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Human Medicines Division

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 08 – 11 June 2020

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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## **1. Introduction**

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

The Chairperson opened the 08–11 June 2020 meeting held remotely by welcoming all participants. In light of the current crisis (COVID-19 outbreak), the EMA Business Continuity Plan (BCP) and exceptional measures taken to protect the staff members and all delegates, experts and members of the Committee are maintained.

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

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

### **1.2. Agenda of the meeting on 08 – 11 June 2020**

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

### **1.3. Minutes of the previous meeting on 11 - 14 May 2020**

The minutes were adopted by written procedure with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 11-14 May 2020 were published on the EMA website on 19 November 2020 ([EMA/PRAC/624022/2020](#)).

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

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

None

### **2.2. Ongoing procedures**

None

### 2.3. Procedures for finalisation

None

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

### 3.1. Newly triggered procedures

None

### 3.2. Ongoing procedures

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

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Applicant(s): Gedeon Richter Plc.; various

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

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

#### Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of medicinal products containing ulipristal acetate 5 mg after a new case of serious liver injury leading to liver transplantation following exposure to Esmya (ulipristal acetate) was reported despite the implementation of risk minimisation measures (RMMs) in 2018 in line with the conclusions of a previous referral procedure under Article 20 of Regulation (EC) No 726/2004 on Esmya (ulipristal acetate). In March 2020, the PRAC recommended the provisional suspension of the marketing authorisations of ulipristal acetate 5 mg-containing products, until the review is finalised. For further background, see [PRAC minutes March 2020](#).

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

- The PRAC discussed the joint assessment report issued by the Rapporteurs.
- The PRAC adopted a list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable ([EMA/PRAC/121857/2020 Rev.1](#)).
- The PRAC agreed to convene an ad-hoc expert group (AHEG) meeting. The PRAC adopted a list of questions (LoQ) to the AHEG.

Post-meeting note: On 01 July 2020, the PRAC adopted the final list of experts for the AHEG meeting organised on 02 July 2020.

### 3.3. Procedures for finalisation

None

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<sup>1</sup> 5 mg

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

None

### 3.5. Others

None

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

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

See also Annex I 14.1.

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

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Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of psychiatric disorders

EPITT 19572 – New signal

Lead Member State(s): DK, SE

#### **Background**

Chloroquine and hydroxychloroquine are aminoquinoline antimalarials indicated for the treatment of rheumatoid arthritis, systemic erythematosus lupus and chronic discoid lupus. They are also indicated in adults and adolescents for prophylaxis and treatment of malaria.

During routine signal detection activities, a signal of psychiatric disorders was identified by Spain, based on six cases of psychosis, psychotic disorder, suicide attempt and completed suicide following use of chloroquine or hydroxychloroquine for the treatment of coronavirus disease (COVID-19) retrieved from FEDRA, the Spanish pharmacovigilance database. Denmark as the lead Member State (LMS) for hydroxychloroquine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### **Discussion**

Having considered the available evidence, the PRAC agreed that a further evaluation of the signal on psychiatric disorders with chloroquine and hydroxychloroquine was warranted.

The PRAC appointed Anette Kirstine Stark as Rapporteur for the signal.

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

- The MAHs for the originator chloroquine- and hydroxychloroquine-containing products should submit to EMA, within 30 days, a cumulative review of psychiatric disorders from literature, clinical trials, spontaneous case reports.

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

<sup>3</sup> Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

- The PRAC agreed that EMA would perform additional analyses using electronic health records databases to further assess the use pattern and occurrence of psychiatric events for chloroquine and hydroxychloroquine when used in the licensed indication of rheumatoid arthritis (RA).
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### 4.1.2. Nivolumab – OPDIVO (CAP)

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Applicant(s): Bristol-Myers Squibb Pharma

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of eosinophilic fasciitis

EPITT 19567 – New signal

Lead Member State(s): DE

##### **Background**

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody, indicated as Opdivo a centrally authorised product, as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults, for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. It is also indicated as monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults and for the treatment of advanced renal cell carcinoma after prior therapy in adults, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy and for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy. It is indicated in combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (RCC).

