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SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines Pharmacovigilance and Committees Division

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 11-14 June 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

### Health and safety information

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

### Disclaimers

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

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

### Note on access to documents

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

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## **1. Introduction**

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

The Chairperson opened the 11-14 June 2019 meeting by welcoming all participants.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.1](#)). All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chairperson welcomed Helena Panayiotopoulou, replacing Andri Andreou, as the new member for Cyprus and noted that Panagiotis Psaras is the new alternate for Cyprus, replacing Ioannis Kkolos.

### **1.2. Agenda of the meeting on 11-14 June 2019**

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 13-16 May 2019**

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 13-16 May 2019 were published on the EMA website on 17 October 2019 ([EMA/PRAC/482452/2019](#)).

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

### **2.1. Newly triggered procedures**

None

### **2.2. Ongoing procedures**

None

## 2.3. Procedures for finalisation

None

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

### 3.1. Newly triggered procedures

#### 3.1.1. Leuprorelin<sup>1</sup> (NAP) – EMEA/H/A-31/1486

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Applicant(s): various

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Eva Segovia

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

#### Background

Leuprorelin is a gonadotrophin-releasing hormone (GnRH) analogue indicated for the treatment of advanced hormone-dependent prostate cancer.

The German Federal Institute for Drugs and Medical Device ([BfArM](#)) sent a letter of [notification](#) dated 07 June 2019, triggering a referral procedure under Article 31 of Directive 2001/83/EC for the review of leuprorelin-containing products. The review covering depot formulations was initiated after reports indicated that handling errors with the products during preparation and administration can cause some patients to receive insufficient amounts of their medicine, potentially leading to a lack of efficacy. The most common handling errors reported were syringe issues leading to leakage, issues with the safety needle and handling errors associated with products viscosity. The issue was first reviewed at PRAC in 2014 as a signal of 'wrong technique in drug usage process' (EPITT 17753) and since that time, several risk minimisation measures (RMMs) have been introduced to reduce the number of handling errors. In 2019, the PRAC remained concerned with the high number of medication errors still occurring with Eligard (leuprorelin). For further background, see [PRAC minutes May 2019](#). As the significant number of medication errors, observed for leuprorelin-containing depot products remain a serious risk to public health, it was considered that further action is warranted to further characterise and mitigate the risk of handling errors and associated risk of lack of efficacy of leuprorelin-containing depot-injections. Therefore, BfArM considered in the interest of the Union to refer the matter to PRAC to give its recommendation as to whether marketing authorisation(s) for these medicinal products should be maintained, varied, suspended, or revoked.

#### Discussion

The PRAC noted the notification letter from the BfArM and appointed Željana Margan Koletić as Rapporteur and Eva Segovia as Co-Rapporteur for the procedure.

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

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<sup>1</sup> Depot formulation(s)

### Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAH ([EMA/PRAC/317692/2019](#)) and a timetable for the procedure ([EMA/PRAC/317693/2019](#)).
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure<sup>2</sup> ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure as needed.

See EMA press release ([EMA/316598/2019](#)) entitled 'Review of handling errors with depot formulations of leuprorelin medicines started'.

### 3.2. Ongoing procedures

None

### 3.3. Procedures for finalisation

None

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

None

### 3.5. Others

None

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

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

See Annex I 14.1.

### 4.2. New signals detected from other sources

None

### 4.3. Signals follow-up and prioritisation

- 4.3.1. Dipeptidyl peptidase-4 (DPP-4) inhibitors:  
alogliptin – VIPIDIA (CAP) - EMEA/H/C/002182/SDA/011; linagliptin – TRAJENTA (CAP) - EMEA/H/C/002110/SDA/017; saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/SDA/043; sitagliptin – JANUVIA (CAP) -

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

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

<sup>4</sup> Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required



EMA/H/C/000722/SDA/038, RISTABEN (CAP) - EMA/H/C/001234/SDA/016, TESAVEL (CAP) - EMA/H/C/000910/SDA/032, XELEVIA (CAP) - EMA/H/C/000762/SDA/037; vildagliptin - GALVUS (CAP) - EMA/H/C/000771/SDA/047, JALRA (CAP) - EMA/H/C/001048/SDA/031, XILIXARX (CAP) - EMA/H/C/001051/SDA/031; Glucagon-like peptide-1 (GLP-1) receptor agonists: albiglutide - EPERZAN<sup>5</sup>; dulaglutide - TRULICITY (CAP) - EMA/H/C/002825/SDA/012; exenatide - BYDUREON (CAP) - EMA/H/C/002020/SDA/026, BYETTA (CAP) - EMA/H/C/000698/SDA/046; liraglutide - SAXENDA (CAP) - EMA/H/C/003780/SDA/018, VICTOZA (CAP) - EMA/H/C/001026/SDA/037; lixisenatide - LYXUMIA (CAP) - EMA/H/C/002445/SDA/015; semaglutide - OZEMPIC (CAP) - EMA/H/C/004174/SDA/006

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Applicant(s): AstraZeneca AB (Bydureon, Byetta, Onglyza), Boehringer Ingelheim (Tranjenta), Eli Lilly Nederland B.V. (Trulicity), GlaxoSmithKline Trading Services limited (Eperzan), Merck Sharp & Dohme B. V. (Januvia, Ristaben, Tesavel, Xelevia), Novartis Europharm Limited (Galvus, Jalra, Xiliarx), Novo Nordisk A/S (Ozempic, Saxenda, Victoza), Sanofi-aventis groupe (Lyxumia), Takeda Pharma A/S (Vipidia)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of increased risk of cholangiocarcinoma in adults with type 2 diabetes mellitus (T2DM)

EPITT 19343 – Follow-up to January 2019

### **Background**

For background information, see [PRAC minutes January 2019](#).

The MAHs for Ozempic (semaglutide)/Saxenda and Victoza (liraglutide), for Onglyza (saxagliptin)/Bydureon and Byetta (exenatide), for Trulicity (dulaglutide), for Galvus/Jalra and Xiliarx (vildagliptin), for Tranjenta (linagliptin), for Vipidia (alogliptin), for Januvia/Ristaben/Tesavel/Xelevia (sitagliptin) and for Lyxumia (lixisenatide) replied to the request for information on the signal of cholangiocarcinoma and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence including the information provided by the MAHs and clarifications received from the study authors on the signal of increased risk of cholangiocarcinoma, the PRAC agreed that there is at the moment insufficient evidence to support a causal association with incretin based products (dipeptidyl peptidase-4 (DPP-4) inhibitor- and glucagon-like peptide-1 (GLP-1) receptor agonist-containing products). Therefore, the PRAC agreed that no further regulatory action is warranted at this stage.

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

- The MAHs for DPP-4 inhibitor-containing products and GLP-1 receptor agonist-containing products should continue to monitor these events as part of routine safety surveillance.

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#### **4.3.2. Loperamide (NAP)**

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Applicant(s): various

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<sup>5</sup> European Commission (EC) decision on the withdrawal of the marketing authorisation(s) dated 29 October 2018

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of Brugada syndrome in the context of abuse with loperamide

EPITT 19379 – Follow-up April 2019

### **Background**

For background information, see [PRAC minutes April 2019](#).

The MAH Janssen Pharmaceutica NV for the originator product containing loperamide replied to the request for information on the signal of Brugada syndrome in the context of abuse with loperamide and the responses were assessed by the Rapporteur.

### **Discussion**

The PRAC considered the comments received from the MAH and agreed on the final wording for updating the product information as regards unmasking of existing Brugada syndrome in case of loperamide overdose. As a consequence, all MAHs of loperamide-containing products should amend their product information accordingly.

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

- The MAHs for loperamide-containing products should submit to relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending the product information<sup>6</sup>.

For the full PRAC recommendation, see [EMA/PRAC/303951/2019](#) published on 8 July 2019 on the EMA website.

## **4.3.3. Propylthiouracil (NAP)**

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Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of risk of congenital anomalies

EPITT 19358 – Follow-up to February 2019

### **Background**

For background information, see [PRAC minutes February 2019](#).

The MAHs Admeda Arzneimittel, RPH Pharmaceuticals and Takeda replied to the request for information on the signal of congenital anomalies and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence in EudraVigilance and the available non-clinical and epidemiological studies, the PRAC agreed that although there was no clear specific pattern of congenital anomalies and that non-clinical studies and epidemiological studies report conflicting results as regards congenital anomalies, the MAHs of propylthiouracil-containing medicinal products should update their product information to inform women of childbearing potential on the potential risk of propylthiouracil use during pregnancy. The PRAC also

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<sup>6</sup> Update of SmPC sections 4.4 and 4.9

agreed that individual benefit/risk assessment is necessary before treatment with propylthiouracil during pregnancy.

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

- The MAHs for propylthiouracil-containing products should submit to relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending the product information<sup>7</sup>.

For the full PRAC recommendation, see [EMA/PRAC/303951/2019](#) published on 8 July 2019 2019 on the EMA website.

#### **4.3.4. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/SDA/045; NAPs**

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Applicant(s): Bayer AG, various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of premature ending of GALILEO<sup>8</sup> study in patients who have received an artificial heart valve through a transcatheter aortic valve replacement (TAVR)

EPITT 19294 – Follow-up to September 2018

#### **Background**

For background information, see [PRAC minutes September 2018](#).

The MAH for Xarelto (rivaroxaban) replied to the request for information on the signal of premature ending of the GALILEO study in patients who have received an artificial heart valve through a trans-catheter aortic valve replacement (TAVR) and the responses were assessed by the Rapporteur.

#### **Discussion**

Having considered the final results of the early terminated GALILEO study, including the increased risk of all-cause mortality, thromboembolic events and bleeding and the available evidence in clinical trials and spontaneous reporting, the PRAC agreed that rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone TAVR. The PRAC agreed that MAHs of rivaroxaban-containing products should amend their product information accordingly.

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

- The MAHs for rivaroxaban-containing products should submit to the EMA or the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending the product information<sup>9</sup>.

For the full PRAC recommendation, see [EMA/PRAC/303951/2019](#) published on 8 July 2019 on the EMA website.

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<sup>7</sup> Update of SmPC section 4.6. The package leaflet is to be updated accordingly

<sup>8</sup> A global multicentre, open-label, randomised, event-driven, active-controlled study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to optimize clinical outcomes

<sup>9</sup> Update of SmPC section 4.4

#### 4.3.5. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/SDA/006

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Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Signal of dermatitis exfoliative generalised

EPITT 19354 – Follow-up to February 2019

##### **Background**

For background information, see [PRAC minutes February 2019](#).

The MAH for Cosentyx (secukinumab) replied to the request for information on the signal of dermatitis exfoliative generalised and the responses were assessed by the Rapporteur.

##### **Discussion**

Having considered the available evidence from EudraVigilance, the literature and the cumulative review provided by the MAH, the PRAC agreed that there is a plausible causal association between treatment with secukinumab and the occurrence of exfoliative dermatitis. Therefore, the PRAC agreed that the product information should be updated accordingly.

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

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

For the full PRAC recommendation, see [EMA/PRAC/303951/2019](#) published on 8 July 2019 on the EMA website.

#### 4.3.6. Sulfasalazine (NAP)

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Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of interference with dihydronicotinamide-adenine dinucleotide / dihydronicotinamide-adenine dinucleotide phosphate (NADH/NADP) reaction assays

EPITT 19351 – Follow-up to February 2019

##### **Background**

For background information, see [PRAC minutes February 2019](#).

Pfizer, the MAH of the originator sulfasalazine-containing product(s) replied to the request for information on the signal of interference with dihydronicotinamide-adenine dinucleotide/dihydronicotinamide-adenine dinucleotide phosphate (NADH/NADP) reaction assays and the responses were assessed by the Rapporteur.

##### **Discussion**

Based on the assessment of the available data from EudraVigilance and the literature, the PRAC considered that there is a risk of interference with NADH/NADP(H) based assays with

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<sup>10</sup> Update of SmPC section 4.8. The package leaflet is to be updated accordingly

sulfasalazine. Therefore, the PRAC agreed that the MAHs for the sulfasalazine-containing products should amend the product information accordingly.

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

- The MAHs for sulfasalazine-containing products should submit to relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update the product information<sup>11</sup>.

For the full PRAC recommendation, see [EMA/PRAC/303951/2019](#) published on 08 July 2019 on the EMA website.

#### **4.3.7. Temozolomide - TEMODAL (CAP) - EMEA/H/C/000229/SDA/042; TEMOMEDAC (CAP), TEMOZOLOMIDE ACCORD (CAP), TEMOZOLOMIDE HEXAL (CAP), TEMOZOLOMIDE SANDOZ (CAP), TEMOZOLOMIDE SUN (CAP), TEMOZOLOMIDE TEVA (CAP); NAP**

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Applicant(s): Accord Healthcare S.L.U. (Temozolomide Teva), Hexal AG (Temozolomide Hexal), Merck Sharp & Dohme B.V. (Temodal), Sandoz GmbH (Temomedac, Temozolomide Sandoz), Sun Pharmaceutical Industries Europe B.V. (Temozolomide Sun), Teva B.V. (Temozolomide Teva), various

PRAC Rapporteur: Martin Huber

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

EPITT 19332 – Follow-up to January 2019

#### **Background**

For background information, see [PRAC minutes January 2019](#).

The MAH for Temodal (temozolomide) replied to the request for information on the signal of drug reaction with eosinophilia and systemic symptoms (DRESS) and the responses were assessed by the Rapporteur.

#### **Discussion**

Having considered the available evidence in EudraVigilance and in the literature, alongside the known association of temozolomide with severe skin reactions, the PRAC agreed that there is a plausible causal association between temozolomide and the occurrence of DRESS. Therefore, the PRAC agreed that the product information should be updated accordingly.

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

- The MAHs for temozolomide-containing products should submit to the EMA or to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend the product information to add DRESS as an undesirable effect<sup>12</sup>.

For the full PRAC recommendation, see [EMA/PRAC/303951/2019](#) published on 8 July 2019 on the EMA website.

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<sup>11</sup> Update of SmPC sections 4.4 and 4.5. The package leaflet is to be updated accordingly

<sup>12</sup> Update of SmPC section 4.8

#### 4.3.8. Topiramate (NAP)

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Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of uveitis

EPITT 19345 – Follow-up to January 2019

##### **Background**

For background information, see [PRAC minutes January 2019](#).

The MAH Janssen-Cilag replied to the request for information on the signal of uveitis and the responses were assessed by the Rapporteur.

##### **Discussion**

Having considered the available evidence including reports of bilateral uveitis developing shortly after the initiation of topiramate treatment with no confounding disease and relatively rapid resolution of uveitis after cessation of topiramate treatment, the PRAC concluded that there is a plausible causal association between topiramate and the occurrence of uveitis. Therefore, the PRAC agreed that the product information of topiramate-containing products should be updated accordingly.

