sup>52</sup> and academia recommendation<sup>53</sup>.

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<sup>52</sup> Study 241501: a prospective, non-interventional study to evaluate the safety and efficacy of Obizur in real life practice (EU)

<sup>53</sup> Tiede et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020; Vol 105 no.7

## **9. Product related pharmacovigilance inspections**

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

None

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

None

### **9.3. Others**

None

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

#### **11.1.1. Bupropion (NAP) - NL/H/xxxx/WS/397**

Applicant(s): GSK R&D (Wellbutrin SR/Wellbutrin XR/Elontril, Zyban/Zyntabac)

PRAC Lead: Liana Gross-Martirosyan

Scope: PRAC consultation on a national worksharing variation assessing a cumulative review of serotonin syndrome from clinical trials, post-marketing sources and literature as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00000461/201812) concluded in September 2019, on request of the Netherlands

## Background

Bupropion is an anti-depressant indicated for the treatment of depression and other conditions.

In the context of the evaluation of a national worksharing variation assessing a cumulative review of serotonin syndrome from clinical trials, post-marketing sources and literature, following the conclusion of the last PSUSA procedure in September 2019, the Netherlands, as reference Member State (RMS) and lead MS (LMS) requested PRAC advice on its assessment. For further background, see [PRAC minutes September 2019](#).

## Summary of advice

- Based on the review of the available information, the PRAC supported the RMS's assessment and agreed that there is sufficient evidence to support a causal association between administration of bupropion and serotonin syndrome. Therefore, the PRAC supported the proposed amendment of the product information.

### 11.1.2. Oxaliplatin (NAP) - ES/H/0609/II/052/G

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Applicant(s): Pfizer (Oxaliplatin Hospira 5 mg/mL)

PRAC Lead: Eva Segovia

Scope: PRAC consultation on a national grouped type II variation to add a warning on immunosuppressant effects/increased susceptibility to infections associated with vaccines and to include 'focal nodular hyperplasia' as an adverse drug reaction (ADR) to the product information, on request of Spain

## Background

Oxaliplatin is a third-generation platinum agent indicated for the treatment of colon cancer after complete resection of primary tumour and for the treatment of metastatic colorectal cancer.

In the context of the evaluation of a type II variation procedure to add a warning on immunosuppressant effects/increased susceptibility to infections associated with vaccines and to include 'focal nodular hyperplasia' as an adverse drug reaction, Spain requested PRAC advice on its assessment.

## Summary of advice

- Based on the review of the available information, the PRAC supported the assessment conducted by Spain and agreed that there was sufficient evidence to update the product information concerning the interaction with live or live attenuated vaccines, and regarding the undesirable effect focal nodular hyperplasia.

## 11.2. Other requests

### 11.2.1. Levonorgestrel<sup>56</sup> (NAP) - DE/H/PSUFU/00001856/201905

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Applicant(s): Bayer (Mirena, Jaydess/Flere/Luadei/Skyla, Kyleena); Gedeon Richter (Levosert)

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<sup>56</sup> Levonorgestrel intrauterine device (LNG-IUD)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a PSUR follow-up (PSU FU) procedure on a review of cases reporting meningioma together with a causality assessment, biological plausibility and literature analysis, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00001856/201905) concluded in January 2020, on request of Germany

### **Background**

Levonorgestrel (LNG) is a second-generation progestin (synthetic progesterone) indicated for hormonal contraception, for the treatment of heavy menstrual bleeding and in several EU countries for idiopathic menorrhagia and protection from endometrial hyperplasia during oestrogen replacement therapy.

In the context of the evaluation of a PSUR follow-up (PSU FU) procedure on a review of cases reporting meningioma, as requested in the assessment of the last PSUSA procedure, Germany as the lead Member State (LMS) requested PRAC advice on its assessment. For further background, refer to [PRAC minutes January 2020](#).

### **Summary of advice**

- Based on the review of the available information, the PRAC supported the PRAC lead's assessment and agreed that meningioma should be included as an important potential risk in the summary of safety concerns of upcoming PSURs covering levonorgestrel-containing intrauterine devices (IUDs). The PRAC also supported that the LMS requests further information from the MAH(s), including comments on a proposal for updating the product information and a proposal for a direct healthcare professional communication (DHPC). The PRAC also advised that further consideration on the applicability of the regulatory actions to levonorgestrel-releasing subdermal implant and oral levonorgestrel-only containing contraceptives should be given at a later stage.

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

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

None

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

None

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

#### **12.3.1. EMA working parties – reactivation**

PRAC lead: Sabine Straus

Early 2020, the EMA Management Board (MB) adopted a set of high-level principles and proposals directing the future design and operations of EMA working parties. The EMA Secretariat initiated the implementation of the project in order to translate the adopted proposals into a new operating model for the range of working parties included in the scope

of the review. The PRAC discussed and agreed some proposals for reactivating the EMA working parties, some of which had been on hold during the EMA's [Brexit preparedness business continuity plan \(BCP\)](#). In line with the EMA [Regulatory science strategy to 2025](#), the EMA is aiming to increase capability and redesign the operations of relevant working parties to ensure wider knowledge exchange.

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

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

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

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

None

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

### **12.6.1. Coronavirus (COVID-19) pandemic - multicentre observational study on use of steroids in COVID-19 patients**

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PRAC lead: Antoine Pariente

The EMA secretariat together with the investigators updated the PRAC on the progress of the project for [real-world monitoring of treatments for COVID-19](#). This project includes the identification of large national cohorts of COVID-19 patients and appropriate comparator groups, the development of a study protocol template for multinational studies as well as the establishment of a collaborative framework for researchers. This study will describe the utilisation of steroids following diagnosis of COVID-19 patients across different countries and estimate 30- and 90 -day mortality rates and other adverse outcomes of interest.

### **12.6.2. Coronavirus (COVID-19) pandemic - Covid-19 infection and medicines in pregnancy (CONSIGN) – project outline**

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As one of the EMA initiatives for [real-world monitoring of treatments for COVID-19](#), the EMA secretariat together with the investigators updated the PRAC on the progress of the CONSIGN project ('COVID-19 infectiOn aNd medicineS In preGNancy'). This project will collect data on the impact of COVID-19 in pregnancy in order to guide decision-making about vaccine indications, vaccination policies and treatment options for COVID-19 in pregnant women. CONSIGN will analyse existing data sources (e.g. electronic health records, hospital data) and cohorts of pregnant women to provide information on the effect of infection and its treatments in different trimesters of pregnancy and on neonates.

## **12.7. PRAC work plan**

### **12.7.1. PRAC work plan 2020 – mid-year report**

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PRAC lead: Sabine Straus, Martin Huber

The EMA secretariat presented to PRAC an overview of the status of the deliverables described in the PRAC's [work plan 2020](#). The PRAC will initiate its work plan for 2021 taking into account the activities completed, progress made, priorities identified at the level of the Committee, EMA, Heads of Medicines Agencies (HMA) and EU network as well as the EMA business continuity plan (BCP) and the current context of COVID-19.

## **12.8. Planning and reporting**

### **12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q2 2020 and predictions**

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

## **12.9. Pharmacovigilance 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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PRAC lead: Menno van der Elst, Maia Uusküla

None

### **12.10.3. PSURs repository**

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None

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

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The PRAC endorsed the draft revised EURD list, version September 2020, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of September 2020, the updated EURD list was adopted by the CHMP and CMDh at their September 2020 meetings and published on the EMA website on 23/09/2020, see:

[Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list>List of Union reference dates and frequency of submission of periodic safety update reports \(PSURs\)](#)

### **12.11. Signal management**

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

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PRAC lead: Menno van der Elst

The EMA secretariat presented to the PRAC a summary of the activities in preparation for the COVID-19 safety monitoring, stemming from the SMART Methods work of the working group.

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

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

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None

#### **12.12.2. Additional monitoring**

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None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 30/09/2020, 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

### **12.16.2. Pharmacovigilance referrals roadmap – temporary measures**

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PRAC lead: Jean-Michel Dogné, Martin Huber, Adrien Inoubli, Ulla Wändel Liminga

In line with the [work plan 2020](#), the EMA secretariat presented to PRAC the results of an analysis of temporary measures used within the framework of pharmacovigilance referral procedures between July 2012 and December 2019. PRAC members were invited to send comments on the draft temporary measures module for the roadmap on pharmacovigilance referrals by 17 September 2020.

Post-meeting note: On 01 October 2020, PRAC adopted the final report on temporary measures module 1 for the roadmap on pharmacovigilance referrals.