The exposure for Opdivo (nivolumab) is estimated to have been more than 371,405 patients worldwide, in the period from first authorisation in 2014 to 2019.

During routine signal detection activities, a signal of eosinophilic fasciitis was identified by the EMA based on 19 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

##### **Discussion**

Having considered the available evidence from case reports in EudraVigilance and the literature, the PRAC agreed that the signal required further assessment and agreed that the assessment should cover all substances of the therapeutic class of immune checkpoint inhibitors (ICI). The PRAC agreed to request additional information from the MAHs.

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

- The MAHs for Keytruda (pembrolizumab), Opdivo (nivolumab), Yervoy (ipilimumab), Tecentriq (atezolizumab), Bavencio (avelumab), Imfinzi (durvalumab) and Libtayo

(cemiplimab) should submit to the EMA, within 60 days, a cumulative review of all cases of eosinophilic fasciitis associated with the respective ICI medicinal product. The MAHs should discuss the need for amendments to the product information and/or the RMP and make a proposal accordingly.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

## 4.2. New signals detected from other sources

None

## 4.3. Signals follow-up and prioritisation

### 4.3.1. Amitriptyline (NAP); bupropion (NAP); citalopram (NAP); desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), YENTREVE (CAP), XERISTAR (CAP), NAP; escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); milnacipran (NAP); mirtazapine (NAP); naltrexone, bupropion – MYSIMBA (CAP); paroxetine (NAP); sertraline (NAP); trazodone (NAP); venlafaxine (NAP); vortioxetine - BRINTELLIX (CAP)

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Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of post-partum haemorrhage

EPITT 19552 – Follow-up to March 2020

#### Background

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

The Rapporteur performed further assessment via a systematic review of the literature on the signal of post-partum haemorrhage.

#### Discussion

The PRAC considered the known association between bleeding events and selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitor (SNRIs), as well as with vortioxetine and further evidence from observational studies<sup>4 5 6 7 8 9 10</sup>. Based on this evaluation, the PRAC concluded that there is sufficient evidence for establishing causality between the treatment with these substances and the occurrence of post-partum

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<sup>4</sup> Bruning AH et al. Antidepressants during pregnancy and postpartum hemorrhage: a systematic review. *European journal of obstetrics, gynecology, and reproductive biology*. 2015;189:38-47

<sup>5</sup> Jiang HY et al. Antidepressant use during pregnancy and risk of postpartum hemorrhage: A systematic review and meta-analysis. *Journal of psychiatric research*. 2016;83:160-7

<sup>6</sup> Heller HM et al. Increased postpartum haemorrhage, the possible relation with serotonergic and other psychopharmacological drugs: a matched cohort study. *BMC pregnancy and childbirth*. 2017;17(1):166

<sup>7</sup> Huybrechts KF et al. Maternal and fetal outcomes following exposure to duloxetine in pregnancy: cohort study. *BMJ (Clinical research ed)*. 2020;368:m237

<sup>8</sup> Palmsten K et al. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *BMJ (Clinical research ed)*. 2013;347:f4877

<sup>9</sup> Palmsten K et al. Patterns of prenatal antidepressant exposure and risk of preeclampsia and postpartum haemorrhage. *Paediatric and perinatal epidemiology*. 2020. doi: 10.1111/ppe.12660. Online ahead of print

<sup>10</sup> Skalkidou A et al. SSRI use during pregnancy and risk for postpartum haemorrhage: a national register-based cohort study in Sweden. *BJOG: an international journal of obstetrics and gynaecology*. 2020. doi: 10.1111/1471-0528.16210. Online ahead of print



haemorrhage. The PRAC concurred that the product information of citalopram-, desvenlafaxine-, escitalopram-, fluoxetine-, fluvoxamine-, milnacipran-, paroxetine-, sertraline-, venlafaxine -and vortioxetine-containing products should be updated and agreed on a draft wording for updating the product information. Based on the data reviewed, the PRAC concluded that updates of the product information of medicinal products containing mirtazapine, trazodone, amitriptyline, bupropion (including its combination with naltrexone) are not warranted at present. Finally, no updates are necessary for duloxetine-containing products as the product information wording is already adequate.