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

- The MAHs for topiramate-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend the product information to include uveitis as an undesirable effect<sup>13</sup>.

For the full PRAC recommendation, see [EMA/PRAC/303951/2019](#) published on 8 July 2019 on the EMA website.

## 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>).

See also Annex I 15.1.

#### 5.1.1. Cefiderocol - EMEA/H/C/004829

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Scope (accelerated assessment): Treatment of infections due to aerobic Gram-negative bacteria

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

### 5.1.2. Emapalumab - EMEA/H/C/004386, Orphan

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Applicant: Novimmune B.V.

Scope: Treatment of paediatric patients with primary haemophagocytic lymphohistiocytosis (HLH)

### 5.1.3. Fostamatinib - EMEA/H/C/005012

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Scope: Treatment of thrombocytopenia

### 5.1.4. Netarsudil - EMEA/H/C/004583

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Scope: Reduction of elevated intraocular pressure (IOP) in adults with open-angle glaucoma or ocular hypertension

### 5.1.5. Omadacycline tosilate - EMEA/H/C/004715

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Scope: Treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults

### 5.1.6. Quizartinib - EMEA/H/C/004468, Orphan

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Applicant: Daiichi Sankyo Europe GmbH

Scope: Treatment of acute myeloid leukaemia

### 5.1.7. Replication-competent live recombinant vesicular stomatitis virus (rVSVΔG-ZEBOV-GP, live attenuated) expressing the envelope glycoprotein of the Ebolavirus-Zaire Kikwit strain - EMEA/H/C/004554

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Scope (accelerated assessment): Active immunisation of at-risk individuals aged 18 years and older to protect against Ebola virus disease (EVD) caused by Zaire ebolavirus

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

See Annex I 15.2.

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

See Annex I 15.3.

# 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. Acridinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201811

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Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### **Background**

Acridinium bromide is a long-acting muscarinic antagonist (also known as an anticholinergic) and formoterol fumarate dihydrate, a long-acting  $\beta$ 2-adrenergic agonist. In combination acridinium bromide/formoterol fumarate dihydrate is indicated, as Brimica Genuair and Duaklir Genuair, as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of Brimica Genuair and Duaklir Genuair, centrally authorised medicines containing acridinium bromide/formoterol fumarate dihydrate 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 Brimica Genuair and Duaklir Genuair (acridinium bromide/formoterol fumarate dihydrate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to remove 'peripheral oedema' as an undesirable effect. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>14</sup>.
- In the next PSUR, the MAH should closely monitor and review any serious cases of glaucoma and cases of device malfunction.

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. Aflibercept<sup>15</sup> - EYLEA (CAP) - PSUSA/00010020/201811

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Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

#### **Background**

Aflibercept is an inhibitor of vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF). It is indicated, as Eylea, for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular oedema secondary to branch or central retinal vein occlusion (RVO), visual impairment due to diabetic macular

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<sup>14</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>15</sup> Ophthalmological indication(s) only



oedema (DME) and visual impairment due to myopic choroidal neovascularisation (myopic CNV).

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Eylea, a centrally authorised medicine containing aflibercept. The MAH also provided further clarifications at an oral explanation held on 12 June 2019. The Committee issued a recommendation on the marketing authorisation(s) of Eylea (aflibercept).

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Eylea (aflibercept) 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 cumulative review of post-marketing data on macular atrophy/geographic atrophy and maintain macular oedema, congestive heart failure and thrombotic microangiopathy under close monitoring. The MAH should also review and discuss fatal cases with no predisposing factors, the occurrence of macular hole, wound healing complications, arterial and venous thromboembolism, ischaemic colitis, retinal haemorrhage and non-ocular haemorrhage.
- The MAH should submit to the EMA by 3 March 2020 a review of the available epidemiological and clinical data to estimate background incidence of retinal artery occlusion (RAO), including, separately, stenosis, embolism, thrombosis, spasm and occlusion, in the population with similar risk profile as that treated with Eylea (aflibercept). In addition, the MAH should provide a detailed discussion on potential pathophysiological mechanisms for development of RAO and discuss these in relation to aflibercept treatment and provide an overview of pharmacokinetic (PK) and pharmacodynamic (PD) data on systemic exposure including the potential for occurrence of systemic adverse reactions. Furthermore, the MAH should provide an updated causality assessment of all RAO events reported in clinical trials and post-marketing including literature.

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. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/201811**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

#### **Background**

Atezolizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death-ligand 1 (PD-L1). It is indicated, as Tecentriq, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC), subject to certain conditions and for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Tecentriq, a centrally authorised medicine containing atezolizumab 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 Tecentriq (atezolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information that the current undesirable effect of 'infusion related reactions' also includes cases of hypersensitivity and anaphylaxis. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>16</sup>.
- In the next PSUR, the MAH should provide further details on the serious adverse events (AEs) reported in study GO29754<sup>17</sup> and elaborate on the possible explanation for the observed toxicity. The MAH is also requested to discuss the need for reflecting in the product information and/or the risk management plan the precautionary measures implemented in study GO40290<sup>18</sup>, such as screening of Epstein-Barr virus (EBV) infection status. Furthermore, the MAH should provide an updated review on cardiac toxicity and present a cumulative review of ocular toxicity, with a specific focus on retinopathy, acute macular neuroretinopathy and diffuse retinal venulitis.

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. Cabozantinib - CABOMETYX (CAP); COMETRIQ (CAP) - PSUSA/00010180/201811 (with RMP)**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **Background**

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases. It is indicated, as Cabometyx, for the treatment of advanced renal cell carcinoma (RCC), subject to certain conditions, and for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib. It is also indicated, as Cometriq, for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of Cabometyx and Cometriq, centrally authorised medicines containing cabozantinib and issued a recommendation on their marketing authorisations.

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<sup>16</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

<sup>17</sup> A phase 1b study of the safety and pharmacology of atezolizumab (anti-PD-L1 antibody) administered alone or in combination with azacitidine in patients with myelodysplastic syndrome

<sup>18</sup> A phase 2, randomised, blinded, placebo-controlled study of MTIG7192A (an anti- T-cell immuno-receptor with immunoglobulin (Ig) and immuno-receptor tyrosine-based inhibitory motif (ITIM) domains (TIGIT) antibody), in combination with atezolizumab in chemotherapy-naïve patients with locally advanced or metastatic non-small cell lung cancer

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Cabometyx and Cometriq (cabozantinib) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'pain in extremity' as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>19</sup>.

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

#### **6.1.5. Darifenacin - EMSELEX (CAP) - PSUSA/00000933/201810**

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Applicant: Merus Labs Luxco II S.a.r.l.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

#### **Background**

Darifenacin is a selective muscarinic M3 receptor antagonist indicated, as Emselex, for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in adult patients with overactive bladder syndrome.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Emselex, a centrally authorised medicine containing darifenacin 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 Emselex (darifenacin) 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 cumulative review of all cases of fall and confusional state, collected from clinical trials, post-marketing sources and the literature.

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

#### **6.1.6. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/201811**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

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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**

Erenumab is a human monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) receptor. It is indicated, as Aimovig, for prophylaxis of migraine in adults who have at least 4 migraine days per month.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Aimovig, a centrally authorised medicine containing erenumab 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 Aimovig (erenumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypersensitivity reactions including rash, swelling/oedema and urticaria as undesirable effects with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>20</sup>.
- In the next PSUR, the MAH should provide cumulative reviews of suicide/suicidal ideation/suicide attempt, anaphylactic reactions, angioedema and severe cutaneous adverse reactions (SCARs). In addition, the MAH should review data on accidental injection associated with the auto-injector and propose updates of 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.

## **6.1.7. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/201811**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

### **Background**

Etelcalcetide is a synthetic peptide calcimimetic agent indicated, as Parsabiv, for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Parsabiv, a centrally authorised medicine containing etelcalcetide 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 Parsabiv (etelcalcetide) in the approved indication(s) remains unchanged.

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

- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a comprehensive analysis of all available data on gastrointestinal bleeding and ulceration associated with the use of etelcalcetide, with a discussion on possible mechanisms. The MAH should provide a proposal to update 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.

### 6.1.8. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/201811

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

#### **Background**

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase. It is indicated, as Imbruvica, for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), adult patients with previously untreated chronic lymphocytic leukaemia (CLL), as a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy and for the treatment of adult patients with Waldenström's macroglobulinaemia (WM), subject to certain conditions.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Imbruvica, a centrally authorised medicine containing ibrutinib 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 Imbruvica (ibrutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning, and to add *Aspergillus* infection, *Pneumocystis jirovecii* infection, and disseminated cryptococcosis as undesirable effects with a frequency 'uncommon'. In addition, the frequency for the undesirable effect of hepatic failure is revised from 'not known' to 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>21</sup>.
- In the next PSUR, the MAH should provide a thorough cumulative review of all literature with emphasis on studies with outcomes that describe important risks, especially bleeding and atrial fibrillation and provide a cumulative review of cases of pericardial disorders, especially from randomised controlled trials. The MAH should also present cumulative reviews of cases of alopecia, atrioventricular (AV)-block and cardiac failure, splenic rupture, (acute) renal failure, uveitis and macular oedema as well as cases of Guillain-Barre syndrome. Furthermore, the MAH should describe and analyse all cases

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<sup>21</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

of drug-drug interactions with anticoagulants. Finally, the MAH should assess cases of progressive multifocal leukoencephalopathy (PML) and present a full assessment according to the agreed case definition by *Mentzer et al.*<sup>22</sup> and the PRAC PML strategy described by *Segec et al.*<sup>23</sup>.

- The MAH should submit to EMA, within 60 days, a cumulative analysis of all cases reporting hepatic failure with a special focus on cases with fatal outcome.

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. Metformin, saxagliptin - KOMBOGLYZE (CAP) - PSUSA/00002686/201811

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **Background**

Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin, a biguanide. In combination, saxagliptin/metformin is indicated, as Komboglyze, in adults with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximally tolerated dose of metformin alone, in combination with other medicinal products for the treatment of diabetes, including insulin, in patients inadequately controlled with metformin and these medicinal products and in patients already being treated with the combination of saxagliptin and metformin as separate tablets.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Komboglyze, a centrally authorised medicine containing metformin/saxagliptin 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 Komboglyze (metformin/saxagliptin) 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 discussion on cases of lack of efficacy.
- The MAH should submit to the EMA, within 60 days, a discussion on the association between bullous pemphigoid and saxagliptin/metformin and saxagliptin as a single active substance.

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

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<sup>22</sup> Mentzer D et al. Case definition for progressive multifocal leukoencephalopathy following treatment with monoclonal antibodies. *J Neurol Neurosurg Psychiatry*. 2012;83:927-933

<sup>23</sup> Segec A et al. Strategy in regulatory decision-making for management of progressive multifocal leukoencephalopathy. *Clin Pharmacol Ther*. 2015;98(5):502-505

#### 6.1.10. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/201811

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

##### **Background**

Nusinersen is an antisense oligonucleotide (ASO) indicated, as Spinraza, for the treatment of 5q spinal muscular atrophy (SMA).

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Spinraza, a centrally authorised medicine containing nusinersen 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 Spinraza (nusinersen) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'hypersensitivity (e.g. angioedema, urticaria and rash)' as an undesirable effect in the list of post-marketing experience with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>24</sup>.
- In the next PSUR, the MAH should closely monitor cases of neutrophilic eccrine hidradenitis (NEH) and of liver toxicity. In addition, the MAH should continue to monitor and discuss hydrocephalus cases as well as provide a review on the effectiveness of the direct healthcare professional communication (DHPC) distributed in July 2018 as risk minimisation measure to reduce the number of case of hydrocephalus. For further background, see [PRAC minutes July 2018](#)

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. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/201811

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

##### **Background**

Osimertinib is a tyrosine kinase inhibitor (TKI) indicated, as Tagrisso, as monotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations as well as for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

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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

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Tagrisso, a centrally authorised medicine containing osimertinib 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 Tagrisso (osimertinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on Stevens-Johnson syndrome (SJS) and amend existing warnings on interstitial lung disease (ILD) and changes in cardiac contractility. In addition, SJS is added as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>25</sup>.
- In the next PSUR, the MAH should provide a discussion on cases of gastrointestinal perforation.

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.

#### **6.1.12. Pentosan polysulfate sodium<sup>26</sup> - ELMIRON (CAP) - PSUSA/00010614/201812**

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Applicant: bene-Arzneimittel GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### **Background**

Pentosan polysulfate is a semi-synthetic polysulfated xylan indicated, as Elmiron, for the treatment of bladder pain syndrome characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Elmiron, a centrally authorised medicine containing pentosan polysulfate sulfate 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 Elmiron (pentosan polysulfate sulfate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on pigmentary maculopathy. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>27</sup>.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

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<sup>25</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

<sup>26</sup> Centrally authorised product(s) only

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



- In the next PSUR, the MAH should provide a detailed review of all available data on pigmentary maculopathy together with a discussion on the most adequate tool for ophthalmological monitoring of patients treated with pentosane polysulfate sodium. The MAH should also discuss possible risk factors and identify populations at risk as well as the pathogenesis for pigmentary maculopathy. In addition, the MAH should discuss the need to update the product information on pigmentary maculopathy with respect to baseline examination and periodicity of regular ophthalmological examination and instructions to discontinue treatment. Furthermore, the MAH should provide a discussion on the need and options to further characterise this safety concern and the need for further risk minimisation measures.

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. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201812

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### **Background**

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) non-structural protein 5B (NS5B) ribonucleic acid (RNA)-dependent RNA polymerase, indicated as Sovaldi, in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and in adolescents aged 12 to <18 years for HCV genotype specific activity.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Sovaldi, a centrally authorised medicine containing sofosbuvir 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 Sovaldi (sofosbuvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include new information on the impact of direct-acting antiviral (DAAV) therapy on drugs metabolised by the liver and on the potential need for dose adjustment of those drugs when they are co-administered with DAAV therapy. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>28</sup>.

As agreed in the outcome of procedure PSUSA/00010306/201810 for Harvoni (sofosbuvir/ledipasvir) adopted in May 2019, the PRAC considered that the above recommendation for updating the product information to reflect the risk of DAAV therapy affecting other drugs metabolised by the liver is also relevant for other medicinal products within the same therapeutic class (DAAV therapy for HCV). Therefore, the MAHs of centrally

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<sup>28</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

authorised products of the same class should update their product information accordingly. Further consideration should be given at the level of CHMP.

The PRAC also considered that the information regarding the impact of DAAV therapy on tacrolimus and ciclosporin is relevant for tacrolimus- and ciclosporin-containing products. Therefore, the MAHs of tacrolimus- and ciclosporin-containing products should review the need to update their product information in an upcoming regulatory procedure or at the latest within 60 days of the European Commission (EC) decision. Further consideration should be given at the level of CHMP and CMDh. For further background, see [PRAC minutes May 2019](#).

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.