## **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. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – risk minimisation effectiveness evaluation: update to assessment report template

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PRAC lead: Antoine Pariente

The PRAC interest group Impact and the EMA secretariat provided an update to the PRAC on the proposed updated templates of several post-authorisation assessment reports to include an 'impact section', which had previously been developed and aligned with the current revision of the GVP module XVI - Risk minimisation measures: selection of tools and effectiveness indicators. Following discussion, the PRAC requested a revised proposal for prioritising impact research topics for selected procedures, replacing the current monthly notification process. Further discussion is scheduled in October/November 2020.

## 13. Any other business

None

## 14. Annex I – Signals assessment and prioritisation<sup>57</sup>

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

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables<sup>58</sup>.

#### 14.1.1. Anastrozole (NAP)

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Applicant(s): various

PRAC Rapporteur: Zane Neikena

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<sup>57</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>58</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

Scope: Signal of depressed mood disorders

EPITT 19592 – New signal

Lead Member State(s): LV

#### **14.1.2. Filgrastim – ACCOFIL (CAP), FILGRASTIM HEXAL (CAP), GRASTOFIL (CAP), NIVESTIM (CAP), RATIOGRASTIM (CAP), TEVAGRASTIM (CAP), ZARZIO (CAP); NAP**

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

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of immune reconstitution inflammatory syndrome (IRIS)

EPITT 19587 – New signal

Lead Member State(s): FI, NL

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

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of systemic scleroderma

EPITT 19591 – New signal

Lead Member State(s): NL

#### **14.1.4. Tofacitinib – XELJANZ (CAP)**

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Applicant(s): Pfizer Europe MA EEIG (Xeljanz)

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of psychiatric disorders

EPITT 19585 – New signal

Lead Member State(s): NL

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

#### **14.2.1. Ceftriaxone (NAP)**

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Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of hepatitis

EPITT 19603 – New signal

Lead Member State(s): LV

#### 14.2.2. [Sacubitril, valsartan – ENTRESTO \(CAP\); NEPARVIS \(CAP\)](#)

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Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of psychosis and psychotic disorders

EPITT 19600 – New signal

Lead Member State(s): DK

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

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

None

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

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

##### 15.2.1. [Agomelatine - THYMANAX \(CAP\) - EMEA/H/C/000916/WS1849/0045; VALDOXAN \(CAP\) - EMEA/H/C/000915/WS1849/0047](#)

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Applicant(s): Les Laboratoires Servier (Valdoxan), Servier (Ireland) Industries Ltd. (thymanax)

PRAC Rapporteur: Pernille Harg

Scope: Submission of an updated RMP (version 23.1) in order to revise the list of safety concerns, important identified and potential risks in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the completed studies have been deleted and, as agreed in the conclusions of LEG 031 adopted in January 2019, the frequency of the educational material distribution is updated to once yearly

##### 15.2.2. [Clofarabine - EVOLTRA \(CAP\) - EMEA/H/C/000613/II/0069](#)

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of an updated RMP (version 9.0) to reflect amended information regarding the Evoltra (clofarabine) European registry programme and to remove all safety concerns from the list of important identified and potential risks and missing information in line with revision 2 of GVP module V on 'Risk management systems'

##### 15.2.3. [Estrogens conjugated, bazedoxifene - DUAVIVE \(CAP\) - EMEA/H/C/002314/II/0024](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 3.0) in order to include amended study milestones and to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems' and revision 2.0.1 of the guidance on the format of RMP in the EU (template)

#### **15.2.4. Gefitinib - IRESSA (CAP) - EMEA/H/C/001016/II/0033**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 11.0) in order to amend the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and to implement changes agreed in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001518/201807) adopted in February 2019

#### **15.2.5. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0029/G**

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of the submission of an updated RMP (version 6.0) in order to: 1) update the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'; 2) reclassify the risk of gastrointestinal (GI) perforation as requested in the conclusions of the PSUR single assessment (PSUSA) (PSUSA/00010317/201809) concluded in April 2019

#### **15.2.6. Pramipexole - MIRAPEXIN (CAP) - EMEA/H/C/000134/WS1897/0096; SIFROL (CAP) - EMEA/H/C/000133/WS1897/0087**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 12.0) as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002491/201904) adopted in December 2019 in order to remove cardiac failure from the list of important identified risks and to amend the information on dopamine agonist withdrawal syndrome (DAWS) as an important identified risk

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

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

#### **15.3.1. Ambrisentan - VOLIBRIS (CAP) - EMEA/H/C/000839/X/0061/G**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Eva Segovia

Scope: Grouped applications consisting of: 1) extension application to introduce a new

strenght (2.5 mg film-coated tablet); 2) extension of indication to include paediatric use (8 to less than 18 years). The RMP (version 9.0) is updated accordingly

#### **15.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0039**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include in combination with bevacizumab the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy, based on the results of pivotal study YO40245 (IMbrave150): a phase 3, open-label, randomised study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic hepatocellular carcinoma, as well as data from arms A and F of the supportive Phase Ib study GO30140: an open-label, multicentre phase 1b study of the safety and efficacy of atezolizumab administered in combination with bevacizumab and/or other treatments in patients with solid tumours. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Tecentriq (atezolizumab) 1200 mg concentrate for solution for infusion SmPC are updated. The package leaflet and the RMP (version 13.0) are updated in accordance

#### **15.3.3. Avatrombopag - DOPTELET (CAP) - EMEA/H/C/004722/II/0004/G**

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Applicant: Dova Pharmaceuticals Ireland Limited

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 5.3 of the SmPC is updated with data from juvenile toxicity studies; 2) addition of a pack size of 30 tablets with subsequent updates of sections 6.5 and 8 of the SmPC. The package leaflet, labelling and the RMP (version 2.1) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

#### **15.3.4. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0018**

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Extension of indication to include treatment as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 2.3) are updated in accordance. The MAH took the opportunity to include some editorial changes throughout the product information

#### **15.3.5. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRIMBOW (CAP) - EMEA/H/C/004257/X/0008/G**

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (172 µg / 5 µg / 9 µg); 2) update of sections 4.1, 4.2, 4.4, 5.1 and 5.2 to extend the indication to the maintenance treatment in adult patients with asthma who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or who are already treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist plus a long-acting muscarinic antagonist. The RMP (version 6.1) is updated in accordance

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

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Amelia Cupelli

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

#### **15.3.7. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/II/0043**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Update of section 5.3 of the SmPC in order to update non-clinical information following the final results from the six-month transgenic rasH2 mouse carcinogenicity study (listed as a category 3 study). The RMP (version 5.0) is updated accordingly. The MAH took the opportunity to implement changes in the product information in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

#### **15.3.8. Brolucizumab - BEOVU (CAP) - EMEA/H/C/004913/II/0002**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation. The package leaflet and RMP (version 3.0) are updated accordingly

#### **15.3.9. Cholera vaccine, oral, live - VAXCHORA (CAP) - EMEA/H/C/003876/II/0003/G**

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Applicant: Emergent Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Grouped variations consisting of: 1) extension of indication for the active immunisation against disease caused by *Vibrio cholerae* serogroup O1, from the currently approved age range 'adults and children aged 6 years and older' to 'adults and children aged 2 years and older'. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 2.0) are updated in accordance; 2) update section 5.1 of the SmPC to include long-term immunogenicity data supporting Vaxchora (cholera vaccine, oral, live) effectiveness at generating a protective

immune response that persists for 2 years following vaccination; based on the final results from study PXVX-VC-200-006: a randomised, double-blind, placebo-controlled trial aimed to assess the safety and immunogenicity of Vaxchora in children 2 to <18 years of age. The MAH took the opportunity to include editorial changes in the SmPC and Annex II

#### 15.3.10. [Clopidogrel - ISCOVER \(CAP\) - EMEA/H/C/000175/WS1769/0140; PLAVIX \(CAP\) - EMEA/H/C/000174/WS1769/0138](#)

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include adult patients with high risk transient ischemic attack (TIA) (ABCD<sup>2</sup> score  $\geq 4$ ) or minor ischemic stroke (IS) (National Institutes of Health Stroke Scale (NIHSS)  $\leq 3$ ) within 24 hours of either the TIA or IS event. The new indication is based on the results of 1) study POINT: a double-blind, randomised, placebo-controlled phase 3 study on platelet-oriented inhibition in new TIA and minor IS; 2) study CHANCE: a double-blind, randomised, placebo-controlled phase 3 study comparing the effects of a 3-month clopidogrel regimen, combined with acetylsalicylic acid (ASA) during the first 21 days, versus ASA alone for the acute treatment of TIA or minor stroke. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly