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

- The MAHs for originator medicinal products containing citalopram, desvenlafaxine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine and vortioxetine should provide comments to EMA, within 60 days, on the proposed updates to the product information.
- The MAH for the original medicinal product containing amitriptyline should monitor haemorrhage and post-partum haemorrhage events in the next PSUR<sup>11</sup>.

For the full PRAC recommendation, see [EMA/PRAC/311314/2020](#) published on 06/07/2020 on the EMA website.

#### **4.3.2. Desogestrel (NAP)**

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Applicant(s): various

PRAC Rapporteur: Annika Folin

Scope: Signal of suppressed lactation

EPITT 19504 - Follow-up to January 2020

#### **Background**

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

The MAH Merck Sharp & Dohme BV replied to the request for information on the signal of suppressed lactation and the responses were assessed by the Rapporteur.

#### **Discussion**

Having reviewed the cumulative review provided by the MAH, including the available data from clinical trials, literature and EudraVigilance, the PRAC agreed that the information included in the product information of desogestrel-containing products with regard to lactation was no longer current and should be updated accordingly.

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

- The MAHs for desogestrel-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend<sup>12</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/311314/2020](#) published on 06/07/2020 on the EMA website.

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<sup>11</sup> Data lock point (DLP): 10/01/2021

<sup>12</sup> Update of SmPC sections 4.6 and 5.1. The package leaflet is to be updated accordingly

### 4.3.3. Macrogol 3350<sup>13 14</sup> (NAP); macrogol 4000<sup>15 16</sup> (NAP)

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Applicant(s): various

PRAC Rapporteur: Ilaria Baldelli

Scope: Signal of colitis ischaemic

EPITT 19517 – Follow-up to February 2020

#### **Background**

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

The MAHs Alfasigma, Aurobindo, B. Braun, GB Pharma Services, Dr Falk Pharma, Helsinn, Ipsen, Lainco, Mip-Ipr, Norgine, Orion Pharma, Perffarma, Polifarma, QualitecFarma, Recordati, Skillpharma, Sofar and Tillots Pharma AG replied to the request for information on the signal of colitis ischaemic and the responses were assessed by the Rapporteur.

#### **Discussion**

Having considered the available evidence from case reports in EudraVigilance and in the literature, the PRAC agreed that there is sufficient evidence on the relationship between the use of macrogol and the occurrence of ischaemic colitis that warrants an update of the product information.

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

- The MAHs for macrogol-containing products (all molecular weights and combinations) authorised for bowel preparation should submit to relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending the product information<sup>17</sup>.

For the full PRAC recommendation, see [EMA/PRAC/311314/2020](#) published on 06/07/2020 on the EMA website.

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

### 4.4.1. Abiraterone acetate - ZYTIGA (CAP) - EMEA/H/C/002321/II/0061

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to add a warning on hypoglycaemia based on the final signal recommendation adopted in January 2020 (EPITT 19445) on interaction between abiraterone and sulphonylureas. The package leaflet is updated accordingly. The MAH took the opportunity to introduce some minor updates to Annex II of the product information

#### **Background**

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<sup>13</sup> With or without electrolytes

<sup>14</sup> And combination(s)

<sup>15</sup> With or without electrolytes

<sup>16</sup> And combination(s)

<sup>17</sup> Update of SmPC section 4.4. The package leaflet is to be updated accordingly

Abiraterone acetate is an androgen biosynthesis inhibitor, indicated, as Zytiga, with prednisone or prednisolone for the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT), for the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated and for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Based on the evaluation of a signal procedure concluded in January 2020 on the interaction between abiraterone and sulphonylureas (EPITT 19445), the MAH Zytiga (abiraterone) submitted to EMA a variation to update the product information to add a warning on hypoglycaemia. For background information, see [PRAC minutes January 2020](#). The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

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

- Based on the available data and the Rapporteur's assessment, the PRAC supported to update<sup>18</sup> the product information to reflect a warning on hypoglycaemia.