#### 6.1.14. Tolvaptan<sup>29</sup> - JINARC (CAP) - PSUSA/00010395/201811

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

##### **Background**

Tolvaptan is a vasopressin antagonist indicated, as Jinarc, to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.

Based on the assessment of the periodic safety update report (PSUR), the PRAC reviewed the benefit-risk balance of Jinarc, a centrally authorised medicine containing tolvaptan 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 Jinarc (tolvaptan) 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 cumulative review of mortality cases. In addition, the MAH should further review cases of pharmacodynamic interaction between tolvaptan and warfarin.

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

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<sup>29</sup> Treatment of adults with autosomal dominant polycystic kidney disease (ADPKD) to slow the progression of cyst development and renal insufficiency

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

See also Annex I 16.2.

### 6.2.1. Eslicarbazepine acetate - ZEBINIX (CAP); NAP - PSUSA/00001267/201810

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Applicant(s): Bial - Portela & C<sup>a</sup>, S.A. (Zebinix), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### Background

Eslicarbazepine acetate is a carboxamide derivative anti-epileptic medicine indicated for the treatment of adults with partial-onset seizures with or without secondary generalisation and in adolescents and children above 6 years of age, in combination with existing therapies, to treat partial-onset seizures with or without secondary generalisation.

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of Zebinix, a centrally authorised medicine containing eslicarbazepine acetate, and nationally authorised medicines containing eslicarbazepine acetate 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 eslicarbazepine acetate-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include new information from cases of overdose and to include weight increase as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisations should be varied<sup>30</sup>.
- In the next PSUR, the MAH should provide any new information on cardiac arrest and other cardiac events in the context of overdose and in general. The MAH should carefully monitor cases of overdose with regard to cardiac arrest and other cardiac events and should update product information accordingly.

The PRAC considered that PSURs are no longer required for products referred to in Article 10(1), 10a, 16a of Directive 2001/83/EC as generic-medicinal products containing eslicarbazepine have not been placed on the market. The EURD list should be updated accordingly.

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>30</sup> Update of SmPC sections 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Applicant(s): Nordic Group B.V. (Nordimet), Therakind (Europe) Limited (Jylamvo), various  
PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

### **Background**

Methotrexate is an antineoplastic and immunomodulating agent and folic acid analogue indicated for use in rheumatological and dermatological diseases (active rheumatoid arthritis, polyarthritic forms of active, severe juvenile idiopathic arthritis (JIA), and severe, treatment-refractory, disabling psoriasis under certain conditions) as well as in oncology for the maintenance treatment of acute lymphoblastic leukaemia (ALL) under conditions.

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of Jylamvo and Nordimet, centrally authorised medicines containing methotrexate, together with nationally authorised medicines containing methotrexate, 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 methotrexate-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise existing wording for the interaction of methotrexate with nitrous oxide for medicinal products with at least one indication in oncology, to add 'injection site necrosis' as an undesirable effect with a frequency 'not known' for methotrexate-containing pre-filled syringes and pre-filled pens. In addition, the package leaflet is to be updated to reflect that contraindication in pregnancy only relates to non-oncologic indications for medicinal products with at least one indication in oncology. Therefore, the current terms of the marketing authorisations should be varied<sup>31</sup>.
- In the next PSUR, the MAH Medac should provide a cumulative review of cases of swelling to further substantiate the proposal to add swelling to the product information of low-dose methotrexate-containing products. Furthermore, the MAH is requested to provide a cumulative review of cases of paraesthesia/hypoesthesia to further substantiate the proposal to add paraesthesia/hypoesthesia to the product information as undesirable effects.
- In the next PSUR, MAH(s) of methotrexate-containing products with non-oncological indication(s) should provide a cumulative review and discussion on the use of liver biopsies for monitoring hepatotoxicity and a proposal to update the product information as warranted. In addition, MAHs for methotrexate-containing solutions in pre-filled syringes/pre-filled pens should provide a detailed review on all interval and cumulative cases of medication errors. Finally, MAHs of methotrexate-containing products should provide a cumulative review on exfoliative skin conditions and a proposal to update the product information as warranted.

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<sup>31</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

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. Sevelamer - RENAGEL (CAP), RENVELA (CAP), SEVELAMER CARBONATE WINTHROP (CAP); NAP - PSUSA/00002697/201810

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Applicant(s): Genzyme Europe BV (Renagel, Renvela, Sevelamer carbonate Winthrop), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

#### Background

Sevelamer, a non-absorbed phosphate binding crosslinked polymer free of metal and calcium, is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis as well as in adult patients with chronic kidney disease not on dialysis with serum phosphorus  $\geq 1.78$  mmol/L under certain conditions.

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of Renagel, Renvela and Sevelamer Carbonate Winthrop, centrally authorised medicines containing sevelamer, and nationally authorised medicines containing sevelamer, 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 sevelamer-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include crystal deposits in the intestine, gastrointestinal haemorrhage, intestinal ulceration, gastrointestinal necrosis, colitis and intestinal mass as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied<sup>32</sup>.
- In the next PSUR, the MAH should comment on the publication by *Birajdar et al.*<sup>33</sup>, *Uy et al.*<sup>34</sup>, *Okwara et al.*<sup>35</sup> and *Nambiar et al.*<sup>36</sup> and the possibility that the risk of gastrointestinal disorders associated with sevelamer crystals could be increased/aggravated when sevelamer is used concomitantly with acetylsalicylic acid.

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

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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

<sup>33</sup> Birajdar N, Dekate J, Reddy V, Anandh U. Colonic ulcerations in a patient on hemodialysis. *Indian J Nephrol.* 2018;28(4):329-30

<sup>34</sup> Uy PPD. Sevelamer-associated rectosigmoid ulcers in an end-stage renal disease patient presenting as hematochezia. 82nd annual scientific meeting of the American College of Gastroenterology; 10-18 Oct 2017, United States. *Am J Gastroenterol.* 2017;112(1):S1070-1

<sup>35</sup> Okwara CJ, Gulati R, Rustagi T, Birg A, Hanson J, McCarthy D. Upper gastrointestinal bleeding of unusual causation. *Dig Dis Sci.* 2018;63:2541-6

<sup>36</sup> Nambiar S, Pillai UK, Devasahayam J, Oliver T, Karippot A. Colonic mucosal ulceration and gastrointestinal bleeding associated with sevelamer crystal deposition in a patient with end stage renal disease. *Case Rep Nephrol.* 2018:4708068

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

See also Annex I 16.3.

#### 6.3.1. Acitretin (NAP) - PSUSA/00000051/201810

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

##### **Background**

Acitretin is a synthetic aromatic analogue of retinoic acid indicated for the treatment of severe forms of psoriasis including erythrodermic psoriasis and local or generalized pustular psoriasis, and other disorders of keratinisation such as congenital ichthyosis, pityriasis rubra pilaris, Darier's disease and lichen planus.

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing acitretin 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 acitretin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on increased levels of blood lipids and symptoms of pancreatitis. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>37</sup>.
- In the next PSUR, the MAH(s) should closely monitor cases of pancreatitis and provide a detailed review from all sources regarding the risk of pancreatitis. The MAHs should also propose to update 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.

#### 6.3.2. Dextromethorphan (NAP) - PSUSA/00001009/201811

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Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

##### **Background**

Dextromethorphan is a synthetic centrally acting, morphine-derivative compound indicated for the treatment of dry irritant cough.

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<sup>37</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

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dextromethorphan 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 dextromethorphan-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of drug abuse and drug dependence and on the risk of serotonin syndrome, and to also add information on overdose. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>38</sup>.
- In the next PSUR, the MAH(s) should provide a detailed review of cases of hypersensitivity reactions including anaphylactic shock and maculo-papular rash.

The PRAC agreed that the product information updates should be also implemented in the product information of all fixed-drug combination products containing dextromethorphan. Further consideration is to be given at the level of CMDh.

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

### **6.3.3. Letrozole (NAP) - PSUSA/00001842/201810**

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Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

#### **Background**

Letrozole is a non-steroidal aromatase inhibitor indicated for the treatment of hormone receptor positive invasive early breast cancer, hormone-dependent-invasive breast cancer, hormone-dependent advanced breast cancer, advanced breast cancer after relapse or disease progression and neo-adjuvant treatment of postmenopausal women with hormone receptor positive, human epidermal growth factor receptor 2 (HER-2) negative breast cancer, subject to certain conditions.

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing letrozole 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 letrozole-containing product(s) in the approved indication(s) remains unchanged.

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<sup>38</sup> Update of SmPC sections 4.4 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Nevertheless, the product information should be updated to include a warning on the risk of tendonitis and tendon rupture. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>39</sup>.
- In the next PSUR, the MAHs should provide a comprehensive review of skin dystrophies and sexual desire disorders, including data from the literature, clinical development and post marketing, and discuss the need for updating the product information as warranted.

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

#### 6.3.4. Methylphenidate (NAP) - PSUSA/00002024/201810

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

##### **Background**

Methylphenidate is a centrally acting sympathomimetic indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children between the ages of 6 and 18 and adults.

Based on the assessment of the periodic safety update report(s) (PSUR(s)), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing methylphenidate 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 methylphenidate-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on use in pregnancy based on data from a cohort study that did not suggest an increased risk of overall birth defects after intrauterine exposure in the first trimester. However, the risk of cardiac malformations could not be ruled out. In addition, the product information should be updated to include as undesirable effects bruxism with a frequency 'common' and incontinence and trismus with a frequency 'not known'. For medicinal product(s) indicated in adults, the frequency of the undesirable effect on excessive sweating should be updated to 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>40</sup>.
- In the next PSUR, the brand leaders MAHs Novartis/Sandoz and Janssen should provide a cumulative review on cases of stuttering, and discuss the need for updating the product information as warranted. All MAHs should include a cumulative review on drug

<sup>39</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>40</sup> Update of SmPC sections 4.6 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



abuse/misuse/diversion, and discuss the feasibility and proportionality of the implementation of additional risk minimisation measures. In addition, all MAHs should provide a cumulative review on neonatal adaptation after exposure to methylphenidate during pregnancy and make a proposal for updating the product information as applicable. Finally, all MAHs should review the effectiveness of the existing educational materials.

- All MAHs should update their risk management plan (RMP), within 90 days, taking into account the new core safety specification agreed by the PRAC, and should delete specific follow-up questionnaires.

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

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

### 6.4.1. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/LEG 066.3

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to LEG 066.1 [detailed study report of the retrospective analysis of extended interval dosing (EID) versus standard interval dosing (SID), a proposal for further investigation of efficacy and safety in terms of progressive multifocal leukoencephalopathy (PML) risk reduction with EID relative to SID, and updated pharmacokinetic/pharmacodynamic (PK/PD) modelling taking into account body weight and extended dosing intervals, as requested in the conclusions of PSUSA/00002127/201708 adopted by PRAC in March 2018] as per the request for supplementary information (RSI) adopted in January 2019

#### Background

Natalizumab is a selective immunosuppressive agent indicated, as Tysabri, as single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis for patients with a highly active disease despite a full and adequate course of treatment with at least one DMT or for patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in one year, and with one or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on the analysis of extended interval dosing (EID) versus standard interval dosing (SID). For background, see [PRAC minutes March 2019](#). The responses were assessed by the Rapporteur for further PRAC advice.

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

- The PRAC concurred that further analysis is needed in order to conclude on the safety of EID versus SID. The PRAC did not support updating the product information at this stage. Any follow up discussion and request for further analysis will be made as part of the ongoing type II variation procedure: II/0114.

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

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

See also Annex I 17.1.

#### 7.1.1. Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/J/0067.1

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Applicant(s): Fresenius Kabi Deutschland GmbH, B. Braun Melsungen AG

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to PSP/J/0067 [protocol for a joint 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 (EMEA/H/A-107i/1457)] as per the request for supplementary information (RSI) adopted in January 2019

#### 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 ([EMEA/H/A-31/1348](#)) and Article 107i of Directive 2001/83/EC ([EMEA/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 ([EMEA/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](#). The amended draft protocol for a joint non-interventional (PASS) was presented for review by the PRAC.

#### Endorsement/Refusal of the protocol

- The PRAC, having reviewed protocol version 4.0 in accordance with Article 107n of Directive 2001/83/EC, considered that the study is non-interventional and the amendments to the PASS protocol for HES-containing products are endorsed.

#### 7.1.2. Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/S/0068.1

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Applicant: Serumwerk Bernburg AG

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

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to PSP/S/0068 [protocol 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 (EMEA/H/A-107i/1457)] as per the request for supplementary information (RSI) adopted in January 2019

### **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 ([EMEA/H/A-31/1348](#)) and Article 107i of Directive 2001/83/EC ([EMEA/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 ([EMEA/H/A-107i/1457](#)) concluded in 2018, MAHs were required as a condition to the marketing authorisations ([Annex IV](#)) to implement additional risk minimisation measures.

The MAH Serumwerk Bernburg AG submitted to the EMA a protocol for a 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](#). The amended draft protocol for a non-interventional PASS was presented for review by the PRAC.

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

- The PRAC, having reviewed protocol version 2.2 in accordance with Article 107n of Directive 2001/83/EC, considered that the study is non-interventional and the amendments to the PASS protocol for HES-containing products are endorsed.

#### **7.1.3. Nomegestrol acetate, estradiol – ZOELY (CAP) - EMEA/H/C/PSA/S/0038**

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Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Protocol for a prospective observational study to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the risk of VTE in users of combined oral contraceptives (COCs)-containing levonorgestrel

### **Background**

Zoely (nomegestrol acetate/estradiol), is a centrally authorised medicine containing nomegestrol acetate/estradiol, a highly selective progestogen and a natural oestrogen identical to the endogenous human 17 $\beta$ -estradiol, respectively. Zoely (nomegestrol acetate/estradiol) is indicated for use as oral contraception.

The requirement to conduct a post-authorisation safety study (PASS) to further assess the risk of thromboembolic events is reflected in [Annex II-D](#) on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' of the marketing authorisation(s) of Zoely (norgestrel acetate/estradiol). Further to the conclusions dated 2013 of the referral procedure under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1356](#)) for combined oral contraceptives, the MAH for Zoely (norgestrel acetate/estradiol) submitted to the EMA a protocol for a prospective observational study to assess the risk of thromboembolic events in norgestrel/estradiol users. The MAH submitted an amended PASS protocol (version 3) to the EMA for Zoely (norgestrel acetate/estradiol) which was presented for review by the PRAC.

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

- The PRAC, having reviewed protocol version 3 in accordance with Article 107n of Directive 2001/83/EC, considered that the study is non-interventional and the substantial amendments to the PASS protocol for Zoely (norgestrel acetate/estradiol) are endorsed.

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

See Annex I 17.2.

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

See Annex I 17.3.

### **7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>44</sup>**

See also Annex I 17.4.