#### 15.3.11. [Dapagliflozin - EDISTRIDE \(CAP\) - EMEA/H/C/004161/WS1737/0034; FORXIGA \(CAP\) - EMEA/H/C/002322/WS1737/0053](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to add a new indication for the treatment of symptomatic heart failure with reduced ejection fraction in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and labelling are updated in accordance. The RMP (version 18) is updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1). Finally, the MAH took the opportunity to introduce an editorial change in the product information

#### 15.3.12. [Darolutamide - NUBEQA \(CAP\) - EMEA/H/C/004790/II/0002](#)

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Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Update of section 5.1 of the SmPC in order to update efficacy information based on final overall survival (OS) results from study 17772 (ARAMIS) (listed as a post-authorisation efficacy study (PAES) in Annex II): a multinational, randomised, double-blind, placebo-controlled, phase 3 efficacy and safety study of darolutamide in men with high-risk non-metastatic castration-resistant prostate cancer. Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 1.1) are updated accordingly

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

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Tiphaine Vaillant

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

#### 15.3.14. [Defibrotide - DEFITELIO \(CAP\) - EMEA/H/C/002393/II/0048, Orphan](#)

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Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the SmPC section 5.1 based on the results of study DF VOD-2013-03-REG: a multicentre, multinational, prospective observational registry to collect safety and outcome data in patients diagnosed with severe hepatic veno-occlusive disease (VOD) following hematopoietic stem cell transplantation (HSCT) and treated with Defitelio (defibrotide) or supportive care (control group). The RMP (version 8.0) is updated accordingly. In addition, the MAH took the opportunity to introduce minor amendments throughout the product information and to bring it in line with the latest Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' on sodium content. Moreover, the RMP is updated in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010086/201910) adopted in May 2020 to update the list of safety concerns

#### 15.3.15. [Eftrenonacog alfa - ALPROLIX \(CAP\) - EMEA/H/C/004142/II/0029, Orphan](#)

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC to add information on previously untreated patients (PUPs) following the completion of study 998HB303: an open-label, multicentre evaluation of the safety and efficacy of recombinant coagulation factor IX Fc fusion protein (rFIXFc; BIIB029) in the prevention and treatment of bleeding in PUPs with severe haemophilia B (already assessed in procedure P46 006). The package leaflet and the RMP (version 12.1) are updated accordingly

#### 15.3.16. [Enzalutamide - XTANDI \(CAP\) - EMEA/H/C/002639/II/0049](#)

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.7, 4.8, 5.1, 5.2 and 6.6 of the SmPC in order to update efficacy and safety information based on final results from study MDV3100-14 (PROSPER) (listed as a post-authorisation efficacy study (PAES) in Annex II): a phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in patients with non-metastatic castration-resistant prostate cancer. The package leaflet, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 14.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet, to introduce

few editorial updates and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.17. Eravacycline - XERAVA (CAP) - EMEA/H/C/004237/X/0009

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Applicant: Tetrphase Pharmaceuticals Ireland Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to add a new strength of 100 mg for eravacycline powder for concentrate for solution for infusion. The RMP (version 3.0) is updated in accordance. Additionally, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

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

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

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

#### 15.3.19. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0110

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include the prevention of head and neck cancers causally related to certain oncogenic human papillomavirus types. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 23.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.20. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS1783/0077; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS1783/0081

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Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults with no epidermal growth factor receptor (EGFR) or anaplastic large-cell lymphoma kinase (ALK) positive tumour mutations for combination of Opdivo (nivolumab) and Yervoy (ipilimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. The

RMPs (version 17.0 for Opdivo (nivolumab), version 27.0 for Yervoy (ipilimumab)) are updated accordingly

#### 15.3.21. Iron - VELPHORO (CAP) - EMEA/H/C/002705/X/0020/G

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Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped application consisting of: 1) extension application to add a new pharmaceutical form with a new strength - powder for oral suspension 125 mg, 2) extension of indication to add the use of Velphoro (iron) for the control of serum phosphorus levels in paediatric patients 2 years of age and older with chronic kidney disease (CKD) stages 4-5 (defined by a glomerular filtration rate (GFR)  $<30$  mL/min/1.73 m<sup>2</sup>) or with CKD on dialysis, based on the results from study PA-CL-PED-01: an open-label, randomised, active-controlled, parallel group, multicentre, phase 3 study investigating the safety and efficacy of Velphoro (iron) and calcium acetate in paediatric and adolescent CKD patients with hyperphosphataemia. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The package leaflet, labelling and the RMP (version 7.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.22. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0086, Orphan

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to extend the indication of Kalydeco (ivacaftor) granules in the treatment of infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis who have one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.9) are updated in accordance

#### 15.3.23. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/X/0083/G, Orphan

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped variations consisting of: 1) extension application to add a new strength of 75 mg film-coated tablets of ivacaftor to enable administration to patients aged 6 to less than 11 years; 2) update of sections 4.1, 4.2 and 6.5 the SmPC for the 150 mg film-coated tablet presentations to extend the indication for use in children aged 6 to less than 11 years old in combination with tezacaftor/ivacaftor and to bring it in line with the new dosage form (75 mg film-coated tablets of ivacaftor). The package leaflet and the RMP (version 8.6) are updated in accordance. In addition, the MAH took the opportunity to implement minor updates throughout the product information

#### 15.3.24. Levetiracetam - KEPRA (CAP) - EMEA/H/C/000277/WS1664/0187

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Update of section 4.2 of the SmPC to recommend the same dosing for monotherapy and adjunctive therapy based on data from modelling and simulation project. The package leaflet and the RMP (version 9.1) are updated accordingly. The MAH took the opportunity to move Braille to another box section and to review and adapt the German product information in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.25. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/II/0016

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Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.0) are updated in accordance. Furthermore, the MAH took the opportunity to update the RMP in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and the outcome of the referral procedure for methotrexate-containing products under Article 31 of Directive 2001/83/EC (EMA/H/A-31/1463) finalised in July 2019

#### 15.3.26. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/II/0014, Orphan

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to change posology recommendations and add special warnings and precautions for use in the paediatric population following the occurrence of severe dose limiting toxicities (DLTs) based on findings in study CPKC412A2218 (currently on clinical hold): a phase 2, open-label, single arm study to evaluate the safety, efficacy, and pharmacokinetics of twice daily midostaurin (PKC412) combined with standard chemotherapy and as a single agent post-consolidation therapy in children with untreated FMS-like tyrosine kinase 3 (FLT3)-mutated acute myeloid leukaemia (AML). The package leaflet and the RMP (version 5.0) are updated accordingly. The MAH took the opportunity to introduce minor editorial changes in the product information and to bring it in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.27. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/II/0019, Orphan

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Extension of indication to include the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in

response (complete or partial) following completion of first-line platinum-based chemotherapy. As a consequence, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated in accordance. The RMP is also brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and includes updated due dates for category 3 studies. Finally, the MAH took the opportunity to introduce minor corrections throughout the product information

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

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Applicant: MendeliKABS Europe Limited

PRAC Rapporteur: Amelia Cupelli

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

#### **15.3.29. Nitisinone - ORFADIN (CAP) - EMEA/H/C/000555/II/0071**

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Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of adult patients with alkaptonuria (AKU). As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 10 of the SmPC are updated. The package leaflet and the RMP (version 5.2) are updated in accordance. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems'

#### **15.3.30. Oritavancin - ORBACTIV (CAP) - EMEA/H/C/003785/II/0030**

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from study 14-TMC-01 (listed as a category 3 study in the RMP): a surveillance study investigation, part of the global SENTRY antimicrobial surveillance programme platform, to monitor the activity of oritavancin against Gram-positive clinical isolates collected from U.S. and European medical centres (in fulfilment of MEA 003.4). The RMP (version 3.0) is updated accordingly

#### **15.3.31. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/X/0056**

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new route of administration (intramuscular use) for the 125 µg solution for injection. The RMP (version 5.1) is updated accordingly

#### **15.3.32. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/II/0007/G, Orphan**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of an update of sections 4.4, 4.8 and 5.1 of the SmPC

based on final results from: 1) study 1655-003 (listed as a category 3 study in the RMP): a long-term extension of a phase 2, open-label, dose-finding study; 2) study 165-302 (listed as a category 3 study in the RMP): a phase 3, randomised, double-blind, placebo-controlled, four-arm, discontinuation study to evaluate executive function in adults with phenylketonuria. The RMP (version 2.0) is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes in the product information

#### **15.3.33. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0090**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include in the currently approved treatment in adults of relapsed or refractory classical Hodgkin lymphoma (rrcHL) paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) following at least one prior therapy when ASCT is not a treatment option, based on the results of study KEYNOTE-204: a randomized, open-label, phase 3 trial evaluating pembrolizumab monotherapy versus brentuximab vedotin for the treatment of patients with rrcHL and supportive data from updated analysis of KEYNOTE-087 (pivotal study supporting the initial rrcHL indication): a phase 2 clinical trial of pembrolizumab in subjects with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL). 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 28.1) are updated accordingly