## **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. Bupivacaine - EMEA/H/C/004586**

Scope: Management of prolonged acute pain and reduction in need for opioids in adults compared to immediate-release bupivacaine

#### **5.1.2. Defatted powder of *Arachis hypogaea* L., semen (peanuts) - EMEA/H/C/004917**

Scope: Oral immunotherapy (OIT) for patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy

#### **5.1.3. Dostarlimab - EMEA/H/C/005204**

Scope (accelerated assessment): Treatment of deficient mismatch repair (dMMR),

<sup>18</sup> Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly

microsatellite instability-high (MSI-H) endometrial cancer (EC)

#### 5.1.4. Fenfluramine - EMEA/H/C/003933, Orphan

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Applicant: Zogenix GmbH

Scope: Treatment of seizures associated with Dravet syndrome in children aged 2 years to 17 years and adults

For further reference see, [PRAC minutes March 2020](#).

#### 5.1.5. Remdesivir - EMEA/H/C/005622<sup>19</sup>

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

At an extraordinary meeting convened remotely on 18 June 2020, the PRAC reviewed the proposed RMP in the context of an initial marketing authorisation application procedure. The PRAC is responsible for providing advice to the CHMP.

#### 5.1.6. Sodium thiosulfate - EMEA/H/C/005130

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Scope: Prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours

#### 5.1.7. Somapacitan - EMEA/H/C/005030, Orphan

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Applicant: Novo Nordisk A/S

Scope: Replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD)

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

See also Annex I 15.2.

#### 5.2.1. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1747/0231; LIFMIOR<sup>20</sup> - EMEA/H/C/004167/WS1747/0025

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 7.0) to revise the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to implement the outcomes of variation WS/1270 adopted in January 2019 and periodic single assessment procedure (PSUSA) PSUSA/001295/201902 adopted in September 2019 as requested by PRAC/CHMP in order to remove or consolidate several risks. Finally, the MAH removed the addendum to RMP (version 6.3), introduced some clinical and post-marketing data updates and reflected the completion of post-authorisation

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<sup>19</sup> PRAC advice adopted at an extraordinary meeting convened remotely on 18 June 2020

<sup>20</sup> Marketing authorisation(s) cessation dated 16 February 2020

studies

## Background

Etanercept is a tumour necrosis factor alfa (TNF- $\alpha$ ) inhibitor indicated, as Enbrel, for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis (AS), plaque psoriasis and paediatric plaque psoriasis under certain conditions.

The PRAC is evaluating a worksharing variation procedure for Enbrel, a centrally authorised medicine containing etanercept, in order to provide an updated RMP in line with a revised list of safety concerns according to current guidelines and in line with the outcome of several completed procedures, including the periodic single assessment procedure (PSUSA) PSUSA/001295/201902 adopted in September 2019. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. For further background, see [PRAC minutes February 2020](#).

## Summary of advice

- The RMP (version 7.4) for Enbrel (etanercept) in the context of the variation procedure under evaluation is considered acceptable.
- The PRAC supported the removal of the existing educational material for prescribers on 'potential for medication errors' as these risk and risk minimisations are well integrated in clinical practice and adequately controlled by routine risk minimisation measures (RMMs). Also, the most recent cumulative review of medication errors events showed that the vast majority were non-serious. The patient card should be maintained. Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly.