#### **7.4.1. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0035**

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Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study CMO-EPI-EYE-0522 (listed as a category 3 study in the RMP): an observational, cross-sectional study conducted in France, Germany, Spain, and the UK aiming at assessing the effectiveness of the educational material provided to treating physicians

#### **Background**

Ozurdex is a centrally authorised medicine containing dexamethasone, an anti-inflammatory corticosteroid as an intravitreal implant. Ozurdex (dexamethasone) is indicated for the treatment of adult patients with macular oedema following branch or central retinal vein occlusion (RVO) for the treatment of patients with visual impairment due to diabetic macular oedema who are pseudophakic or who are considered insufficiently

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<sup>42</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

<sup>43</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>44</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

responsive to, or unsuitable for non-corticosteroid therapy and for the treatment of patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

As requested in the risk management plan (RMP), the MAH conducted a non-imposed non-interventional PASS (CMO-EPI-EYE-0522) to assess the effectiveness of the educational material for Ozurdex (dexamethasone) provided to treating physicians. The Rapporteur assessed the MAH's final study report.

#### **Summary of advice**

- Based on the available data and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report could be recommended for approval, provided that satisfactory responses to a request for supplementary information (RSI) are submitted.
- The MAH is requested to submit to the EMA, within 30 days, responses to the RSI as agreed by the PRAC, including further clarifications on the survey data, a proposal for updating the product information, an updated version of the Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and an updated version of the RMP. The MAH should also discuss the grounds to recommend prophylactic antibiotic prior to Ozurdex (dexamethasone) injection and whether the product information should be amended accordingly.

#### **7.4.2. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0085**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study CNTO148ART4002 (listed as a category 3 study in the RMP): an observational phase 4 study using the Optum Research Database (ORD) to estimate the long-term safety profile in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) who are initiating Simponi (golimumab) treatment and/or other types of biologic and non-biologic treatments. The RMP (version 20.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems' in order to reflect changes in the categorisation of safety concerns. Annex II and Annex III-A on 'Labelling' of the product information are also updated to remove congestive heart failure and to add breakthrough infection after administration of live vaccine in infants exposed to golimumab in utero from the patient reminder card and labelling. Furthermore, the MAH took the opportunity to make some editorial changes in the product information

#### **Background**

Simponi is a centrally authorised medicine containing golimumab, an inhibitor of tumour necrosis factor alpha (TNF- $\alpha$ ). Simponi (golimumab) is indicated for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis (pJIA), psoriatic arthritis (PsA), axial spondyloarthritis, ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axial SpA) and ulcerative colitis (UC), subject to certain conditions.

As requested in the risk management plan (RMP) of Simponi (golimumab), the MAH conducted a non-imposed non-interventional PASS (CNTO148ART4002) to estimate the long-term safety profile in patients with RA, PsA and AS who are initiating Simponi (golimumab)

treatment and/or other types of biologic and non-biologic treatments. The Rapporteur assessed the MAH's final study report together with the responses from the MAH to the request for supplementary information (RSI). For further background, see [PRAC minutes January 2019](#) and [PRAC minutes April 2019](#).

#### **Summary of advice**

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report can be recommended for approval.
- The PRAC agreed with removing congestive heart failure (CHF) from the list of safety concerns of the RMP and the patient reminder card as the product information covers adequately CHF.

### **7.4.3. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0218**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final study report from the Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) cohort 2 portion of the registry: a German rheumatoid arthritis (RA) registry established as a prospective observational cohort study on the long-term safety and effectiveness of biologic disease-modifying anti-rheumatic drugs (DMARDs) in patients with RA. The RMP (version 19) is updated accordingly. The MAH also revised the RMP list of safety concerns as requested in the conclusions of procedure LEG 156 adopted in October 2017

#### **Background**

Remicade (infliximab) is a centrally authorised medicine containing infliximab, an inhibitor of tumour necrosis factor alfa (TNF- $\alpha$ ). Remicade (infliximab) is indicated for the treatment of rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis (UC), ankylosing spondylitis (AS), psoriatic arthritis and psoriasis, subject to certain conditions.

As requested in the risk management plan (RMP) of Remicade (infliximab), the MAH conducted a non-imposed non-interventional PASS from the RABBIT cohort 2 portion (German registry) on the long-term safety and effectiveness of biologic DMARDs in patients with RA. The Rapporteur assessed the MAH's final study report together with the responses from the MAH to the request for supplementary information (RSI). For further background, see [PRAC minutes January 2019](#) and [PRAC minutes April 2019](#).

#### **Summary of advice**

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report can be recommended for approval.
- The PRAC agreed with removing congestive heart failure (CHF) from the list of safety concerns of the RMP and the patient reminder card as the product information covers adequately CHF.

## **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.

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

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

See Annex I 18.1.

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

See Annex I 18.2.

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

See Annex I 18.3.

# **9. Product related pharmacovigilance inspections**

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

None

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

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

### 9.3. Others

None

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

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

#### 10.1.1. Tacrolimus – ADVAGRAF (CAP), MODIGRAF (CAP) - EMEA/H/C/WS1511/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: PRAC consultation on a grouped variation consisting of: 1) update of sections 4.5 and 4.8 of the SmPC to add the drug-drug interaction with letemovir and to add febrile neutropenia with a frequency 'unknown', based on a cumulative review of the MAH's safety database; 2) update of section 4.6 of the SmPC to add information on pregnancy and lactation following the cumulative review of the cases reported in the MAH's global safety database, published literature and the transplantation pregnancy exposure registry. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes throughout the product information and to implement the wording from the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

#### Background

Tacrolimus is a calcineurin inhibitor and immunosuppressant indicated, as Advagraf, for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and for the treatment of allograft rejection. It is also indicated, as Modigraf, for the prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients and for the treatment of allograft rejection, subject to certain conditions.

A type II worksharing variation proposing to update the product information of Advagraf (tacrolimus) and Modigraf (tacrolimus) on use during pregnancy and lactation is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

#### Summary of advice

- Based on the review of the available information, the PRAC noted that a substantial proportion of pregnancies from the registry were confounded by the concomitant administration of other teratogenic medicinal products. The PRAC considered the need for immunosuppressive treatment in transplant patients and the absence of clinical alternatives which are safe in pregnancy, and the information on use in pregnancy currently included in the product information of tacrolimus-containing products.
- The PRAC advised that an update of the product information was not currently warranted, with regard to information on the use in pregnancy, recommendations for women of child-bearing potential to use reliable contraception during treatment and recommendations for men to consider the use of appropriate contraception during treatment.



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

None

## 10.3. Other requests

### 10.3.1. Direct-acting oral anticoagulants (DOACs): apixaban – ELIQUIS (CAP); dabigatran etexilate – PRADAXA (CAP); rivaroxaban – XARELTO (CAP) - EMEA/H/A-5(3)/1478

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Applicant(s): Bayer AG (Xarelto), Boehringer Ingelheim (Pradaxa), Bristol-Myers Squibb Pharma EEIG (Eliquis)

PRAC Rapporteur: Ulla Wändel-Liminga

Scope: PRAC consultation on the review under Article 5(3) of Regulation (EC) No 726/2004 of the results of a study (EU PAS register 16014) commissioned by the EMA: an observational study assessing the risk of major bleedings with direct oral anticoagulants (DOACs): Eliquis (apixaban), Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban) when used to prevent blood clotting in patients with non-valvular atrial fibrillation (irregular rapid contractions of the heart), in comparison with other oral anticoagulants, using databases available in the EU

#### Background

Eliquis (apixaban), Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban) are direct-acting oral anticoagulants (DOACs) which are direct factor Xa inhibitors. They are indicated with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, and in combination with ASA for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

The PRAC was presented the results of a pharmacoepidemiology study<sup>45</sup> commissioned by the EMA (EU PAS register [EUPAS16014](#)), in the context of a review under [Article 5\(3\)](#) of Regulation (EC) No 726/2004 (EMEA/H/A-5(3)/1478). The study investigated the risk of major bleeding, such as gastrointestinal bleeding, intracranial bleeding and haemorrhagic stroke, associated with use of DOACs when compared to other oral anticoagulants (OACs), i.e. vitamin K antagonists (VKAs), in patients with non-valvular atrial fibrillation (NVAf) overall and in relevant clinical and demographical subgroups in a real-life setting; together with utilisation of DOACs in the EU for treatment of NVAf and prescribers' compliance with recommendations included in the product information of each DOAC.

#### Summary of advice

- Based on the available data, the PRAC agreed that, overall, the data assessed regarding bleeding risk and pattern do not bring substantial new knowledge in comparison with the currently described safety profile of these medicinal products, as reflected in their respective product information. The PRAC noted that bleedings and anaemia are included as undesirable effects for all DOACs with a frequency 'common'. The PRAC

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<sup>45</sup> Characterising the risk of major bleeding in patients with non-valvular atrial fibrillation: non-interventional study of patients taking direct oral anticoagulants in the EU

considered that further data are required from the authors of the pharmacoepidemiology study, in order to conclude on updating the product information on 'special warnings and precautions for use' with a recommendation for regular reviews of patients during treatment with a DOAC.

- The PRAC supported obtaining further clarifications from the authors on key points in relation to definition of contraindications in the different study databases, before a final conclusion on the need for additional measures, and on the type of measures, as well as communication of the study results, can be reached.

### 10.3.2. Doxorubicin hydrochloride

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PRAC Rapporteur: Eva Jirsová

Scope: PRAC consultation on mitigating the risk of medication error due to possible confusion between liposomal formulations and non-liposomal formulations

#### **Background**

Doxorubicin is an anthracycline cytotoxic agent indicated for the treatment of patients with metastatic breast cancer, advanced ovarian cancer, progressive multiple myeloma, and acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma, subject to certain conditions. Liposomal formulations of doxorubicin where the active substance is encapsulated into pegylated liposomes offer a reduced toxicity profile, especially doxorubicin-induced cumulative cardiotoxicity compared to the free drug formulation, due to their different biodistribution. Unlike free doxorubicin, pegylated liposomal doxorubicin is associated with low concentrations of doxorubicin in the circulation with limited distribution to the myocardium, resulting in a lower rate of cardiotoxicity compared to free doxorubicin. Given the difference in pharmacokinetic profiles and dosing schedules, liposomal formulations of doxorubicin should not be used interchangeably with other formulations of doxorubicin hydrochloride.

The CHMP requested advice from the PRAC, based on concerns about medication errors and product confusion between liposomal and non-liposomal doxorubicin formulations.

#### **Summary of advice**

- Based on the review of the available data, including EudraVigilance case reports, the PRAC agreed on the need to address the risk of medication errors between non-liposomal formulations and liposomal formulations of doxorubicin. The PRAC also highlighted the need to distinguish between pegylated and non-pegylated liposomal forms, as these have different pharmacokinetics (PK), dosing and safety profile. In order to avoid medication errors when prescribing, dispensing and administering doxorubicin containing products, the PRAC considered that healthcare professionals (HCPs) should be able to clearly distinguish between liposomal (pegylated and non-pegylated) and non-liposomal formulations of doxorubicin. The PRAC considered that this issue could be resolved through routine risk minimisation measures (RMMs), with a focus on differentiation by means of the product naming strategy. Moreover, the PRAC considered that any other risk minimisation measures (RMMs) should be routine and applied consistently across medicinal products.
- The PRAC agreed that the approach endorsed by CHMP and CMDh for doxorubicin should also apply to other medicinal products where liposomal (pegylated and non-pegylated)/non-liposomal formulations co-exist with different risk for each formulation.

Applicant(s): Guerbet (Optimark) on behalf of a consortium

PRAC Rapporteur: Patrick Batty

Scope: PRAC consultation on the assessment of the interim analysis report for study ALS-Gd64/001: exploratory evaluation of the potential for long-term retention in the bone of gadolinium (Gd) in the bones of patients who have received Gd-based contrast agents (GdCAs): gadoversetamide, gadoteric acid-, gadobutrol-, gadoxetic acid-, gadopentetic acid- and gadodiamide-containing medicinal products, according to their medical history

#### **Background**

Gadolinium containing contrast agents (GdCAs) are chemical complexes of gadolinium and different types of chelators used as contrast enhancers in magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA).

The PRAC was consulted on the interim analysis report of study ALS-Gd64/001 which aimed to address the condition to evaluate the potential for long-term accumulation of gadolinium in human bone, resulting from the referral procedure concluded in 2010 under Article 31 of Directive 2001/83/EC on GdCAs ([EMEA/H/A-31/1097](#)). For further background, see [PRAC minutes June 2016](#). The PRAC is responsible for providing advice to CHMP on request.

#### **Summary of advice**

- Based on the available limited interim study results, the PRAC considered that the levels of gadolinium in skin were low for all GdCAs and in terms of bone accumulation, macrocyclic agents showed low deposition levels, which for the majority of patients exposed to macrocyclic agents were within the range in the unexposed control group. The PRAC agreed that an update of the product information for GdCAs, namely gadoversetamide-, gadoteric acid-, gadobutrol-, gadoxetic acid-, gadopentetic acid- and gadodiamide-containing products was currently not warranted.
- The PRAC considered that sufficient data have been collected in the study for a final report to be submitted, and requested that the MAHs should submit this final report. The final report should include full clinical data from the study and a discussion of the results in light of the available literature on bone and skin retention of gadolinium.

## **10.4. Scientific Advice**

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

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

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

None

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<sup>46</sup> Marketing authorisation(s) expired on 25 July 2017

## 11.2. Other requests

### 11.2.1. Fingolimod - FI/H/1028/001/DC

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PRAC Lead: Kirsti Villikka

Scope: PRAC consultation on the evaluation of initial marketing authorisation application(s) under the decentralised procedure for generic fingolimod-containing medicinal products on request of Finland

#### Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated as single disease modifying therapy (DMT) in highly active relapsing remitting multiple sclerosis (RRMS) for adult patients and paediatric patients aged 10 years and older under certain conditions.

In the context of the evaluation of initial marketing authorisation application (MAA) procedure for generic fingolimod-containing products, Finland requested PRAC advice on its assessment.

#### Summary of advice

- Based on the review of the available information, the PRAC supported the assessment from Finland
- The PRAC agreed that companies of generic fingolimod-containing products should align their additional risk minimisation measures (RMMs), with special focus on educational materials, with the originator medicinal product containing fingolimod.

### 11.2.2. Iron complex<sup>47</sup>:

Ferric carboxymaltose (NAP); iron (III) isomaltoside 1000 (NAP); iron(III)-hydroxide sucrose (NAP)

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Applicant(s): Vifor France (Ferinject, Monofer, Venofer)

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on the evaluation of annual reports of hypersensitivity reactions, fatal cases and pregnancy cases, as required in the conclusions of the referral procedure on iron-containing products<sup>48</sup> under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1322) concluded in 2013, on request of Sweden

#### Background

Ferric carboxymaltose, iron (III) isomaltoside 1000 and iron(III)-hydroxide sucrose are parenteral iron products indicated for the treatment of iron deficiency anaemia and other types of anaemias.