#### **15.3.34. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/II/0047**

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Applicant: Eisai GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension of indication to include adjunctive treatment in paediatric patients from 2 to 11 years of age in partial-onset (focal) seizures with or without secondary generalisation and primary generalised tonic-clonic seizures with idiopathic generalised epilepsy. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.3) are updated accordingly

#### **15.3.35. 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

15.3.36. [Rituximab - BLITZIMA \(CAP\) - EMEA/H/C/004723/WS1893/0034; RITEMVIA \(CAP\) - EMEA/H/C/004725/WS1893/0034; TRUXIMA \(CAP\) - EMEA/H/C/004112/WS1893/0037](#)

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Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final clinical study report (CSR) for study CT-P10 3.4: a phase 3, randomised, parallel-group, active-controlled, double-blind study to compare efficacy and safety between CT-P10 and Rituxan (rituximab) in patients with low tumour burden follicular lymphoma (LTBFL). The RMP (version 10.1) is updated accordingly

15.3.37. [Rituximab - MABTHERA \(CAP\) - EMEA/H/C/000165/II/0177](#)

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final clinical study report (CSR) for study WA29330 (PEMPHIX): a randomised, double-blind, double-dummy, active-comparator, multicentre study to evaluate the efficacy and safety of rituximab versus mycophenolate mofetil (MMF) in patients with pemphigus vulgaris in order to fulfil the post authorisation measure (PAM) in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' following 48 week safety follow up period of the study. The RMP (version 22.0) is updated accordingly

15.3.38. [Romiplostim - NPLATE \(CAP\) - EMEA/H/C/000942/II/0077](#)

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to add the use of romiplostim in adult patients who have had immune thrombocytopenia (ITP) for  $\leq 12$  months and who have had an insufficient response to corticosteroids or immunoglobulins. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 20.0) are updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.39. [Rucaparib - RUBRACA \(CAP\) - EMEA/H/C/004272/II/0020](#)

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Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update the information on the use of rucaparib in patients with hepatic impairment based on final results from Part I of study CO-338-078 (listed as a category 3 study in the RMP): a phase 1, open-label, parallel group study to determine the pharmacokinetics, safety and tolerability of rucaparib in patients with an advanced solid tumour and either moderate hepatic impairment or normal hepatic function. The package leaflet and the RMP (version 4.0) are updated accordingly. The MAH took the opportunity to introduce minor corrections in the SmPC, to update the list

of local representatives in the package leaflet, and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1).and in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

#### 15.3.40. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/X/0059

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension application to add a new strength of 300 mg (in 2 mL) solution for injection in pre-filled syringe and pre-filled pen. The RMP (version 7.0) is updated in accordance

#### 15.3.41. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/II/0076

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include adolescents and children older than 7 years to the existing indication of treatment of narcolepsy with cataplexy in adults. 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 and the RMP (version 9.0) are updated accordingly

#### 15.3.42. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0037

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 5.1 of the SmPC in order to update the description of the potential risk of emergence of drug resistance with tedizolid phosphate based on final results from study 'surveillance of tedizolid activity and resistance (STAR)' (listed as a category 3 study in the RMP); a surveillance study established in January 2014 to monitor tedizolid susceptibility activity and emergence of resistance across the US, 11 European Union countries, Russia and Turkey. The RMP (version 6.2) is updated accordingly

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

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) extension application to add a new strength of 7 mg film-coated tablet for use in paediatric patients from 10 years of age and older with relapsing remitting multiple sclerosis (MS); 2) extension of indication to include treatment of paediatric patients aged 10 years and older with relapsing remitting MS for Aubagio (teriflunomide) 14 mg tablet. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet, labelling and the RMP (version 6.0) are updated in accordance. The MAH also applied for an extension of the market protection of one additional year in line with the guidance on elements required to support significant clinical benefit in comparison with existing therapies of a new therapeutic indication

#### 15.3.44. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/X/0015/G, Orphan

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of: 1) extension application to add a new strength of 50/75 mg film-coated tablets of tezacaftor/ivacaftor to enable administration to patients aged 6 to less than 11 years; 2) update of sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.1 of the SmPC for the 100/150 mg film-coated tablet presentations to extend the indication for use in children aged 6 to less than 11 years old in combination with ivacaftor and to bring it in line with the new dosage form. The package leaflet and the RMP (version 2.1) are updated in accordance. In addition, the MAH took the opportunity to implement minor updates in the product information

#### 15.3.45. Thiotepa - TEPADINA (CAP) - EMEA/H/C/001046/X/0036

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Applicant: Adienne S.r.l.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (400 mg powder and solvent for solution for infusion). The RMP (version 14) is updated accordingly

#### 15.3.46. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/II/0049

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include, in co-administration with acetylsalicylic acid (ASA), the prevention of stroke in adult patients with acute ischaemic stroke or transient ischaemic attack (TIA), based on the final results of study D5134C00003 (THALES): a phase 3, international, multicentre, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of ticagrelor and ASA compared with ASA in the prevention of stroke and death in patients with acute ischaemic stroke or transient ischaemic attack. 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 13.0) are updated in accordance

#### 15.3.47. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0025

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from study A3921092 (listed as a category 3 study in the RMP): a long term, open-label extension study of tofacitinib for the treatment of adult patients with psoriatic arthritis (PsA). The RMP (version 11.1) is updated accordingly. The MAH took the opportunity to update the milestones for study A3921347: a prospective, non-interventional active surveillance study examining tofacitinib safety in ulcerative colitis (UC)

#### 15.3.48. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0004

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of active psoriatic arthritis in adult patients. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 2.0) are updated in accordance. The MAH took the opportunity to introduce minor updates to Annex II

#### 15.3.49. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0005

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of active ankylosing spondylitis in adult patient. 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 3.0) are updated in accordance. The MAH took the opportunity to introduce minor editorial changes throughout the SmPC and Annex II

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

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

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

##### 16.1.1. Adalimumab - AMGEVITA (CAP); HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP); HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP) - PSUSA/00010783/201912

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Applicant(s): Amgen Europe B.V. (Amgevita), Mylan S.A.S (Hulio), AbbVie Deutschland GmbH & Co. KG (Humira), Sandoz GmbH (Halimatoz, Hefiya, Hyrimoz), Fresenius Kabi Deutschland GmbH (Idacio), Samsung Bioepis NL B.V. (Imraldi)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.2. Albutrepenonacog alfa - IDELVION (CAP) - PSUSA/00010497/202001

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.3. Apalutamide - ERLEADA (CAP) - PSUSA/00010745/202001

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

#### 16.1.4. Asparaginase<sup>59</sup> - SPECTRILA (CAP) - PSUSA/00010445/202001

Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.1.5. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/202001

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

#### 16.1.6. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP); TRIMBOW (CAP); TRYDONIS (CAP) - PSUSA/00010617/202001

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

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.1.7. Birch bark extract<sup>60</sup> - EPISALVAN (CAP) - PSUSA/00010446/202001

Applicant: Amryt GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

#### 16.1.8. Botulinum toxin type A - NUCEIVA (CAP) - PSUSA/00010796/202001

Applicant: Evolus Pharma Limited

PRAC Rapporteur: Adam Przybylkowski

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<sup>59</sup> Centrally authorised product(s) only

<sup>60</sup> Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

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**16.1.9. Brexpiprazole - RXULTI (CAP) - PSUSA/00010698/202001**

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Michal Radik

Scope: Evaluation of a PSUSA procedure

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**16.1.10. Budesonide<sup>61</sup> - JORVEZA (CAP) - PSUSA/00010664/202001**

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Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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**16.1.11. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/202001**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

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**16.1.12. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/202001**

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Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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**16.1.13. Colistimethate sodium<sup>62</sup> - COLOBREATHE (CAP) - PSUSA/00009112/202002**

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Applicant: Teva B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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**16.1.14. Dapagliflozin, metformin - EBYMECT (CAP); XIGDUO (CAP) - PSUSA/00010294/202001**

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Applicant(s): AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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<sup>61</sup> Centrally authorised product(s) only

<sup>62</sup> Dry inhalation powder only

**16.1.15. Dasabuvir - EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - PSUSA/00010773/202001**

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Applicant(s): AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

**16.1.16. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - PSUSA/00010701/202002**

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Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

**16.1.17. Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/202001**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

**16.1.18. Elosulfase alfa - VIMIZIM (CAP) - PSUSA/00010218/202002**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