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

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

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

## 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.

The PRAC is evaluating a type II variation procedure for Jinarc, a centrally authorised medicine containing tolvaptan, to update the RMP to include dehydration and the pregnancy prevention programme as additional risk minimisation measures (aRMM) in order to align the RMP with Annex II-D. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

### Summary of advice

- The RMP for Jinarc (tolvaptan) in the context of the variation procedure under evaluation could be considered acceptable provided that an update to RMP version 14.4 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the MAH should provide clarifications on inconsistencies between statements in the company core data sheet (CCDS) and the product information with regards to dose limits for teratogenic effects.

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

See also Annex I 15.3.

### 5.3.1. Stiripentol - DIACOMIT (CAP) - EMEA/H/C/000664/X/0032

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Applicant: Biocodex

PRAC Rapporteur: Maia Uusküla

Scope: Extension application to add a new strength of 100 mg capsules. The RMP (version 2.0) is updated in accordance

#### Background

Stiripentol is an antiepileptic indicated, as Diacomit, for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose patients with severe myoclonic epilepsy in infancy whose seizures are not adequately controlled with clobazam and valproate.

The CHMP is evaluating an extension application for Diacomit, a centrally authorised product containing stiripentol, in order to add a new strength of 100 mg capsules. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

#### Summary of advice

- The RMP for Diacomit (stiripentol) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 2.0 is submitted.
- The PRAC agreed that the MAH should review the proposed safety specification to remove the important identified risks and important potential risks unless details on the post-marketing survey conducted in Japan reveals the occurrence of adverse drug reactions (ADRs) under actual conditions of use of Diacomit (stiripentol) and long-term treatment. In addition, 'safety in children under 3 years of age' should be classified as missing information in the PSUR safety specification and a detailed review should be provided with the next PSUR<sup>21</sup>.

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<sup>21</sup> Data lock point (DLP): 04/11/2020

## 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. Artemimol, piperazine tetraphosphate - EURARTESIM (CAP) - PSUSA/00001069/201910

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Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### Background

Artemimol/piperazine tetraphosphate are antimalarials indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, adolescents, children and infants 6 months and over and weighing 5 kg or more.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Eurartesim, a centrally authorised medicine containing artemimol/piperazine tetraphosphate 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 Eurartesim (artemimol/piperazine tetraphosphate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on the risk of resistance development in *P. falciparum* against artemisinins and/or piperazine and to add a warning on geographical drug resistance. In addition, the interaction with efavirenz should be added and the interaction with some medicinal products that were withdrawn in the EU (such as amprenavir, nelfinavir and nefazodone) should be removed and replaced with darunavir and lopinavir. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>22</sup>.
- In the next PSUR, the MAH should monitor possible effects on female fertility.

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. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/201911

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

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<sup>22</sup> Update of SmPC sections 4.1, 4.4 and 4.5. 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

Atezolizumab is an immunoglobulin G1 (IgG1) monoclonal antibody indicated, as monotherapy, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumours have a programmed death-ligand 1 (PD-L1) expression  $\geq 5\%$ . It is also indicated, as monotherapy, for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy and in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic NSCLC. It is also indicated, in combination with nab-paclitaxel, for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumours have PD-L1 expression  $\geq 1\%$  and who have not received prior chemotherapy for metastatic disease.

Based on the assessment of the 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 uveitis and psoriasis as undesirable effects with a frequency 'rare' and 'uncommon', respectively. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>23</sup>.
- In the next PSUR, the MAH should provide a cumulative review of case of atezolizumab-induced bullous pemphigoid and discuss the biologic plausibility, in line with the study by *Leavitt et al*<sup>24</sup>. The MAH should also provide a discussion on several studies that report case of atezolizumab-induced tumour lysis syndrome (TLS) as well as a detailed cumulative review of cases of arthritis from clinical trial, post-marketing and literature data. The MAH should also provide a cumulative review of cases of sarcoidosis and discuss data supporting the occurrence of immune checkpoint inhibitor (ICI) induced sarcoidosis-like reactions. Finally, the MAH should provide a detailed cumulative review of cases of generalised oedema/capillary leak syndrome. For all reviews, the MAH should 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.