Further to the conclusions of a referral procedure on intravenous (IV) iron-containing products under Article 31 of Directive 2001/83/EC concluded in 2013 ([EMEA/H/A-31/1322](#)), MAHs of iron gluconate- (sodium ferric gluconate), iron sucrose-, iron dextran-, iron (ferric) carboxymaltose-, and iron (III) isomaltoside 1000-containing products were required to submit, as a condition to the marketing authorisations, annual cumulative reviews of

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<sup>47</sup> For intravenous (I.V.) use only

<sup>48</sup> Iron complex: iron gluconate (sodium ferric gluconate), iron sucrose, iron dextran, iron (ferric) carboxymaltose, and iron (III) isomaltoside 1000

hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data.

In the context of the evaluation of annual reports of hypersensitivity reactions, fatal cases and pregnancy cases for iron complex products- iron gluconate (sodium ferric gluconate), iron sucrose, iron dextran, iron (ferric) carboxymaltose and iron (III) isomaltoside 1000, Sweden requested PRAC advice on its assessment.

#### **Summary of advice**

- Based on the review of the available information, the PRAC supported the assessment from Sweden and concurred that that continued submissions of annual cumulative reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases for iron complex products<sup>49</sup> are no longer useful. The PRAC confirmed that submissions and assessment of these data sets should continue within PSURs from the respective MAHs. MAHs should maintain consistency in the presentation of data across the class, including continuing to use the same data lock point (DLP), exposure and event definitions and classification of severity for the different products.
- The MAHs should submit a variation to the relevant National Competent Authorities (NCAs) of the Member States, to remove this specific condition from their respective marketing authorisation. All other conditions should remain unchanged and be adhered to in line with agreed timelines. Further consideration is to be given at the level of the CMDh.

## **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**

None

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

None

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

None

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<sup>49</sup> Apply to all parenteral iron-complex medicinal products which were part of the referral procedure under Article 31 of Directive 2001/83/EC and which have submissions of annual cumulative reviews of such data as a specific condition to their respective marketing authorisation(s)

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

None

## **12.7. PRAC work plan**

None

## **12.8. Planning and reporting**

None

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

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

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None

### **12.9.2. Pharmacovigilance inspections**

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None

### **12.9.3. Pharmacovigilance audits**

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None

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

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

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None

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

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PRAC Lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list. The PRAC also adopted the 'reflection of biological reference products and biosimilars in the EURD list - guidance when to consider separate entries'.

### **12.10.3. Periodic safety update reports single assessment (PSUSA) – Joint PRAC/CMDh action group on 'other consideration' section – call for volunteers**

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The MEA Secretariat launched a call for volunteers for enriching the joint PRAC/CMDh action group, a dedicated group of PRAC and CMDh members and pharmacovigilance assessors set up to review the wording and criteria for inclusion of topics in the section dedicated to 'other consideration' in periodic safety update report (PSUR) single assessment (PSUSA) assessment report. Members were invited to express interest by 24 June 2019.

Post-meeting note: Martin Huber, Michal Radik, Jana Lukacisinova and Menno van der Elst

volunteered to be part of the joint PRAC/CMDh action group to review the section on 'other consideration'.

#### **12.10.4. PSURs repository**

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None

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

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The PRAC endorsed the draft revised EURD list, version June 2019, 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 June 2019, the updated EURD list was adopted by the CHMP and the CMDh at their June 2019 meetings and published on the EMA website on 12 July 2019, 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 June 2019 SMART meeting was cancelled.

### **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 26 June 2019, 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

### **12.15.3. Post-authorisation Safety Studies - Guidance for assessors to request the conduct of a PASS**

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PRAC Lead: Ulla Wändel Liminga

The PRAC was provided with guidance on the aspects to be considered for requesting a post-authorisation safety study (PASS) to ensure that studies will be feasible and bring meaningful results, including the need for additional data, the time frame for obtaining results and the expectation of meaningful data for regulatory decisions. Further discussion will take place at the PRAC strategic review and learning meeting (SRLM) organised in Helsinki, Finland in October 2019 under the auspices of the Finnish presidency of the European Union (EU).

## **12.16. Community procedures**

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

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None

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

None



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

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

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None

### **12.18.2. Safety communication**

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None

## **12.19. Continuous pharmacovigilance**

### **12.19.1. Incident management**

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None

## **12.20. Others**

### **12.20.1. Strategy on measuring the impact of pharmacovigilance - PRAC interest group (IG) Impact – update on activities**

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PRAC Lead: Antoine Pariente

The PRAC was given an update on the interest group's activities over the past 18 months following the appointment of its new chair and discussed the future direction of the group's work.

The EMA Secretariat announced that Antoine Pariente was appointed as the new Chairperson of the PRAC interest group (IG) impact, taking over from Valerie Strassmann. The PRAC thanked her for her contribution to the IG and overall to the PRAC over the years.

## **13. Any other business**

None

## **14. Annex I – Signals assessment and prioritisation<sup>50</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>51</sup>.

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<sup>50</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 Procedures). 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>51</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

#### 14.1.1. Azacitidine – VIDAZA (CAP)

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Applicant(s): Celgene Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

**Action:** For adoption of PRAC recommendation

EPITT 19422 – New signal

Lead Member State(s): NL

#### 14.1.2. Durvalumab – IMFINZI (CAP)

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Applicant(s): AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of pemphigoid

**Action:** For adoption of PRAC recommendation

EPITT 19416 – New signal

Lead Member State(s): NO

#### 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 gastrointestinal ulcer

**Action:** For adoption of PRAC recommendation

EPITT 19427 – New signal

Lead Member State(s): NL

### 14.2. New signals detected from other sources

## 15. Annex I – Risk management plans

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

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

#### 15.1.1. Azacitidine - EMEA/H/C/005300

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Scope: Treatment of myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML)

#### [15.1.2. Bortezomib - EMEA/H/C/005074](#)

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Scope: Treatment of multiple myeloma

#### [15.1.3. Clopidogrel, acetylsalicylic acid - EMEA/H/C/004996](#)

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Scope: Secondary prevention of atherothrombotic events

#### [15.1.4. Lacosamide - EMEA/H/C/005243](#)

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Scope: Treatment of epilepsy

#### [15.1.5. Rituximab - EMEA/H/C/005387](#)

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Scope: Treatment of non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL)

#### [15.1.6. Rituximab - EMEA/H/C/004807](#)

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Scope: Treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis

### **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. Adalimumab - HULIO \(CAP\) - EMEA/H/C/004429/II/0009](#)

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Applicant: Mylan S.A.S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 2.2) to modify the post-authorisation measure (listed as a category 3 study in the RMP): a longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies, proposing to use the Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) registry instead of the initially identified British Society for Rheumatology Biologics Register- Rheumatoid Arthritis (BSRBR-RA)

#### [15.2.2. Apremilast - OTEZLA \(CAP\) - EMEA/H/C/003746/II/0023](#)

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Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated the RMP (version 11.0) in order to reclassify and/or rename the known safety concerns associated with the use of Otezla (apremilast) in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

### 15.2.3. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/II/0016

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 4.0) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the MAH implemented the changes requested in the conclusions of MEA 003.3 adopted at the November 2018 PRAC meeting (held on 29-31 October 2018)

### 15.2.4. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0064

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated of the RMP (version 16.0) to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template) and consequential removal of the food interaction and drug-drug interactions (DDI) from the list of important identified risks. In addition, 'drug reaction with eosinophilia and systemic symptoms (DRESS)' is reclassified from important potential risk to important identified risk as requested in the conclusions of PSUSA/00000939/201710 procedure adopted in May 2018. Furthermore, the healthcare professional (HCP) guide is also updated. The MAH took the opportunity to include minor changes throughout the RMP

### 15.2.5. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0013

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 4.0-s1) to remove exposure during lactation as missing information based on a literature review

### 15.2.6. Human normal immunoglobulin - KIOVIG (CAP) - EMEA/H/C/000628/II/0091

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 9.0) in order to include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as a new indication and update the list of safety concerns to bring it in line with revision 2 of GVP module V on 'Risk management systems'

### 15.2.7. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0024

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 11.1) in order to update the study design for study E7080-G000-218 (MEA 007): a randomised, phase 2 trial to assess safety and efficacy of lenvatinib at two different starting doses (18 mg vs. 14 mg one a day (QD)) in combination with everolimus (5 mg QD) in renal cell carcinoma following one prior vascular

endothelial growth factor (VEGF)-targeted treatment; from double-blind to open label as requested in the conclusion of MEA 006.1 adopted by the CHMP in February 2019. In addition, the MAH took the opportunity to introduce minor administrative changes to the RMP

#### 15.2.8. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0051, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 19) in order to reflect deletion/changes in the categorisation of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the RMP is updated to reflect the change of categorisation of posterior reversible encephalopathy syndrome (PRES) as requested in the conclusions of PSUSA/00010128/201712 procedure adopted in July 2018; to correct the categorisation of study AP24534-14-203; a randomised, open-label, phase 2 trial of ponatinib in patients with resistant chronic phase chronic myeloid leukaemia to characterise the efficacy and safety of a range of doses, from a category 3 study to category 1 study in the RMP and Annex II and to revise the due date for the submission of its study report to August 2021, as described in the product information and as agreed in the conclusions of ANX 016 procedure adopted by the CHMP in September 2017

#### 15.2.9. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/II/0034

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 8.0) in order to remove 'bleeding disorders' as an important potential risk as requested in the conclusions of PSUSA/00009282/201805 procedure adopted in January 2019. In addition, the MAH took the opportunity to reflect changes in the categorisation of safety concerns and remove/reclassify additional pharmacovigilance activities (category 4) in line with revision 2 of the guidance on the format of RMP in the EU (template)

#### 15.2.10. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/II/0031

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 6.0) in order to implement changes in line with revision 2 of the guidance on the format of RMP in the EU (template) and to introduce changes to pre-clinical, clinical and post-marketing exposure information, and to update the due date of drug utilisation study (DUS) Z7219N02: a European multicentre retrospective-prospective cohort study to observe safinamide safety profile and pattern of use in clinical practice during the first post-commercialisation phase; from July 2019 to 28 February 2020

### 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. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/X/0019/G

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to introduce a new presentation of 40 mg/0.8 mL solution for injection in vials, to allow the administration to paediatric patients requiring less than a full 40 mg dose; 2) update of the product information for the pre-filled syringe (EU/1/17/1216/001-004) and pre-filled pen (EU/1/17/1216/005-008) presentations in line with the dosage regimen changes introduced with the extension application. The RMP (version 3.0) is updated accordingly. In addition, the applicant took the opportunity to implement minor editorial changes in Module 3.2. Quality - Product

#### 15.3.2. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0047, Orphan

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Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include non-ambulatory patients with Duchenne muscular dystrophy. As supportive data, the variation includes the final results of the long term clinical study PTC-124-GD-019-DMD: an open-label study for previously treated ataluren (PTC124) patients with nonsense mutation dystrophinopathy. 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 8.0) are updated accordingly

#### 15.3.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0062

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include patients aged 5 years and older in the current approved indication for the powder for solution for infusion 120 mg/mL and 400 mg/mL based on the results of study BEL114055: a multicentre, randomised parallel group, placebo-controlled double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of belimumab, a human monoclonal anti-BLyS antibody, plus standard therapy in paediatric patients with systemic lupus erythematosus (SLE). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated with safety and efficacy information. In addition, sections 4.2, 5.1 and 5.2 of the SmPC for the solution for injection in pre-filled pen and pre-filled syringe, 200 mg are updated to reflect the paediatric data available for the intravenous formulation. The package leaflet is updated accordingly. Furthermore, the RMP (version 28.0) is updated accordingly and with revision 2 of the guidance on the format of RMP in the EU (template). Finally, the MAH took the opportunity to introduce some editorial changes in the product information and bring it in line with the latest quality review

document (QRD) template (version 10.0)

#### 15.3.4. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0067

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.1 of the SmPC based on final results from study BEL115471/HGS1006-C1112 (listed as a category 3 study in the RMP): a phase 3/4, multicentre, randomised, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab in African-American/Black subjects with systemic lupus erythematosus. The RMP (version 31) is updated accordingly

#### 15.3.5. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/II/0041

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Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Extension of indication to include paediatric patients from birth to less than 2 months old based on results from study D3720C00009 (C2661002) an open-label, multicentre study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline in neonates and young infants with late-onset sepsis. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, the package leaflet and the RMP (version 17.0) are updated accordingly

#### 15.3.6. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/II/0043

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Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Update of section 4.2 of the SmPC in order to provide dosing recommendations for a high-dose regimen of ceftaroline fosamil in paediatric patients from 2 months to less than 18 years of age for the treatment of complicated skin and soft tissue infections (cSSTI) for which *Staphylococcus aureus* is known or suspected of having minimum inhibitory concentrations (MIC) of 2 or 4 mg/L based on the final study report of extrapolation study PMAR-EQDD-C266b-DP4-826. The RMP (version 18.0) is updated accordingly

#### 15.3.7. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1539/0029; FORXIGA (CAP) - EMEA/H/C/002322/WS1539/0048; dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS1539/0035; XIGDUO (CAP) - EMEA/H/C/002672/WS1539/0046

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Worksharing variations consisting of an update of sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC of Forxiga (dapagliflozin), Edistride (dapagliflozin), Xigduo (dapagliflozin/metformin) and Ebymect (dapagliflozin/metformin) in order to modify the current indication for improvement of glycaemic control based on final results from study D1693C00001 (DECLARE) (listed as a category 3 study in the RMP): 'dapagliflozin effect on cardiovascular events a multicentre, randomised, double-blind, placebo-controlled trial to

evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes' for the prevention of new or worsening heart failure (HF) or cardiovascular (CV) death and for the prevention of new or worsening nephropathy. The package leaflets are updated accordingly. The RMPs for Edistride and Forxiga (version 17) and Ebymect and Xigduo (version 11) are updated accordingly. In addition, the MAH took the opportunity to update the warning on lactose in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. The MAH also took the opportunity to introduce minor editorial changes in the product information

#### **15.3.8. Docetaxel - DOCETAXEL ZENTIVA (CAP) - EMEA/H/C/000808/WS1550/0058; TAXOTERE (CAP) - EMEA/H/C/000073/WS1550/0131**

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Applicant: Aventis Pharma S.A.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone, for the treatment of patients with metastatic hormone-sensitive prostate cancer for Taxotere (docetaxel) and Docetaxel Zentiva (docetaxel). As a consequence, sections 4.1, 4.2, 4.4 and 4.8 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly. In addition, the MAH took the opportunity to update information impacting the local representatives in the package leaflet

#### **15.3.9. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0017**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include a new indication in adult patients with chronic rhinosinusitis with nasal polyposis. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly

#### **15.3.10. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0049**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia. 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 50.0) are updated accordingly