**16.1.19. Eptifibatide - INTEGRILIN (CAP) - PSUSA/00001246/202001**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

**16.1.20. Etanercept - BENEPALI (CAP); ENBREL (CAP); ERELZI (CAP) - PSUSA/00010795/202002**

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Applicant(s): Samsung Bioepis NL B.V. (Benepali), Pfizer Europe MA EEIG (Enbrel), Sandoz GmbH (Erelzi)

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

**16.1.21. Fampridine - FAMPYRA (CAP) - PSUSA/00001352/202001**

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

#### 16.1.22. Glucagon<sup>63</sup> - BAQSIMI (CAP) - PSUSA/00010826/202001

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.23. Glycerol phenylbutyrate - RAVICTI (CAP) - PSUSA/00010454/202001

Applicant: Immedica Pharma AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

#### 16.1.24. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/202001

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

#### 16.1.25. Hydrocortisone<sup>64</sup> - ALKINDI (CAP) - PSUSA/00010674/202002

Applicant: Diurnal Europe BV

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### 16.1.26. Inotersen - TEGSEDI (CAP) - PSUSA/00010697/202001

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.27. L-lysine hydrochloride, L-arginine hydrochloride - LYSAKARE (CAP) - PSUSA/00010786/202001

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### 16.1.28. Lixisenatide - LYXUMIA (CAP) - PSUSA/00010017/202001

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

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<sup>63</sup> Centrally authorised product(s) only

<sup>64</sup> Centrally authorised product(s) for adrenal insufficiency, paediatric use only

Scope: Evaluation of a PSUSA procedure

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**16.1.29. Lonoctocog alfa - AFSTYLA (CAP) - PSUSA/00010559/202001**

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Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

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**16.1.30. Macimorelin - MACIMORELIN AETERNA ZENTARIS (CAP) - PSUSA/00010746/202001**

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Applicant: Aeterna Zentaris GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

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**16.1.31. Mercaptamine<sup>65</sup> - CYSTADROPS (CAP) - PSUSA/00010574/202001**

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Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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**16.1.32. Metreleptin - MYALEPTA (CAP) - PSUSA/00010700/202001**

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Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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**16.1.33. Neratinib - NERLYNX (CAP) - PSUSA/00010712/202001**

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Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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**16.1.34. Omalizumab - XOLAIR (CAP) - PSUSA/00002214/201912**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

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**16.1.35. Phenylephrine, ketorolac - OMIDRIA (CAP) - PSUSA/00010419/202001**

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Applicant: Omeros Ireland Limited

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<sup>65</sup> Indicated for the treatment of corneal cystine crystal deposit

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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**16.1.36. Plerixafor - MOZOBIL (CAP) - PSUSA/00002451/201912**

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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**16.1.37. Romosozumab - EVENITY (CAP) - PSUSA/00010824/202001**

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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**16.1.38. Rufinamide - INOVELON (CAP) - PSUSA/00002671/202001**

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Applicant: Eisai GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

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**16.1.39. Silodosin - SILODYX (CAP); UROREC (CAP) - PSUSA/00002701/202001**

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Applicant(s): Recordati Ireland Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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**16.1.40. Smallpox vaccine (live, modified vaccinia Ankara virus) - IMVANEX (CAP) - PSUSA/00010119/202001**

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Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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**16.1.41. Sorafenib - NEXAVAR (CAP) - PSUSA/00002773/201912**

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Applicant: Bayer AG

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

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**16.1.42. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/202001**

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Applicant: Vanda Pharmaceuticals Germany GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**16.1.43. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/202002**

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

**16.1.44. Tipranavir - APTIVUS (CAP) - PSUSA/00002973/201912**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

**16.1.45. Tisagenlecleucel - KYMRIA (CAP) - PSUSA/00010702/202002**

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Applicant: Novartis Europharm Limited, ATMP<sup>66</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.46. Vismodegib - ERIVEDGE (CAP) - PSUSA/00010140/202001**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

**16.1.47. Zanamivir<sup>67</sup> - DECTOVA (CAP) - PSUSA/00010763/202001**

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

None

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<sup>66</sup> Advanced therapy medicinal product

<sup>67</sup> Centrally authorised product(s) only

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

#### **16.3.1. 5-fluorouracil<sup>68</sup> (NAP) - PSUSA/00010000/202001**

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### **16.3.2. Alitretinoin<sup>69</sup> (NAP) - PSUSA/00010710/202001**

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### **16.3.3. Dactylis glomerata L., Phleum pratense L., Anthoxanthum odoratum L., Lolium perenne L., Poa pratensis L.<sup>70 71</sup> (NAP) - PSUSA/00010465/201912**

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Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

#### **16.3.4. Amisulpride (NAP) - PSUSA/00000167/202001**

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Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

#### **16.3.5. Beta-alanine (NAP) - PSUSA/00010510/202001**

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Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

#### **16.3.6. Bismuth, lidocaine, zinc oxide (NAP); lidocaine, zinc oxide (NAP) - PSUSA/00010621/202001**

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Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

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<sup>68</sup> For topical formulation(s) only

<sup>69</sup> For oral use only

<sup>70</sup> Allergen for therapy

<sup>71</sup> Sublingual tablet(s) only

16.3.7. Calcium chloride, glucose, magnesium chloride hexahydrate, sodium chloride, sodium hydrogen carbonate (NAP) - PSUSA/00010375/201912

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.8. Celiprolol (NAP) - PSUSA/00000617/202001

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Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.9. Cyanocobalamin, diclofenac, pyridoxine, thiamine (NAP) - PSUSA/00001041/202001

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Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.10. Human  $\alpha_1$ -proteinase inhibitor<sup>72</sup> (NAP) - PSUSA/00000108/201912

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.11. Landiolol (NAP) - PSUSA/00010570/202002

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.12. Lidocaine, phenazone (NAP) - PSUSA/00002359/202001

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Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.13. Metamizole sodium, triacetonamine tosilate (NAP) - PSUSA/00001999/202001

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Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

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<sup>72</sup> All except centrally authorised product(s)

Scope: Evaluation of a PSUSA procedure

#### **16.3.14. Omega-3-acid ethyl esters (NAP) - PSUSA/00010312/202001**

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Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

#### **16.3.15. Sertindole (NAP) - PSUSA/00002695/202001**

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

#### **16.3.16. Sodium benzoate, grindelia<sup>73</sup>, polygala<sup>74</sup> (NAP) - PSUSA/00010543/201912**

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Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### **16.3.17. Tizanidine (NAP) - PSUSA/00002977/201912**

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Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### **16.3.18. Varicella-zoster immunoglobulin (NAP) - PSUSA/00010266/201912**

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Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

#### **16.4.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/LEG 011**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Detailed review of cases with potential increase of immunosuppression-related serious infections, opportunistic infections and varicella-zoster infections when baricitinib is used in combination with other rheumatoid arthritis (RA) drugs as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010578/201908)

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<sup>73</sup> Tincture

<sup>74</sup> Syrup

adopted in March 2020

#### **16.4.2. Choriogonadotropin alfa - OVITRELLE (CAP) - EMEA/H/C/000320/LEG 055**

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Detailed review of criteria for classification of events as 'non-reactions' and methodology for causality assessment as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000736/201909) adopted in April 2020

#### **16.4.3. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/LEG 070.1**

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to LEG 070 [analyses of cumulative data on pregnancy including foetal outcomes as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002127/201908) adopted in February 2020] as per the request for supplementary information (RSI) adopted in April 2020

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

None

### **16.6. Expedited summary safety reviews<sup>75</sup>**

#### **16.6.1. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/MEA 017**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Third expedited monthly summary safety report for remdesivir for July 2020 including spontaneously reported data and data from compassionate use and expanded access programmes for the duration of the coronavirus disease (COVID-19) pandemic

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

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

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<sup>75</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

## **17.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>76</sup>**

### **17.1.1. Blinatumomab – BLINCYTO (CAP) - EMEA/H/C/PSA/S/0057**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Amendment to a protocol previously agreed in February 2020 for study 20180130: an observational PASS to describe the long-term safety profile of first-relapse B-precursor acute lymphocytic leukaemia (ALL) paediatric patients who have been treated with blinatumomab or chemotherapy prior to undergoing haemopoietic stem cell transplant (HSCT)

### **17.1.2. Valproate (NAP) - EMEA/H/N/PSA/J/0059**

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Amendment to a joint protocol previously agreed in February 2020 for a joint survey among healthcare professionals (HCP) to assess the knowledge of HCP and behaviour with regard to the pregnancy prevention programme (PPP), the receipt/use of direct healthcare professional communication (DHPC) and educational materials as well as for a survey among patients to assess the knowledge of patients with regards to PPP and receipt/use of educational materials, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMA/H/A-31/1454)