### 6.1.3. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/201911

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

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<sup>23</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>24</sup> Leavitt E, Holland V. A case of atezolizumab-induced photodistributed bullous pemphigoid. *Dermatologic Therapy*. 2019;32:e12924. <https://doi.org/10.1111/dth.12924>



Scope: Evaluation of a PSUSA procedure

### **Background**

Erenumab is a human monoclonal antibody indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

Based on the assessment of the 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 a new warning on constipation including information on characteristic signs and consideration to seek medical attention and to discontinue treatment with erenumab in case of severe constipation. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>25</sup>.
- In the next PSUR, the MAH should provide an updated cumulative review of cases of alopecia and a cumulative review of cases of severe constipation with a proposal for further risk minimisation measures, 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.

#### **6.1.4. Fluciclovine (<sup>18</sup>F) - AXUMIN (CAP) - PSUSA/00010594/201911**

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Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

### **Background**

Fluciclovine (<sup>18</sup>F) is a diagnostic radiopharmaceutical indicated for positron emission tomography (PET) imaging to detect recurrence of prostate cancer in adult men with a suspected recurrence based on elevated blood prostate specific antigen (PSA) levels after primary curative treatment.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Axumin, a centrally authorised medicine containing fluciclovine (<sup>18</sup>F) 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 Axumin (fluciclovine (<sup>18</sup>F)) in the approved indication(s) remains unchanged.

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<sup>25</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

- Nevertheless, the product information should be updated to include a warning concerning bladder voiding instructions prior to administration. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>26</sup>.
- In the next PSUR, the MAH should monitor cases of fluciclovine (<sup>18</sup>F) uptake in the celiac ganglia and consider an update of the educational materials, as warranted.

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

### 6.1.5. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - PSUSA/00009175/201911

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### Background

Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) is an adjuvanted non-infectious recombinant papillomavirus vaccine indicated for use from the age of 9 years old for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic human papillomavirus (HPV) types.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cervarix, a centrally authorised medicine containing human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) and issued a recommendation on its marketing authorisation(s).

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Cervarix (human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 90 days, a detailed review of the data on autoimmunity and autoantibodies from the study by *Hineno et al.*<sup>27</sup> taking into consideration the review of *Blitshetyn et al.*<sup>28</sup>.
- In the next PSUR, the MAH should provide information on the use of Cervarix (human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)) in human

<sup>26</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

<sup>27</sup> Hineno A, Shu-ichi Ikeda, Scheibenbogen C, Heidecke H, Schulze-Forster K, Junker, et al. Autoantibodies against autonomic nerve receptors in adolescent Japanese girls after immunization with human papillomavirus vaccine. *Ann Arthritis Clin Rheumatol.* 2019;2(2):1014

<sup>28</sup> Blitshetyn S, Brinth L, Hendrickson JE, Martinez-Lavin M. Autonomic dysfunction and HPV immunization: an overview. *Immunol Res.* 2018;66(6):744-54

immunodeficiency virus (HIV)-infected subjects or subjects with known immune deficiencies, data on exposure to the vaccine during pregnancy and a literature review on potential immune mediated diseases (pIMDs) and autonomic disorders.

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.

#### 6.1.6. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/201911

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

##### **Background**

Ibrutinib is a protein kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma, as a single agent. It is indicated, as Imbruvica, alone or in combination with obinutuzumab, for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). It is also indicated, as a single agent or in combination with bendamustine and rituximab, for the treatment of adult patients with CLL who have received at least one prior therapy. Moreover, as a single agent, it is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. In combination with rituximab, it is also indicated for the treatment of adult patients with WM.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Imbruvica, a centrally authorised medicine(s) containing ibrutinib and issued a recommendation on its marketing authorisation(s). An oral explanation with the MAH took place at the meeting.