#### **15.3.11. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/II/0009/G**

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Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 5.2 of the SmPC



in order to update the safety information based on results from pharmacokinetic (PK) study ELX-PK-01 (listed as a category 3 study in the RMP): a single-dose, open-label, PK study of eluxadoline in healthy subjects with normal renal function and patients with renal impairment; 2) update of sections 4.4 and 4.8 of the SmPC following an update of the company core data sheet (CCDS) based on the review of clinical safety data and post-marketing safety data. In addition, the MAH took the opportunity to introduce minor changes throughout the SmPC, in particular the MAH updated section 4.3 to add clarification in line with section 4.4 as well as section 5.1 to add the pharmacotherapeutic group and anatomical therapeutic chemical (ATC) code. The package leaflet and the RMP (version 3.0) are updated accordingly

#### 15.3.12. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/X/0004

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Extension application to add a new strength of 100 mg/mL solution for injection in pre-filled syringe for Emgality (galcanezumab) associated with a new indication to include treatment of episodic cluster headache. The RMP (version 1.1) is updated accordingly

#### 15.3.13. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/II/0015

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 4.5 of the SmPC in order to remove the statement on potential drug interactions with drugs that inhibit organic cation transporter 1 (OCT1) based on the final results from study V8953M-SPD503: a non-clinical study on transporter interaction - OCT1 inhibition. The RMP (version 3.0) is updated accordingly

#### 15.3.14. Human normal immunoglobulin - FLEBOGAMMA DIF (CAP) - EMEA/H/C/000781/II/0059/G

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC for Flebogamma DIF (human normal immunoglobulin) 100 mg/mL in order to update the safety information based on the final results from study IG0601: A multicentre, prospective, open-label, clinical trial to assess the safety and the efficacy of a new intravenous immune globulin (IGIV3I Grifols 10%) in patients with idiopathic (immune) thrombocytopenic purpura. The package leaflet is updated accordingly; 2) update of section 4.8 of the SmPC to revise the adverse drug reactions for both strengths based on all completed studies previously submitted. The package leaflet is updated accordingly; 3) update of SmPC according to the 'Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg)' (EMA/CHMP/BPWP/94038/2007 Rev. 5) which came into effect on 01 January 2019. The package leaflet and the RMP (version 7.0) are updated accordingly

### 15.3.15. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0046, Orphan

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include treatment of adult patients with Waldenström's macroglobulinaemia (WM) in combination with rituximab, based on the results of the final clinical study report of study PCYC-1127-CA: a randomised, double-blind, placebo-controlled, phase 3 study of ibrutinib or placebo in combination with rituximab in subjects with WM (iNNOVATE study). As a consequence, sections 4.1 and 4.8 of the SmPC are updated accordingly. The RMP (version 12) is updated accordingly. In addition, the MAH took the opportunity to update the SmPC and package leaflet with minor editorial/administrative changes

### 15.3.16. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0047, Orphan

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to extend the existing indication on chronic lymphocytic leukaemia (CLL) to include the combination use with obinutuzumab for the treatment of adult patients with previously untreated CLL, based on the data from study PCYC-1130-CA: a randomised, multicentre, open-label, phase 3 study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in subjects with treatment-naïve CLL or small lymphocytic lymphoma. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 12) are updated accordingly. In addition, the MAH took the opportunity to update the SmPC and package leaflet with minor editorial/administrative changes

### 15.3.17. Insulin aspart - FIASP (CAP) - EMEA/H/C/004046/II/0010

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of children and adolescents aged 1 year and above based on data from study NN1218-4101: a phase 3b study on efficacy and safety of faster-acting insulin aspart compared to Novorapid (insulin aspart) both in combination with insulin degludec in children and adolescents with type 1 diabetes; supported by data from study NN1218-4371: a trial comparing the pharmacokinetic properties of fast-acting insulin aspart between children, adolescents and adults with type 1 diabetes; and study NN1218-3888: a trial investigating the pharmacokinetic properties of Fiasp (insulin aspart) in children, adolescents and adults with type 1 diabetes. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the corresponding sections of the package leaflet are updated accordingly. In addition, the MAH took the opportunity to introduce other non-related minor or editorial changes throughout the product information to increase readability/consistency

### 15.3.18. Insulin glargine - TOUJEO (CAP) - EMEA/H/C/000309/II/0108

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Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the treatment of diabetes mellitus in adolescents and children from the age of 6 years based on the 6-month on-treatment data of study EFC13597: a 6-month, multicentre, randomised, open-label, 2-arm, Parallel-group study comparing the efficacy and safety of a new formulation of insulin glargine and Lantus (insulin glargine) injected once daily in children and adolescents age 6-17 years with type 1 diabetes mellitus (T1DM) with a 6-month safety extension period study. 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 6.0) are updated accordingly

### 15.3.19. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/II/0011

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment in combination with metformin of adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or basal insulin, based on phase 3 study EFC13794: a 26-week randomised, open-label, active controlled, parallel-group study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with type 2 diabetes inadequately controlled on glucagon-like peptide-1 (GLP-1) receptor agonist and metformin (alone or with pioglitazone and/or sodium-glucose co-transporter-2 (SGLT2) inhibitors), followed by a fixed ratio combination single-arm 26-week extension period. 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 4.0) are updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in Denmark, the Netherlands and the UK in the package leaflet and to implement minor editorial changes in the Annexes

### 15.3.20. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0064

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC in order to update the safety information following final results from study CA184143 (listed as a category 3 study in the RMP (post-authorisation measure MEA 017.11)): a multi-national, prospective, observational study in patients with unresectable or metastatic melanoma. The RMP (version 26.0) is updated accordingly. In addition, the MAH took the opportunity to update the RMP in regards to already assessed MEA 036.1 concerning protocol synopsis on the extension of the Dutch Melanoma Treatment Registry (DMTR) to paediatric melanoma patients treated with ipilimumab. Furthermore the MAH took the opportunity to request a 6-month shift in the dates associated to the next implementation steps of the DMTR extension (registration of paediatric patients in the DMTR register and final clinical study report (CSR) submission). Finally, the MAH introduced some editorial changes in section 5.1 of the SmPC to provide

more clarity on whether studies relate to melanoma or renal cell carcinoma (RCC) and to monotherapy or combination therapy with nivolumab

#### 15.3.21. [Lacosamide - VIMPAT \(CAP\) - EMEA/H/C/000863/II/0073/G](#)

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.5 and 4.8 of the SmPC in order to include new safety information on cardiac arrhythmias based on safety signal assessment report (SSAR); 2) update of section 4.8 of the SmPC to update the frequency of some adverse events (AEs) based on data obtained from the updated safety pool analysis (Pool DBC-1) which consists of the combined data from SP667, SP754, SP755, and EP0008. All of these studies were randomised, double-blind, placebo-controlled, parallel-group, adjunctive therapy studies in subjects with epilepsy. The package leaflet and the RMP (version 13.0) are updated accordingly

#### 15.3.22. [Liraglutide - VICTOZA \(CAP\) - EMEA/H/C/001026/II/0049](#)

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of children and adolescents (age 10-17 years) with type 2 diabetes mellitus (T2DM) based on results from: 1) study NN2211-1800: a phase 1 clinical pharmacology, multicentre, randomised, double-blind placebo controlled trial, and 2) study NN2211-3659: a phase 3a efficacy and safety, multicentre, randomised, parallel group, placebo controlled trial with a 26-week double blind period followed by a 26-week open label period (main part). 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 30) are updated accordingly. Furthermore, the MAH took the opportunity to include a warning on sodium in section 4.4 of the SmPC and the package leaflet in line with the revised European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

#### 15.3.23. [Methoxy polyethylene glycol-epoetin beta - MIRCERA \(CAP\) - EMEA/H/C/000739/II/0068](#)

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report for study BH21260 (listed as a category 3 study in the RMP): a randomised, controlled, open-label, multicentre, parallel-group study to assess all-cause mortality and cardiovascular morbidity in patients with chronic kidney disease (CKD) on dialysis and those not on renal replacement therapy under treatment with Mircera (methoxy polyethylene glycol-epoetin beta) or erythropoiesis-stimulating agents (ESAs) of reference (in fulfilment of post-approval commitment MEA 008.5). The RMP (version 12.0) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

#### 15.3.24. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0026, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include a new indication for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to introduce minor linguistic corrections to the Annexes in French and Swedish

#### 15.3.25. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0014, Orphan

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study SM202 (EMBRACE or CS7) (listed as a category 3 study in the RMP): a phase 2, randomised, double-blind, sham-procedure-controlled study to assess the safety and tolerability and explore the efficacy of nusinersen (ISIS 396443 (BIIB058)) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in clinical studies ISIS 396443-CS3B: a phase 3, randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of nusinersen administered intrathecally in patients with infantile-onset spinal muscular atrophy; or ISIS 396443-CS4: a phase 3, randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of nusinersen administered intrathecally in patients with later-onset spinal muscular atrophy; due to age at screening and/or survival motor neuron 2 (SMN2) copy number. The RMP (version 10.1) is updated accordingly

#### 15.3.26. Palbociclib - IBRANCE (CAP) - EMEA/H/C/003853/II/0019/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of section 4.8 of the SmPC in order to include interstitial lung disease (ILD)/pneumonitis as adverse drug reactions (ADRs) based on a safety cumulative review together with a reclassification of the risk from potential to be identified in the RMP. The package leaflet and the RMP (version 1.6) are updated accordingly. The MAH also submitted the updated RMP in order to remove long term use from missing information in the list of safety concerns. In addition, the MAH proposes to change the due date for the submission of the final clinical study report (CSR) of study A5481027 (listed as a category 3 study in the RMP): a multicentre, randomised, double-blind phase 3 study of palbociclib (oral cyclin-dependent kinase (CDK) 4/6 inhibitor) plus letrozole versus placebo plus letrozole for the treatment of previously untreated Asian post-menopausal women with estrogen receptor (ER) (+), human epidermal growth factor receptor 2 (HER2) (-) advanced breast cancer

#### 15.3.27. Pasireotide - SIGNIFOR (CAP) - EMEA/H/C/002052/II/0041/G, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.8 of the SmPC based on the final clinical study report (CSR) from study CSOM230B2219 (listed as a category 3 study in the RMP): a multicentre, randomised, open-label, phase 4 study to investigate the management of pasireotide-induced hyperglycaemia with incretin based therapy or insulin in adult patients with Cushing's disease or acromegaly. The RMP (version 7.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

#### 15.3.28. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0029

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to reflect the outcome of study D5160C00035 (listed as a category 3 study in the RMP): an open-label, phase 1 study to assess the pharmacokinetics, safety and tolerability of osimertinib following a single oral 80 mg dose to patients with advanced solid tumours and normal renal function or severe renal impairment. The RMP (version 13) is updated accordingly

#### 15.3.29. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0027

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Cyramza (ramucirumab) as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alfa fetoprotein (AFP)  $\geq$  400 ng/mL, after prior sorafenib therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.1) are updated accordingly

#### 15.3.30. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0076

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) 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 the RMP (version 19.0) are updated accordingly

#### 15.3.31. Rufinamide - INOVELON (CAP) - EMEA/H/C/000660/II/0052, Orphan

Applicant: Eisai GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section 4.2 of the SmPC in order to include an additional method of administration via feeding tube for Inovelon (rufinamide) oral suspension, as requested in the conclusions of variation II/45 adopted by CHMP in June 2018. The RMP (version 11) is updated accordingly

### 15.3.32. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/II/0024

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Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC with information on the glycaemic efficacy and renal safety of dapagliflozin in patients with type 2 diabetes mellitus (T2DM) and moderate renal impairment (chronic kidney disease (CKD) 3A) based on final results from study D1690C00024 (DERIVE) (dapagliflozin): a multicentre, Double-blind, placebo-controlled, parallel group, randomised, phase 3 study to evaluate the glycaemic efficacy and renal safety of dapagliflozin in patients with T2DM and CKD 3A who have inadequate glycaemic control, and to reflect a change in renal cut-off value for saxagliptin. The package leaflet and the RMP (version 4.1) are updated accordingly. In addition, the MAH took the opportunity to update section 2, 4.8, 5.2 of the SmPC and Annex II to include the required excipient information in relation to sodium levels and lactose following the update to the Annex to the European Commission (EC) guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', as well as to bring the product information in line with EMA guidance on 'Compilation of quality review of documents (QRD) decisions on stylistic matters in product information' (EMA/25090/2002 Rev.18)

### 15.3.33. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/II/0022

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Update of Sections 4.2, 4.4 and 4.5 of the SmPC in order to update the safety information based on the final results from study AC-065-117 (listed as a category 3 study in the RMP): clinical pharmacology drug-drug interaction (DDI) study evaluating the effect of clopidogrel a moderate inhibitor of CYP2C8<sup>52</sup>, on the pharmacokinetics of selexipag and its active metabolite ACT-333679. The package leaflet and the RMP (version 6.1) are updated accordingly. In addition, the MAH took the opportunity to correct minor discrepancies in the SmPC

### 15.3.34. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS1518/0055; sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/WS1518/0077; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS1518/0034; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/WS1518/0025

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Worksharing variation to update sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Eplclusa (sofosbuvir/velpatasvir) and Harvoni (sofosbuvir/ledipasvir), sections 4.2, 4.4, 5.1 and 5.2 for Sovaldi (sofosbuvir) and sections 4.2, 4.8 and 5.2 for Vosevi (sofosbuvir/velpatasvir/voxilaprevir) in order to add new information regarding the use of sofosbuvir-containing products in patients with renal impairment, based on the final results from studies: 1) GS-US-342-4062 (listed as a category 3 study in the RMP): a phase 2,

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<sup>52</sup> Cytochrome P450 2C8

multicentre, open-label study to evaluate the efficacy and safety of sofosbuvir/velpatasvir for 12 weeks in subjects with chronic hepatitis C virus (HCV) infection who are on dialysis for end stage renal disease; 2) GS-US-337-4063 (listed as a category 3 study in the RMP): a phase 2, multicentre, open-label study to evaluate the efficacy and safety of ledipasvir/sofosbuvir in subjects with genotype 1, 4, 5 and 6 chronic HCV infection who are on dialysis for end stage renal disease; 3) GS-US-334-0154 (listed as a category 3 study in the RMP): a phase 2b, open label study of 200 mg or 400 mg Sofosbuvir+ribavirin for 24 weeks in genotype 1 or 3 HCV infected subjects with renal insufficiency; 4) study GS-US-338-1125: a phase 1, open-label, parallel-group, single-dose study to evaluate the pharmacokinetics of voxilaprevir in subjects with normal renal function and severe renal impairment. The package leaflet is updated accordingly. The RMPs for Eplclusa (version 4.1), Harvoni (version 5.1), Sovaldi (version 8.1) and Vosevi (version 2.1) are updated accordingly