## **17.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>77</sup>**

### **17.2.1. Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/MEA 002.1**

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Applicant: Evolus Pharma Limited

PRAC Rapporteur: Adam Przybylowski

Scope: MAH's response to MEA 002 [protocol for study EV-010: a non-interventional post-authorisation safety study of Nuceiva (botulinum toxin type A) for the treatment of moderate-to-severe glabellar lines] as per the request for supplementary information (RSI) adopted in March 2020

### **17.2.2. Diboterminalfa - INDUCTOS (CAP) - EMEA/H/C/000408/LEG 074.3**

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Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 074.2 [protocol for a cross-sectional study to evaluate the effectiveness of additional risk minimisation measures: a survey amongst physicians to assess their knowledge and understanding of selected risks of Inductos (diboterminalfa) in

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<sup>76</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>77</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

Europe] as per the request for supplementary information (RSI) adopted in April 2020

#### **17.2.3. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 008.4**

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 008.3 [protocol for study 109MS402: Biogen multiple sclerosis (MS) pregnancy exposure registry to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product] as per the request for supplementary information (RSI) adopted at the November 2019<sup>78</sup> PRAC meeting, together with the fourth annual progress report for study 109MS402

#### **17.2.4. Hydroxycarbamide - XROMI (CAP) - EMEA/H/C/004837/MEA 002**

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Applicant: Nova Laboratories Ireland Limited

PRAC Rapporteur: Laurence de Fays

Scope: Protocol for a healthcare professional (HCP) survey to assess HCPs' understanding of the content of the educational materials distributed as an additional risk minimisation measure (RMM) [final study report expected 8-12 months after the protocol approval] (from initial marketing authorisation/opinion)

#### **17.2.5. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/MEA 015.4**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Amendment to protocol previously agreed in January 2018 together with interim results for study GS-EU-313-4172: a non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL)

#### **17.2.6. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 020.1**

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Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: MAH's response to MEA 020 [protocol for study CT-P13 4.8: an observational, prospective cohort study to evaluate the safety of Remsima (infliximab) subcutaneous in patients with rheumatoid arthritis (RA)] as per the request for supplementary information (RSI) adopted in March 2020

#### **17.2.7. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.4**

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

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<sup>78</sup> Held 29-31 October 2019

Scope: MAH's response to MEA 001.3 [protocol for a long-term observational study to evaluate and further characterize the events of thrombocytopenia, glomerulonephritis and retinal toxicity/eye disease related to vitamin A deficiency when Tegsedi (inotersen) is prescribed in normal clinical practice, consisting of a protocol for a cohort of inotersen-exposed patients (TEG4001) and a protocol for an external comparator cohort (TEG4003)] as per the request for supplementary information (RSI) adopted in April 2020

#### **17.2.8. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 002.4**

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002.3 [protocol for study TEG4002: a retrospective chart review for evaluating adherence to and effectiveness of the proposed platelet monitoring schedule, proposed cut-off points, dose adaptation, and initiation of corticosteroids on thrombocyte recovery] as per the request for supplementary information (RSI) adopted in April 2020

#### **17.2.9. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.3**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 036.2 [amendment to protocol previously agreed in November 2018 for study CA184-557: extension of the long-term follow-up of ipilimumab in the Dutch melanoma treatment registry (DMTR) to include paediatric subjects and collect safety data to obtain additional safety information in paediatric patients] as per the request for supplementary information (RSI) adopted in March 2020

#### **17.2.10. Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/MEA 001.2**

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Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001.1 [protocol for an observational PASS of patients with chronic opioid use for non-cancer and cancer pain who have opioid-induced constipation (OIC) [final clinical study report (CSR) expected in January 2026]] as per the request for supplementary information (RSI) adopted in May 2020

#### **17.2.11. Netarsudil - RHOKIINSA (CAP) - EMEA/H/C/004583/MEA 001**

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Applicant: Aerie Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Eva Segovia

Scope: Protocol for study AR-13324-OBS02: a non-interventional, observational cohort study to investigate the long-term safety of netarsudil beyond 12 months treatment [final clinical study report (CSR) expected in June 2026] (from opinion/initial marketing authorisation)

#### 17.2.12. Osilodrostat - ISTURISA (CAP) - EMEA/H/C/004821/MEA 003

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Applicant: Recordati Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Protocol for a registry: a multi-country, observational study to collect clinical information on patients with endogenous Cushing's syndrome treated with osilodrostat and to document the long-term safety [final study results expected in December 2027] (from initial marketing authorisation/opinion)

#### 17.2.13. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 003

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Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for non-interventional study ALN-TTR02-010: patisiran-lipid nanoparticle (LNP) observational pregnancy surveillance programme

#### 17.2.14. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.1

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Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 003 [protocol for study 165-501: a multicentre, prospective global observational study to evaluate the long term safety of subcutaneous injections of pegvaliase in patients with phenylketonuria [final clinical study report (CSR) expected in Q2 2030]] as per the request for supplementary information (RSI) adopted in March 2020

#### 17.2.15. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.1

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Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 005 [protocol for study 165-504: a prospective global multicentre observational safety surveillance study to assess maternal, foetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding [final clinical study report (CSR) expected in Q2 2030]] as per the request for supplementary information (RSI) adopted in March 2020

#### 17.2.16. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 5879) - EMEA/H/W/002300/MEA 003.2

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Amended protocol previously agreed in May 2018 for study EPI-MAL-003 (listed as a category 3 study in the RMP): a phase 4 prospective observational study to evaluate the

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<sup>79</sup> Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

safety, effectiveness and impact of Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)) in young children in sub-Saharan Africa in order to estimate the incidence of potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with the vaccine

#### **17.2.17. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001.2**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 001.1 [protocol for study P19-633: a post-marketing registry-based prospective cohort study of long-term safety of risankizumab in real world setting in Denmark and Sweden [final study report expected in December 2031]] as per the request for supplementary information (RSI) adopted in March 2020

#### **17.2.18. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 002.2**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.1 [protocol for study P16-751 on pregnancy exposures and outcomes in psoriasis patients treated with risankizumab: a cohort study utilising large healthcare databases with mother-baby linkage in the United States [final study report expected in Q3 2026] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in March 2020

#### **17.2.19. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/MEA 003.7**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a protocol previously agreed in December 2012 for post-marketing surveillance study 20070797: a population based prospective study evaluating the short and long term safety of romiplostim treatment in real-life clinical practice in adult patients with chronic idiopathic (immune) thrombocytopenic purpura (ITP) based on national health registry systems in Denmark, Sweden, and Norway (Nordic Country Patient Registry for Romiplostim [NCPRR])

#### **17.2.20. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.1**

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 001 [protocol for study OP0005: a European non-interventional PASS to study the adherence to the risk minimisation measures (RMMs) in the product information by estimating the compliance with contraindications and target indication(s) amongst incident romosozumab users, and analysing the utilisation pattern using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in March 2026]] as per the request for supplementary information (RSI) adopted in April 2020

#### 17.2.21. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.1

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 002 [Protocol for study OP0004: a European non-interventional PASS to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in December 2026]] as per the request for supplementary information (RSI) adopted in April 2020

#### 17.2.22. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.1

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 003 [rotocol for study OP0006: a European non-interventional PASS to evaluate potential differences in terms of serious infection between romosozumab and currently available therapies used in comparable patients in real-world conditions using the EU-adverse drug reactions (EU-ADR) Alliance [final study results expected in December 2024]] as per the request for supplementary information (RSI) adopted in April 2020

#### 17.2.23. Ropeginterferon alfa-2b - BESREMI (CAP) - EMEA/H/C/004128/MEA 001.3

Applicant: AOP Orphan Pharmaceuticals AG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 001.2 [protocol for EUPAS29462 study: a prospective, multicentre, non-interventional observational PASS to further investigate the safety and tolerability of ropeginterferon alfa-2b in polycythaemia vera patients with a special focus on hepatotoxicity to evaluate the effectiveness of risk minimisation measures and to evaluate cardiovascular safety during titration phase [final study report expected in Q3 2023]] as per the request for supplementary information (RSI) adopted April 2020

#### 17.2.24. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 047

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for study SWIBREG-UST UC: an observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using the Swedish Inflammatory Bowel Disease Register (SWIBREG) as requested in the conclusions of variation II/071 finalised in July 2019 [final clinical study report (CSR) expected in May 2027]

#### 17.2.25. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 048

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for study SNDS-UST UC: an observational PASS to describe the safety of ustekinumab and other ulcerative colitis treatments in a cohort of patients with ulcerative colitis using the French administrative healthcare database (SNDS<sup>80</sup>) as requested in the conclusions of variation II/071 finalised in July 2019 [final clinical study report (CSR) expected in May 2027]