##### **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 on splenic rupture following discontinuation of ibrutinib treatment as well as warnings on cardiac failure and on haemophagocytic lymphohistiocytosis (HLH). In addition, cardiac failure and neutrophilic dermatoses should be added as undesirable effects with a frequency 'common' and 'uncommon' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>29</sup>.
- In the next PSUR, the MAH should provide a detailed review of cases of nail and nail bed disorders. The MAH should also provide cumulative reviews of cases of fatal cardiovascular events, of cases of uveitis with a special caution on cases with macular oedema, of cases of pyogenic granuloma, of cases of pseudolymphoma, of cases of dry

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<sup>29</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

eye as well as of cases of eye/retinal haemorrhage especially those leading to blindness, together with a proposal for updating the product information as appropriate. Moreover, the MAH should provide a cumulative analysis of toxic skin eruption, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS). Furthermore, the MAH should provide a detailed analysis of all new cases reporting Guillain-Barre syndrome (GBS), renal failure and cardiac tamponade/pericardial disorders. Finally, the MAH should add HLH as an important potential risk in the PSUR.

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. Ixazomib - NINLARO (CAP) - PSUSA/00010535/201911

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### **Background**

Ixazomib is a selective and reversible proteasome inhibitor indicated as Ninlaro for the treatment of adult patients with multiple myeloma who have received at least one prior therapy, in combination with lenalidomide and dexamethasone.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ninlaro, a centrally authorised medicine containing ixazomib 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 Ninlaro (ixazomib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on thrombotic microangiopathy and to add thrombotic microangiopathy as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>30</sup>.
- The MAH should submit to EMA, within 60 days, a review of acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumour lysis syndrome as undesirable effects and calculate their frequencies as applicable.
- In the next PSUR, the MAH should provide a cumulative review of cases of cytolytic hepatitis and discuss a possible cross reaction with other proteasome inhibitors with a proposal for updating the product information, as appropriate.

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

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<sup>30</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

### 6.1.8. Rotavirus vaccine pentavalent (live, oral) - ROTATEQ (CAP) - PSUSA/00002666/201911

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Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### **Background**

Rotavirus vaccine pentavalent (live, oral) is a viral vaccine indicated as RotaTeq for the active immunisation of infants from the age of 6 weeks to 32 weeks for prevention of gastroenteritis due to rotavirus infection.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of RotaTeq, a centrally authorised medicine containing rotavirus vaccine pentavalent (live, oral) 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 RotaTeq (rotavirus vaccine pentavalent (live, oral)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the use of the vaccine in children who have been in utero exposed to immunosuppressive treatment. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>31</sup>.
- In the next PSUR, the MAH should present an updated comprehensive review of cases of Kawasaki disease and reviews for cases of immune thrombocytopenia (ITP)/thrombocytopenia, hematemesis and gastrointestinal necrosis.

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. Tenofovir alafenamide - VEMLIDY (CAP) - PSUSA/00010575/201911

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

#### **Background**

Tenofovir alafenamide is a reverse transcriptase inhibitor indicated as Vemlidy for the treatment of chronic hepatitis B in adults and adolescents (aged 12 years and older with body weight at least 35 kg).

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<sup>31</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

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Vemlidy (tenofovir alafenamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be amended to update the existing warning on nephrotoxicity with information regarding monitoring of renal function. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>32</sup>.
- In the next PSUR, the MAH should closely monitor cases of ocular effects (posterior uveitis), lactic acidosis, bone events, renal events, increased cholesterol and triglycerides with associated cardiovascular events as well as cases of drug ineffectiveness.

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.

Additionally, the PRAC considered that the warning on monitoring of laboratory parameters indicative of renal damage is also relevant for fixed dose combinations (FDC) of medicinal products containing tenofovir alafenamide for the treatment of HIV-infection and agreed that the product information of these medicinal products should be updated accordingly.

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

See Annex I 16.2.

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

See also Annex I 16.3.

### **6.3.1. Lenograstim (NAP) - PSUSA/00001839/201910**

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Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

#### **Background**

Lenograstim is a recombinant human granulocyte colony-stimulating factor (G-CSF) indicated to reduce the duration of neutropenia and its complications and for mobilisation of peripheral blood progenitor cells (PBPCs) for patients and donors.