#### 15.3.35. Teriparatide - MOVYMIA (CAP) - EMEA/H/C/004368/II/0010

Applicant: Stada Arzneimittel AG

PRAC Rapporteur: Ronan Grimes

Scope: Submission of the final clinical study report from study RGB1023031: a phase 3, multicentre, randomised, active-controlled, parallel-group, comparative study to evaluate the efficacy and safety of Movymia (teriparatide) to the originator medicinal product containing teriparatide in patients with osteoporosis at high risk of fracture. The RMP (version 1.3) is updated accordingly

#### 15.3.36. Teriparatide - TERROSA (CAP) - EMEA/H/C/003916/II/0009

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ronan Grimes

Scope: Submission of the final clinical study report from study RGB1023031: a phase 3, multicentre, randomised, active-controlled, parallel-group, comparative study to evaluate the efficacy and safety of Terrosa (teriparatide) to the originator medicinal product containing teriparatide in patients with osteoporosis at high risk of fracture. The RMP (version 1.3) is updated accordingly

#### 15.3.37. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0012

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension application to introduce a new pharmaceutical form (prolonged-release tablet) associated with a new strength (11 mg), and presented in pack sizes of 28, 30, 90 and 91 tablets. The line extension includes a change in pharmacokinetics. The RMP (version 4.0) is updated accordingly

#### 15.3.38. Trifluridine, tipiracil - LONSURF (CAP) - EMEA/H/C/003897/II/0012

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin



Scope: Extension of indication to include the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, platinum-, and either a taxane- or irinotecan-based chemotherapy. 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. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. The RMP (version 6.1) is also updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

#### 15.3.39. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0071

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to include treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies. As a consequence, the SmPC, package leaflet and RMP (version 15.0) are updated

#### 15.3.40. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/II/0035

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Applicant: Correvio

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information following updates to the company core safety datasheet (CCDS) based on the results of an integrated safety analysis performed on data of existing clinical studies with a stronger emphasis on treatment-related adverse drug reactions (ADRs) and an incidence rate above one percent. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the RMP is updated in line with the results from the completed observational cohort SPECTRUM study (study 6621-049): a prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant intravenous (IV) sterile concentrate currently under assessment in variation II/34. Furthermore, the MAH took the opportunity to update sections 4.2, 4.4, 4.6, 4.7, 4.8, 5.1, 5.2, 5.3, 6.4 of the SmPC, Annex II, labelling and package leaflet in order to include editorial changes, to correct typographical errors and to bring the product information in line with the latest quality review of documents (QRD) template (version 10). The package leaflet is also updated in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and the EMA Annex to the EC guideline

## 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. Autologous CD34<sup>+</sup> enriched cell fraction that contains CD34<sup>+</sup> cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - PSUSA/00010505/201811**

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Applicant: Orchard Therapeutics (Netherlands) BV, ATMP<sup>53</sup>

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### **16.1.2. Benralizumab - FASENRA (CAP) - PSUSA/00010661/201811**

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Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

### **16.1.3. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201812**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

### **16.1.4. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/201811**

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Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

### **16.1.5. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/201811**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

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

#### 16.1.6. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/201811

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.7. Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/201811

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

#### 16.1.8. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/201812

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.1.9. Elotuzumab - EMLICITI (CAP) - PSUSA/00010500/201811

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.10. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/201811

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

#### 16.1.11. Empagliflozin, linagliptin - GLYXAMBI (CAP) - PSUSA/00010539/201811

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### 16.1.12. Fluciclovine (18F) - AXUMIN (CAP) - PSUSA/00010594/201811

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

**16.1.13. Follitropin alfa - BEMFOLA (CAP); GONAL-F (CAP); OVALEAP (CAP) - PSUSA/00001463/201810**

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Applicant(s): Gedeon Richter Plc. (Bemfola), Merck Europe B.V. (Gonal-f), Theramex Ireland Limited (Ovaleap)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.1.14. Follitropin alfa, lutropin alpha - PERGOVERIS (CAP) - PSUSA/00001464/201810**

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

**16.1.15. Follitropin delta - REKOVELLE (CAP) - PSUSA/00010554/201811**

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Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.1.16. Fondaparinux - ARIXTRA (CAP) - PSUSA/00001467/201812**

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Applicant: Aspen Pharma Trading Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

**16.1.17. Glibenclamide<sup>54</sup> - AMGLIDIA (CAP) - PSUSA/00010690/201811**

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Applicant: Ammtek

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

**16.1.18. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - PSUSA/00009175/201811**

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

**16.1.19. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/201811**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

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<sup>54</sup> Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

#### 16.1.20. Ixazomib - NINLARO (CAP) - PSUSA/00010535/201811

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### 16.1.21. Ketoconazole<sup>55</sup> - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201811

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

#### 16.1.22. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/201811

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.23. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/201811

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.24. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - PSUSA/00010296/201811

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

#### 16.1.25. Necitumumab - PORTRAZZA (CAP) - PSUSA/00010471/201811

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

#### 16.1.26. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/201811

Applicant: Novo Nordisk A/S

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.27. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/201811

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.28. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/201811

Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

#### 16.1.29. Prasterone<sup>56</sup> - INTRAROSA (CAP) - PSUSA/00010672/201811

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.30. Rituximab - BLITZIMA (CAP); MABTHERA (CAP); RITEMVIA (CAP); RITUZENA (CAP); RIXATHON (CAP); RIXIMYO (CAP); TRUXIMA (CAP) - PSUSA/00002652/201811

Applicant(s): Roche Registration GmbH (MabThera), Sandoz GmbH (Rixathon, Riximyo), Celltrion Healthcare Hungary Kft. (Blitzima, Ritemvia, Rituzena, Truxima)

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

#### 16.1.31. Rotavirus vaccine pentavalent (live, oral) - ROTATEQ (CAP) - PSUSA/00002666/201811

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.32. Rurioctocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/201811

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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<sup>56</sup> Pessary, vaginal use only

#### 16.1.33. Sapropterin - KUVAN (CAP) - PSUSA/00002683/201812

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.34. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/201812

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.1.35. Semaglutide - OZEMPIC (CAP) - PSUSA/00010671/201811

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### 16.1.36. Susoctocog alpha - OBIZUR (CAP) - PSUSA/00010458/201811

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.37. Tenofovir alafenamide - VEMLIDY (CAP) - PSUSA/00010575/201811

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

#### 16.1.38. Venetoclax - VENCLYXTO (CAP) - PSUSA/00010556/201812

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

#### 16.1.39. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/201811

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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

### **16.2.1. Bosentan - STAYVEER (CAP), TRACLEER (CAP); NAP - PSUSA/00000425/201811**

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Applicant(s): Janssen-Cilag International NV (Stayveer, Tracleer), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

### **16.3.1. Azelastine, fluticasone (NAP) - PSUSA/00010067/201810**

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### **16.3.2. Benzydamine (NAP) - PSUSA/00000375/201810**

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Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

### **16.3.3. Bromocriptine (NAP) - PSUSA/00000438/201810**

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Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

### **16.3.4. Ceftazidime (NAP) - PSUSA/00000608/201810**

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

### **16.3.5. Clindamycin (NAP) - PSUSA/00000795/201810**

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure



#### 16.3.6. [Dexketoprofen \(NAP\) - PSUSA/00000997/201810](#)

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Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### 16.3.7. [Didanosine \(NAP\) - PSUSA/00001054/201810](#)

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Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

#### 16.3.8. [Flutamide \(NAP\) - PSUSA/00001453/201810](#)

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### 16.3.9. [Human coagulation factor VIII, human von Willebrand factor \(NAP\) - PSUSA/00001621/201810](#)

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Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.3.10. [Meningococcal group C polysaccharide conjugate vaccine \(NAP\) - PSUSA/00001971/201810](#)

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Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### 16.3.11. [Methoxyflurane \(NAP\) - PSUSA/00010484/201811](#)

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.3.12. [Milrinone \(NAP\) - PSUSA/00002064/201810](#)

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.3.13. Nimodipine (NAP) - PSUSA/00002166/201811

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Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

### 16.3.14. Piretanide (NAP) - PSUSA/00002433/201810

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Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

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

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

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

#### 17.1.1. Acridinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) Acridinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - EMEA/H/C/PSA/S/0037

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Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Substantial amendment to the previously agreed common protocol in July 2013 on 'acridinium bromide PASS to evaluate the risk of cardiovascular endpoints, potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for acridinium bromide-containing products

#### 17.1.2. Dexketoprofen, tramadol (NAP) - EMEA/H/N/PSP/S/0062.2

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

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to PSP/J/0062.1 [protocol for a drug utilisation study (DUS) on dexketoprofen-tramadol (DKP-TRAM) fixed combination to evaluate the pattern of prescriptions of DKP-TRAM and assess the risk of adverse events (AE) (e.g. nausea, vomiting, diarrhoea, vertigo) in DKP-TRAM vs. tramadol monotherapy (including tramadol-paracetamol combinations) users, with a special focus on patients 75 years old and over] as

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

per the request for supplementary information (RSI) adopted in January 2019

### **17.1.3. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064.2**

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Applicant: Medice Arzneimittel Pütter GmbH & Co. KG (Medikinet Retard)

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0064.1 [protocol for a multicentre, observational, prospective PASS to evaluate the safety concerns of long-term cardiovascular and psychiatric risks within the adult attention deficit/hyperactivity disorder (ADHD) population taking Medikinet Retard (methylphenidate hydrochloride) according to normal standard clinical practice] as per the request for supplementary information (RSI) adopted in January 2019

### **17.1.4. Oral retinoids: acitretin (NAP), alitretinoin (NAP), isotretinoin (NAP) - EMEA/H/N/PSP/J/0069.1**

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Applicant: F. Hoffmann-La Roche Ltd. (on behalf of a consortium)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to PSP/J/0069 [protocol for a joint drug utilisation study (DUS) to describe the prescribing practices before and after the update of the pregnancy prevention programme (PPP) for the following oral retinoids: acitretin, alitretinoin and isotretinoin in order to assess the effectiveness of the updated risk minimisation measures (RMMs) in women of childbearing potential, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC for retinoids for oral use completed in 2018 (EMEA/H/A-31/1446)] as per the request for supplementary information (RSI) adopted in January 2019

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

### **17.2.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/MEA 003**

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Applicant: Kite Pharma EU B.V., ATMP<sup>59</sup>

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for study KT-EU-471-0116: a prescriber survey to assess the prescribers' understanding of serious neurologic adverse reactions and cytokine release syndrome (CRS) (from initial opinion/MA)

### **17.2.2. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.1**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 035 [protocol for study 20180204: a registry study to evaluate the incidence and risk of hypocalcaemia in paediatric patients treated with cinacalcet with secondary hyperparathyroidism receiving maintenance dialysis within the

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<sup>58</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by the PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

<sup>59</sup> Advanced therapy medicinal product

International Pediatric Dialysis Network (IPDN) registry] as per the request for supplementary information (RSI) adopted in October 2018

### **17.2.3. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/MEA 042**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 20190038 V1: a retrospective cohort study assessing the incidence of cardiovascular and cerebrovascular events among postmenopausal women and men with osteoporosis who initiated treatment with denosumab or zoledronic acid

### **17.2.4. Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/MEA 019.4**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 019.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

### **17.2.5. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 008.2**

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Updated protocol for study 109MS402: Biogen multiple sclerosis pregnancy exposure registry to prospectively evaluate pregnancy outcomes in women with multiple sclerosis (MS) who were exposed to a registry-specified Biogen MS product during the eligibility window for that product

### **17.2.6. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 007.4**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 007.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.7. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/REC 001.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: MAH's response to REC 001.1 [protocol for study R668-AD-1225: a non-imposed, interventional PASS: an open-label study of dupilumab in patients with atopic dermatitis who participated in previous dupilumab clinical trials, five year open label extension study] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.8. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/MEA 004.4

Applicant: Merck Sharp & Dohme B.V

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 004.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.9. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 002.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 002 [protocol for study BO40853: a PASS based on healthcare professional (HCP) and patient/carer survey to evaluate the awareness, knowledge and compliance of HCPs and patients/carers to the additional risk minimisation measures (guide for HCPs, patient/carer guide, patient alert card), in relation to the safety concerns of thromboembolic events, thrombotic microangiopathy as well as life-threatening bleeding due to misinterpretation of the standard coagulation tests [final study report due date: 30/04/2021] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.10. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 004.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a previously agreed protocol in September 2016 for study 1245.97: a study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 mellitus diabetes (T2DM): a multi-database European study to add Finnish national registries to the study as additional data sources to evaluate the main study outcomes

#### 17.2.11. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a previously agreed protocol in September 2016 for study 1245.97: a study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 mellitus diabetes (T2DM): a multi-database European study to add Finnish national registries to the study as additional data sources to evaluate the main study outcomes

#### 17.2.12. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 047.2

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 047.1 [protocol for study No GS EU 276 4487: a prospective, longitudinal, observational registry of emtricitabine/tenofovir disoproxil fumarate for human immunodeficiency virus 1 (HIV-1) pre-exposure prophylaxis (PrEP) in the European Union] as per the request for supplementary information (RSI) adopted at the November 2018 PRAC meeting

#### 17.2.13. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58<sup>60</sup>) - EMEA/H/W/002320/MEA 002

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study FEXINC09395: a prospective observational study of the safety of fexinidazole for human African trypanosomiasis [final clinical study report expected in September 2023] (from initial opinion/MA)

#### 17.2.14. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/MEA 006.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 006.2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

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<sup>60</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)

#### 17.2.15. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/MEA 004.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 004.1 [protocol for study CSIMM000265: a retrospective cohort study using health administrative claims databases to assess adverse pregnancy and infant outcomes in women with psoriasis who were exposed to guselkumab versus other biologic therapies during pregnancy] as per the request for supplementary information (RSI) adopted in February 2019

#### 17.2.16. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.1

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001 [protocol for 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 January 2019

#### 17.2.17. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 002.1

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002 [protocol for a study to evaluate and further characterise the events of thrombocytopenia, glomerulonephritis and retinal toxicity/eye disease related to vitamin A deficiency when Tegsedi (inotersen) is prescribed in normal clinical practice] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.18. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 017.4

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 017.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.19. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 007.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 007.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.20. Sofosbuvir - SOVALDI (CAP) - EMA/H/C/002798/MEA 024.4

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 024.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.21. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMA/H/C/004210/MEA 008.4

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 008.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.22. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMA/H/C/004350/MEA 002.3

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 002.1 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019



#### 17.2.23. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/MEA 002.1

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002 [protocol for study VX17-661-117 (study 117) (listed as a category 3 study in the RMP): an observational cohort study on utilisation patterns and real-world effects of tezacaftor and ivacaftor combination therapy (TEZ/IVA) in patients with cystic fibrosis (CF) [final report expected in December 2023] as per the request for supplementary information (RSI) adopted in February 2019

#### 17.2.24. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 024.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA-024 [Protocol for study PGL18-002: a retrospective, multi-national, comparative, non-interventional cohort study to investigate the risk of liver injury possibly associated with Esmya (ulipristal acetate) use based on data from various national electronic health record based databases in Europe [final study report expected by Q4 2019] as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.25. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 028.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 028 [protocol for study PGL18-001: a retrospective drug utilisation study (DUS) through a chart review across four major EU countries [final study report expected by Q2 2020], as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

#### 17.2.26. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.4

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Amendment to the previously agreed protocol in February 2017 (MEA 044.2) for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)

#### 17.2.27. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Amendment to protocol (version 3.0) for study P16-562: a prospective

observational study to assess the long term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients [final clinical study report (CSR) planned in December 2025]

#### **17.2.28. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/MEA 001.1**

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 001 [protocol for study VON (BAX0111) VWF-500 COL (listed as a category 3 study in the RMP): a real world safety and effectiveness study of factor replacement for clinically severe von Willebrand disease (VWD) [interim report due date: 30/06/2019; final report due date: 30/06/2022]] as per the request for supplementary information (RSI) adopted in January 2019

### **17.3. Results of PASS imposed in the marketing authorisation(s)<sup>61</sup>**

#### **17.3.1. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/PSR/S/0020**

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Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to PSR/S/0020 [results of an observational 5 year safety study to assess the identified and potential risks of Bronchitol (mannitol) in cystic fibrosis (CF) through a comparison between Bronchitol-exposed patients and unexposed patients matched for key characteristics] as per the request for supplementary information (RSI) adopted in January 2019

### **17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>62</sup>**

#### **17.4.1. Aflibercept - ZALTRAP (CAP) - EMEA/H/C/002532/II/0051**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from study OBS13597 (OZONE) (listed as a category 3 study in the RMP): a prospective international observational cohort non-comparative study describing the safety and effectiveness of Zaltrap (aflibercept) administered in combination with folinic acid, fluorouracil and irinotecan (FOLFIRI) for the treatment of patients with metastatic colorectal cancer in current clinical practice. The RMP (version 4.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

#### **17.4.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/LEG 011**

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Applicant: Gentium S.r.l.