### **17.3. Results of PASS imposed in the marketing authorisation(s)<sup>81</sup>**

None

### **17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>82</sup>**

#### **17.4.1. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/II/0052**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for study B1781044 (listed as a category 3 study in the RMP): a study to estimate the incidence and to compare the risks of endometrial hyperplasia and endometrial cancer in postmenopausal women initiating either Duavive (estrogens conjugated/bazedoxifene) or estrogen + progestin (E+P) combination hormone replacement therapy (HRT)

#### **17.4.2. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - EMEA/H/C/002246/II/0047, Orphan**

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Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study MW2013-06-01 (listed as a category 3 study in the RMP): an international, observational retrospective, data-collection study assessing efficacy of applied risk-minimisation measures in burn patients treated with NexoBrid (concentrate of proteolytic enzymes enriched in bromelain). The RMP (version 7.0) is updated accordingly. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems' and to change the due dates for: 1) study MW2013-06-01 (listed as a category 3 study in the RMP): a drug utilisation study (DUS) for further evaluation of the effectiveness of the risk minimisation activities; 2) study MW2010-03-02 (DETECT) (listed as a category 3 study in the RMP): a multicentre, multinational, randomized, controlled, open-label study, performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid (concentrate of proteolytic enzymes enriched in bromelain) as compared to standard of care (SOC) treatment

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<sup>80</sup> Système National des Données de Santé

<sup>81</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>82</sup> In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

#### 17.4.3. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0068

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report related to the physician survey (NO6987) conducted for Exjade (deferasirox) to assess the impact of educational materials on the prescribers' awareness of doses and biological monitoring recommendations and to assess the awareness and appropriate use of both formulations (dispersible tablets and film-coated tablets). The RMP (version 17.1) is updated accordingly

#### 17.4.4. Dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS1810/0028; dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS1810/0061; dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS1810/0082

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Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report for study 201177 (EuroSIDA) (listed as a category 3 study in the RMP): a prospective observational cohort study to monitor and compare the occurrence of hypersensitivity reactions (HSR) and hepatotoxicity in patients receiving dolutegravir (with or without abacavir) and other integrase inhibitors (with or without abacavir)

#### 17.4.5. Duloxetine - CYMBALTA (CAP) - EMEA/H/C/000572/WS1879/0084; DULOXETINE LILLY (CAP) - EMEA/H/C/004000/WS1879/0021; YENTREVE (CAP) - EMEA/H/C/000545/WS1879/0069

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the results of study F1J-MC-B034: an observational pregnancy registry to monitor women exposed to duloxetine during pregnancy. As a consequence, the RMP (version 14.0) is updated accordingly

#### 17.4.6. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/II/0025

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for study B2311061 (listed as a category 3 study in the RMP): a non-interventional EU drug utilisation study (DUS) to describe baseline characteristics and utilisation patterns of EU patients initiating Duavive (estrogens conjugated/bazedoxifene) or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT) (in fulfilment of MEA 003)

#### 17.4.7. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/WS1861/0037/G; LENVIMA (CAP) - EMEA/H/C/003727/WS1861/0037/G

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Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) submission of the final clinical study report (CSR) for study E7080-G000-201 (study 201): evaluation of the long-term safety of lenvatinib in medullary and iodine-131 refractory, unresectable differentiated thyroid carcinoma (DTC) stratified by histology (in fulfilment of MEA 001 for Lenvima (lenvatinib), and from initial opinion/marketing authorisation for Kisplyx (lenvatinib)); 2) submission of the final CSR for study E7080-G000-303 (study 303): evaluation of the long-term safety of lenvatinib in patients with radioiodine refractory differentiated thyroid cancer (RR-DTC) in a randomized, double-blind, placebo-controlled phase 3 study (in fulfilment of MEA 004 for Lenvima (lenvatinib) and MEA 002 for Kisplyx (lenvatinib)); 3) submission of an updated integrated summary of safety (ISS) including data from DTC subjects in study 201, study 303 and study E7080-J081-208 (study 208): long-term safety profile of lenvatinib in Japanese patients with advanced thyroid cancer. The RMP (version 12) is updated accordingly

#### 17.4.8. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/II/0092

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Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study V72\_38OB (listed as a category 3 study in the RMP): an observational study conducted by Public Health England (PHE) to assess Bexsero (meningococcal group B vaccine (recombinant, component, adsorbed)) effectiveness and impact in infants in the UK upon introduction of the vaccine in the infant National Immunisation Programme (NIP) administered at 2, 4 and 12 months of age. The RMP (version 8.0) is updated accordingly

#### 17.4.9. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/II/0093

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Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study V72\_82OB (listed as a category 3 study in the RMP): an observational study on the safety of Bexsero (meningococcal group B vaccine (recombinant, component, adsorbed)) in pregnant women and their offspring to evaluate pregnancy outcomes among women immunised with the vaccine within 30 days prior to the last menstrual period (LMP) or at any time during pregnancy. The RMP (version 8.0) is updated accordingly

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

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Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Amelia Cupelli

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

#### **17.4.11. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/II/0034**

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report for the survey among healthcare professionals (HCPs) to assess their knowledge on dosing and administration of Obizur (susoctocog alfa) in 6 European countries

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

#### **17.5.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017.6**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 017.5 [third interim report for study ALIROC07997: a non-interventional safety study using healthcare databases to monitor the safety of Praluent (alirocumab) in patients affected with human immunodeficiency virus (HIV)] as per the request for supplementary information (RSI) adopted in March 2020

#### **17.5.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 008**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Yearly report for study CC 10004 PSA-012: evaluation of the long-term safety and safety outcomes for psoriatic arthritis patients treated with Otezla (apremilast) in the British Society for Rheumatology Psoriatic Arthritis Register (BSRBR-PsA)

#### **17.5.3. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.4**

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Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Interim report for study NIS-KYNTHEUM-1345: an observational PASS investigating the risk of suicidal behaviour, serious infections, major adverse cardiovascular events (MACE) and malignancy in psoriasis patients treated with brodalumab. The brodalumab assessment of hazards: a multinational safety (BRAHMS) study in electronic healthcare databases [final report expected in Q3 2030]

#### **17.5.4. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.10**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Second annual progress report for study 1245.96: an observational cohort study using existing data assessing the risks of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infection, and

diabetic ketoacidosis in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors [final clinical study report (CSR) expected in Q3 2021]

#### **17.5.5. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 010.3**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Fourth monitoring interim report for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]

#### **17.5.6. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.7**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Second annual progress report for study 1245.96: an observational cohort study using existing data assessing the risks of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infection, and diabetic ketoacidosis in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors [final clinical study report (CSR) expected in Q3 2021]

#### **17.5.7. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.5**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Fourth monitoring interim report for study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]

#### **17.5.8. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/MEA 009.3**

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Applicant: Shire Services BVBA

PRAC Rapporteur: Annika Folin

Scope: Interim report for study SHP617-400 (EU AIR): a non-interventional (PASS) registry study: A European multicentre, multi-country, post-authorisation observational study (registry) of patients with chronic adrenal insufficiency

#### **17.5.9. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/ANX 011.6**

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Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to ANX 011.5 [fourth interim report for study P08291 (PRO-E2): a prospective observational controlled cohort study to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the VTE risk in users of combined oral contraceptives containing levonorgestrel (as imposed in accordance with Article 10(a) of Regulation (EC) No 726/2004)] as per the request for supplementary information (RSI) adopted in May 2020

#### 17.5.10. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/ANX 001.9

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Applicant: Shionogi B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Fifth annual interim report for a PASS (ENCEPP/SDPP/8585) (listed as a category 1 study in Annex II and the RMP): an observational retrospective cohort study of ospemifene utilising existing databases in Germany, Italy, Spain, and the United States to evaluate the incidence of venous thromboembolism and other adverse events in vulvar and vaginal atrophy (VVA) patients treated with ospemifene as compared to: 1) patients newly prescribed selective oestrogen receptor modulators (SERM) for oestrogen-deficiency conditions or breast cancer prevention and; 2) the incidence in untreated VVA patients [final report expected in February 2021]

#### 17.5.11. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58<sup>83</sup>) - EMEA/H/W/002300/MEA 002.3

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Scientific Opinion Holder (SOH)'s response to MEA 002.2 [interim result for study EPI-MAL-002: a prospective study to estimate the incidence of diseases specified as adverse events of special interest (AESI) leading to hospitalisation or death, and of meningitis in infants and young children in sub-Saharan Africa prior to implementation of Mosquirix (RTS, S/AS01E) [final clinical study report due in December 2022]] as per the request for supplementary information (RSI) adopted in February 2020