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<sup>61</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>62</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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First interim results of a national, post-registration observational study of the long-term safety and health outcome of patients treated with Defitelio (defibrotide), including patients with severe hepatic veno-occlusive disease (VOD) after hematopoietic stem-cell transplantation (HSCT) (DEFIFRANCE registry) as requested in the conclusions of EMEA/H/C/002393/S/0038 adopted in March 2019

#### 17.4.3. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/II/0020, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study ELIGLC06912 (listed as a category 3 study in the RMP) (MEA006): a drug utilisation study (DUS) of eliglustat in the United States (US) population using MarketScan database and the International Collaborative Gaucher Group registry. The RMP (version 6) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

#### 17.4.4. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS1568/0043; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS1568/0041

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report for study HZC102972 (listed as a category 3 study in the RMP): a PASS to further characterise the important potential risk of decreased bone mineral density (BMD) and associated fractures with fluticasone furoate (FF)/vilanterol (VI) in the treatment of chronic obstructive pulmonary disease (COPD) by evaluating the effect of the inhaled corticosteroid fluticasone furoate (FF) on bone mineral density by comparing FF/VI treatment with VI treatment in subjects with moderate COPD

#### 17.4.5. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/WS1596/0172; LIPROLOG (CAP) - EMEA/H/C/000393/WS1596/0133

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from an on-going review of adverse drug events related to Humalog (insulin lispro) (MEA 028) and Liprolog (insulin lispro) (MEA 021) (listed as a category 3 study in the RMP): a post approval safety surveillance programme for lot-specific adverse event review to evaluate any potential change in frequency of hypersensitivity, immunogenicity, and lack of drug effect (LODE) events for insulin lispro synthesized via streamlined lispro drug substance process (sKPB)

#### 17.4.6. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0110, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final results of study CC-5013-PASS-001: a non-interventional PASS to characterise and determine the incidence of adverse events of special interest specifically neutropenia, thrombocytopenia, acute and opportunistic infections, bleeding events, venous thromboembolism, cardiac disorders, neuropathy, rash, hypersensitivity, hypothyroidism and renal failure in subjects treated with lenalidomide in a naturalistic setting

#### **17.4.7. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/II/0030**

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Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from drug utilisation study AMDC-204-403 EU (listed as a category 3 study in the RMP): a multinational retrospective medical record review to evaluate utilisation patterns of Adasuve (loxapine) for inhalation in agitated persons in routine clinical care. The RMP (version 9.1) is updated accordingly

#### **17.4.8. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/II/0030**

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report for study 178-PV-002: a drug utilisation study (DUS) of mirabegron using real-word healthcare databases from Finland, the Netherlands (NL) and the United Kingdom (UK) (in fulfilment of post-approval commitment MEA 009.2)

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

#### **17.5.1. Autologous CD34<sup>+</sup> enriched cell fraction that contains CD34<sup>+</sup> cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/ANX 004.1**

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Applicant: Orchard Therapeutics (Netherlands) BV, ATMP<sup>63</sup>

PRAC Rapporteur: Menno van der Elst

Scope: Biennial progress report for study GSK2696273 entitled 'adenosine deaminase severe combined immunodeficiency (ADA-SCID) registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and effectiveness' (PSP/004) [final clinical study report (CSR) after the 50<sup>th</sup> patient has 15 year follow-up visit - Q4 2037]

#### **17.5.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.13**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Sixth annual interim report for study BEL116543/HGS1006-C1124: a long-term

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<sup>63</sup> Advanced therapy medicinal product

controlled safety registry evaluating the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus followed for a minimum of 5 years

#### **17.5.3. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 010.2**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third monitoring interim report for PASS 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]

#### **17.5.4. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.2**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third monitoring interim report for PASS 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]

#### **17.5.5. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.11**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Fourth interim report for the ongoing US non-interventional PASS (study B2311060) (listed as a category 3 study in the RMP) including data through the fourth year of PASS to estimate the incidence and compare the risks of endometrial hyperplasia and endometrial cancer among postmenopausal women initiating either Duavive (estrogens conjugated/bazedoxifene) or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT)

#### **17.5.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 005.7**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eighth annual report from the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT): a long-term observational study of the safety of biologic treatments in rheumatoid arthritis [final clinical study report (CSR) expected in December 2022]

#### **17.5.7. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.10**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual interim report for the passive enhanced safety surveillance study (ESS) D2560C00008: a postmarketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age for the 2018-2019 influenza season in England

#### 17.5.8. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 041.2

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Third interim report for the Insuman implantable registry HUBIN-C-06380: a European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman implantable 400 IU/mL (insulin human) in Medtronic MiniMed implantable pump

#### 17.5.9. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/ANX 041.7

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Interim descriptive report for study CC-5013-MDS-012 (listed as a category 1 study in Annex II (PSA/S/0016)): a post-authorisation, non-interventional, retrospective, drug-utilisation study (DUS) to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)

#### 17.5.10. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 023.2

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third progress report for study V72\_820B 'Bexsero pregnancy registry': an observational study of the safety of Bexsero (meningococcal group B vaccine (recombinant, component, adsorbed)) exposure in pregnant women and their offspring

#### 17.5.11. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Second interim results for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterise the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4/2022]

#### 17.5.12. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.5

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Second interim report for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final report expected in Q2/2020]

#### **17.5.13. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002.1**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Second interim results for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterise the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4/2022]

#### **17.5.14. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.2**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Second interim report for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final report expected in Q2/2020]

#### **17.5.15. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.4**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Second annual interim report for PASS AC-065A401 (EXPOSURE): an observational cohort study of pulmonary arterial hypertension (PAH) patients newly treated with either Upravi (selexipag) or any other PAH-specific therapy in routine clinical practice [final study report expected in 2023]

#### **17.5.16. Somatropin - OMNITROPE (CAP) - EMEA/H/C/000607/MEA 012.3**

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Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 012.3 [second interim report for study EP00-501 (PATRO Children): a non-interventional post-marketing surveillance study to collect long-term safety and efficacy of Omnitrope (somatropin) in infants, children and adolescents with growth hormone deficiency and treated within routine clinical practice in Europe] as per the request for supplementary information (RSI) adopted in December 2018

#### 17.5.17. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018.2

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Third yearly progress report for study PGL14-001: a prospective, multinational, multicentre, non-interventional study to evaluate the long-term safety of Esmya (ulipristal acetate) in particular the endometrial safety and the current prescription and management patterns of Esmya (ulipristal acetate) in a long-term treatment setting [final clinical study report (CSR) expected in 2023]

#### 17.5.18. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.3

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: First interval safety report for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)

### **17.6. Others**

#### 17.6.1. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/MEA 004

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Feasibility assessment for a prospective, observational safety study to characterise the risks of the use of apalutamide in non-metastatic castration-resistant prostate cancer (NM-CRPC) patients on androgen deprivation therapy (ADT) with clinically significant cardiovascular conditions [final report expected in 2023]

#### 17.6.2. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/MEA 013.2

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Annual report (integrated safety analysis report) for clinical studies: 1) study BRF113683 (BREAK-3): a two-arm, open-label, randomised phase 3 pivotal study comparing oral dabrafenib with intravenous dacarbazine (DTIC), 2) study MEK115306 (COMBI-d): a two-arm, double-blinded, randomised, phase 3 study comparing dabrafenib and trametinib combination therapy with dabrafenib administered with a trametinib placebo (dabrafenib monotherapy); 3) study MEK116513 (COMBI-v): a 2-arm, randomised, open-label, phase 3 study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma on secondary malignancies in patients treated with dabrafenib in randomised controlled trials to comply with the additional pharmacovigilance activity as requested in the RMP; 4) study BRF115531 (COMBI-AD): a 2-arm, randomised, double-blind, phase 3 study of dabrafenib in combination with trametinib versus two matching placebos in the adjuvant treatment of melanoma after surgical resection



### **17.6.3. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 025.1**

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 025 [feasibility report for a retrospective case control study utilising medical records of transplantation centres in at least five EU Member States as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

### **17.6.4. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 026.1**

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 026 [feasibility report for an observational study using EU registries with biomarker data, as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

### **17.6.5. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 027.1**

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 027 [feasibility report for a genetic analysis (human leukocyte antigen (HLA)) study using data from EU registries with biomarker data in patients with severe drug-induced liver injury (DILI), as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

## **17.7. New Scientific Advice**

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

## **17.8. Ongoing Scientific Advice**

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

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

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

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

Based on the review of the available pharmacovigilance data for the 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/0064 (without RMP)**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

#### **18.1.2. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0029 (without RMP)**

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Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: Annual reassessment of the marketing authorisation

#### **18.1.3. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0063 (without RMP)**

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

#### **18.1.4. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/S/0004 (with RMP)**

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Annual reassessment of the marketing authorisation

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

#### **18.2.1. Nalotimagene carmaleucel - ZALMOXIS (CAP) - EMEA/H/C/002801/R/0015 (with RMP)**

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Applicant: MolMed S.p.A, ATMP<sup>64</sup>

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<sup>64</sup> Advanced therapy medicinal product

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

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

#### **18.3.1. Acridinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/R/0026 (without RMP)**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

#### **18.3.2. Acridinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/R/0026 (without RMP)**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

#### **18.3.3. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/R/0062 (without RMP)**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

#### **18.3.4. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/R/0027 (without RMP)**

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Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

#### **18.3.5. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/R/0036 (with RMP)**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

#### **18.3.6. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/R/0021 (without RMP)**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

### 18.3.7. Nintedanib - VARGATEF (CAP) - EMEA/H/C/002569/R/0025 (with RMP)

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: 5-year renewal of the marketing authorisation

### 18.3.8. Nonacog gamma - RIXUBIS (CAP) - EMEA/H/C/003771/R/0029 (with RMP)

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

### 18.3.9. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/R/0029 (without RMP)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

### 18.3.10. Paliperidone - TREVICTA (CAP) - EMEA/H/C/004066/R/0022 (with RMP)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

### 18.3.11. Rasagiline - RASAGILINE RATIOPHARM (CAP) - EMEA/H/C/003957/R/0014 (without RMP)

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Applicant: Teva B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

### 18.3.12. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/R/0050 (with RMP)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

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 11-14 June 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	No interests declared	Full involvement
Eva Jirsovà	Member	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
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	15.3.10 Eluxadoline - TRUBERZI (CAP)
Adrien Inoubli	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
Sophia Trantza	Alternate	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Ruta Kerpauskiene	Alternate	Lithuania	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
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	4.3.4 Rivaroxaban - XARELTO (CAP), 6.1.2. Afibercept - EYLEA (CAP), 6.3.8. Dextromethorphan (NAP) 10.3.1. Direct-acting oral anticoagulants (DOACs)
Karen Pernille Harg	Alternate	Norway	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
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	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
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No participation	17.2.24. Ulipristal acetate

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			in discussion, final deliberations and voting on:	- ESMYA (CAP), 17.2.25. Ulipristal acetate - ESMYA (CAP), 17.5.17. Ulipristal acetate - ESMYA (CAP) 17.6.3. Ulipristal acetate - ESMYA (CAP), 17.6.4. Ulipristal acetate - ESMYA (CAP), 17.6.5. Ulipristal acetate - ESMYA (CAP)
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Andreas Kirisits	Expert - via telephone*	Austria	No restrictions applicable to this meeting	Full involvement
Martine Sabbe	Expert - via telephone*	Belgium	No interests declared	Full involvement
Charlotte Selvais	Expert - via telephone*	Belgium	No interests declared	Full involvement
Kåre Kemp	Expert - in person*	Denmark	No interests declared	Full involvement
Benedicte Lunddahl Rasmussen	Expert - in person*	Denmark	No interests declared	Full involvement
Nicolas Beix	Expert - in person*	France	No interests declared	Full involvement
Benjamin Burrus	Expert - via telephone*	France	No interests declared	Full involvement
Nathalie Dumarcet	Expert - via telephone*	France	No interests declared	Full involvement
Bilal Majed	Expert - via telephone*	France	No interests declared	Full involvement
Maxim Frizler	Expert - via telephone*	Germany	No interests declared	Full involvement
Kerstin Lösckke	Expert - via telephone*	Germany	No interests declared	Full involvement
Clemens Mittmann	Expert - via telephone*	Germany	No interests declared	Full involvement
Valerie Strassmann	Expert - in person*	Germany	No interests declared	Full involvement
Benjamin Burrus	Expert - via telephone*	France	No interests declared	Full involvement
Grainne Kirwan	Expert - in person*	Ireland	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
Marcel Kwa	Expert - in person*	Netherlands	No interests declared	Full involvement
Rune Kjekken	Expert - in person*	Norway	No restrictions applicable to this meeting	Full involvement
Margarita Magro de la Plaza	Expert - in person*	Spain	No interests declared	Full involvement
Laura Oliveira Santamaria	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Mattia Calissano	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Adrian Evans	Expert - via telephone*	United Kingdom	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:

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