#### 17.5.12. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 003.2

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Interim/progress report for study AC-065A403 (EDUCATE) (listed a category 3 study in the RMP): evaluation of the risk minimisation measures for mEDication errors with Upravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in Clinical prAcTicE

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<sup>83</sup> Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

#### **17.5.13. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/ANX 002.2**

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to ANX 002.1 [interim report for study 156-12-299: a non-interventional PASS to investigate the risks of hepatotoxicity, basal cell carcinoma and glaucoma associated with the use of Jinarc (tolvaptan). In addition, the study investigates pregnancy outcomes in patients treated with Jinarc (tolvaptan), patterns of medicinal product utilisation especially with regards to off-label use and use in patients over 50 years old as well as adverse drug reactions (ADRs) associated with long term use of Jinarc (tolvaptan) [final clinical study report (CSR) expected by: Q1/2026]] as per the request for supplementary information (RSI) adopted in March 2020

#### **17.5.14. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.20**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 022.19 [ninth annual report for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics] as per the request for supplementary information (RSI) adopted in April 2020

#### **17.5.15. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.14**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Tenth annual interim report for study CNT01275PSO4007 (Nordic pregnancy research initiative) (C0743T): exposure to ustekinumab during pregnancy in patients with psoriasis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers

#### **17.5.16. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.5**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: First interim report for study RRA-20745: an observational PASS to describe the safety of ustekinumab and other Crohn's disease treatments in a cohort of patients with Crohn's disease

### **17.6. Others**

#### **17.6.1. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 005.1**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 005 [Evaluation of the MAH's assessment of a letter to the editor in the New England Journal of Medicine (NEJM) entitled 'deaths associated with emicizumab in patients with hemophilia A' published in November 2019] as per the request for supplementary information (RSI) adopted in April 2020

#### **17.6.2. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 060.3**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 060.2 [six-monthly summary report of medication error events reported with the on body injector in the EU market, as requested in the conclusions of variation II/093/G finalised in February 2018] as per the request for supplementary information (RSI) adopted in March 2020

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

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

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

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

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

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

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

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

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

#### **18.1.1. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0066 (without RMP)**

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Applicant: SERB SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

#### **18.1.2. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/S/0006 (without RMP)**

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

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

#### **18.2.1. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/R/0021 (without RMP)**

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

#### **18.2.2. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0023 (without RMP)**

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Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

#### **18.2.3. Polatuzumab vedotin - POLIVY (CAP) - EMEA/H/C/004870/R/0003 (with RMP)**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

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

#### **18.3.1. Amlodipine, valsartan - AMLODIPINE-VALSARTAN MYLAN (CAP) - EMEA/H/C/004037/R/0008 (with RMP)**

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Applicant: Mylan S.A.S

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

#### **18.3.2. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/R/0053 (without RMP)**

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

#### **18.3.3. Ferric maltol - FERACCRU (CAP) - EMEA/H/C/002733/R/0027 (with RMP)**

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Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylowski

Scope: 5-year renewal of the marketing authorisation

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**18.3.4. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/R/0063 (without RMP)**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

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**18.3.5. Lopinavir, ritonavir - LOPINAVIR/RITONAVIR MYLAN (CAP) - EMEA/H/C/004025/R/0014 (without RMP)**

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Applicant: Mylan S.A.S

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

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**18.3.6. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/R/0056 (with RMP)**

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

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**18.3.7. Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/R/0034 (without RMP)**

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

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**18.3.8. Rasagiline - RASAGILINE MYLAN (CAP) - EMEA/H/C/004064/R/0006 (without RMP)**

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Applicant: Mylan S.A.S

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

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**18.3.9. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/R/0039 (without RMP)**

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Applicant: Amgen Europe B.V. ATMP<sup>84</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

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<sup>84</sup> Advanced therapy medicinal product

18.3.10. Zonisamide - ZONISAMIDE MYLAN (CAP) - EMEA/H/C/004127/R/0008 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Rhea Fitzgerald

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 31 August – 03 September 2020 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No restrictions applicable to this meeting	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	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
Adrien Inoubli	Member	France	No interests declared	Full involvement
Tiphaine Vaillant	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Member	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	4.1.4. 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins): atorvastatin (NAP); fluvastatin (NAP); lovastatin (NAP); pitavastatin (NAP); pravastatin (NAP); roorencia suvastatin (NAP); simvastatin (NAP) 4.3.5. Paclitaxel – ABRAXANE (CAP), APEALEA (CAP), PAZENIR (CAP); NAP 6.1.1. Abatacept - ORENCIA (CAP) 15.3.20. Ipilimumab - YERVOY (CAP); nivolumab - OPDIVO (CAP) 16.1.5. Atazanavir, cobicistat - EVOTAZ (CAP) 17.2.9. Ipilimumab - YERVOY (CAP)
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion,	15.3.16. Enzalutamide - XTANDI (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:	15.3.38. Romiplostim - NPLATE (CAP) 16.1.1. Adalimumab - AMGEVITA (CAP); HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP); HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP) 16.1.11. Carfilzomib - KYPROLIS (CAP) 17.1.1. Blinatumomab - BLINCYTO (CAP) 17.2.19. Romiplostim - NPLATE (CAP) 17.5.2. Apremilast - OTEZLA (CAP) 17.6.2. Pegfilgrastim - NEULASTA (CAP) 18.3.9 Talimogene laherparepvec - IMLYGIC (CAP)
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilvinienė	Member	Lithuania	No interests declared	Full involvement
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	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
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	4.3.2. Chloroquine (NAP); hydroxychloroquine (NAP) 4.3.3. Fluoroquinolones: ciprofloxacin (NAP); delafloxacin – QUOFENIX (CAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) 5.3.1. Rivaroxaban – XARELTO (CAP) 11.2.1. Levonorgestrel (NAP) 15.3.12. Darolutamide – NUBEQA (CAP) 16.1.41. Sorafenib – NEXAVAR (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michal Radik	Member	Slovakia	No interests declared	Full involvement
Marek Juracka	Alternate	Slovakia	No interests declared	Full involvement
Jasmina Klopčič	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Antoine Pariente	Member	Independent scientific expert	No participation in final deliberations and voting on:	18.2.2 Obeticholic acid - OCALIVA (CAP)
Stefan Weiler	Member	Independent scientific expert	No participation in discussion, final deliberations and voting on:	3.3.1. Ulipristal acetate – ESMYA (CAP); NAP
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Flora Musuamba Tshinai	Expert - via telephone*	Belgium	No interests declared	Full involvement
Ivona Bahník Biševac	Expert - via telephone*	Croatia	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Livia Puljak	Expert - via telephone*	Croatia	No interests declared	Full involvement
Karin Susanne Erneholm	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg	Expert - via telephone*	Denmark	No interests declared	Full involvement
Helle Gerda Olsen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Marian Hjortlund Allon	Expert - via telephone*	Denmark	No interests declared	Full involvement
Caroline Marie Voss	Expert - via telephone*	Denmark	No interests declared	Full involvement
Krõõt Aab	Expert - via telephone*	Estonia	No interests declared	Full involvement
Pierre Demolis	Expert - via telephone*	France	No interests declared	Full involvement
Nicole Bick	Expert - via telephone*	Germany	No interests declared	Full involvement
Dennis Lex	Expert - via telephone*	Germany	No participation in discussion, final deliberations and voting on:	15.3.31. Peginterferon beta-1a – PLEGRIDY (CAP) 16.1.21. Fampridine - FAMPYRA (CAP) 16.4.3. Natalizumab - TYSABRI (CAP) 17.2.3. Dimethyl fumarate - TECFIDERA (CAP)
Elena Wolff-Holz	Expert - via telephone*	Germany	No interests declared	Full involvement
Aine McKenna	Expert - via telephone*	Ireland	No interests declared	Full involvement
Gintare Gilaite	Expert - via telephone*	Lithuania	No interests declared	Full involvement
Quirine Fillekes	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Evelyn Mulder - Olthof	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Fakhredin Sayed Tabatabaei	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Ana Fernández	Expert - via telephone*	Spain	No interests declared	Full involvement
Raquel Granados	Expert - via telephone*	Spain	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
Charlotte Backman	Expert - via telephone*	Sweden	No interests declared	Full involvement
Viveca Odling	Expert - via telephone*	Sweden	No interests declared	Full involvement
Miriam Taekema	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

\* Experts were only evaluated against the agenda topics or activities they participated in

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

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

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

## 21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

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

### Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

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

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

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

(Item 5 of the PRAC minutes)

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

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

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation. PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

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

(Item 7 of the PRAC minutes)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

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

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

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