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<sup>32</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

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lenograstim 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 lenograstim-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include venous thromboembolism and arterial thromboembolism as a warning and as an undesirable effect with a frequency 'not known'. In addition, C-reactive protein increased should be added as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>33</sup>.
- In the next PSUR, the MAH should provide cumulative reviews of cases of disseminated intravascular coagulation, of cases of multiple sclerosis and of cases of immunogenicity related to incidence and clinical implications of anti-G-CSF antibodies. The MAH should also discuss any potential increase of frequency and severity of all important identified and potential risks for patients and donors.

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

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

See also Annex I 16.4.

### **6.4.1. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/LEG 016**

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Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Cumulative review on use of ceftaroline in patients with cystic fibrosis and pooled population pharmacokinetic (PK) report based on recently published studies following the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00010013/201810) adopted in May 2019

#### **Background**

Ceftaroline fosamil is a cephalosporin antibacterial agent indicated, as Zinforo, for the treatment of complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP) in adults and children from the age of 2 months.

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 use of ceftaroline in patients with cystic fibrosis and pooled population pharmacokinetic (PK) report based on recently published studies. For background, see [PRAC minutes May 2019](#). The responses were assessed by the Rapporteur for further PRAC advice.

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<sup>33</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

### Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the product information should be updated<sup>34</sup> to include information about the use in patients with cystic fibrosis.
- The MAH should submit to EMA, within 60 days, a variation to update the product information of Zinforo (ceftaroline fosamil).

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

See Annex I 16.5.

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

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

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

#### Background

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

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

#### Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that further information was necessary before a conclusion can be reached can be made. In particular, the MAH should update the healthcare professional (HCP) reminder card with some key elements, and provide further justification relating to the status of the HCP brochure and patient reminder card.

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<sup>34</sup> Update of SmPC sections 4.4 and 5.2



- The MAH should submit, to the EMA, within 30 days, responses to the request for supplementary information (RSI).

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

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>35</sup>

See also Annex I 17.1.

- 7.1.1. Direct acting antivirals (DAAV):  
Dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir – ZEPATIER (CAP); glecaprevir, pibrentasvir – MAVIRET (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatasvir – EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/PSA/J/0055

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

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Substantial amendment for a joint protocol previously agreed in June 2018 (PSA/J/0028.1) for a non-interventional imposed PASS on early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAAV) therapy in order to estimate the risk of early HCC recurrence associated with DAAV therapy exposure relative to no DAAV therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

#### Background

Dasabuvir is a direct-acting antiviral indicated, as Exviera, for the treatment of chronic hepatitis C infection. Elbasvir and grazoprevir are direct-acting antivirals indicated, as Zepatier, for the treatment of chronic hepatitis C infection. Glecaprevir and pibrentasvir are direct-acting antivirals indicated, as Maviret, for the treatment of chronic hepatitis C infection. Ledipasvir and sofosbuvir are direct-acting antivirals indicated, as Harvoni, for the treatment of chronic hepatitis C infection. Ombitasvir and paritaprevir are direct-acting antivirals. Ritonavir is a protease inhibitor. In combination, ombitasvir/paritaprevir/ritonavir is indicated, as Viekirax, for the treatment of chronic hepatitis C infection. Sofosbuvir is a direct-acting antiviral indicated, as Sovaldi, for the treatment of chronic hepatitis C infection. Sofosbuvir and velpatasvir are direct-acting antivirals indicated, as Epclusa, for the treatment of chronic hepatitis C infection. Sofosbuvir, velpatasvir and voxilaprevir are direct-acting antivirals indicated in combination as Vosevi, for the treatment of chronic hepatitis C infection.

In 2016, a review of direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C in a referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)) was concluded at PRAC to assess the risk of hepatitis B virus (HBV) reactivation as well as the risk of unexpected early hepatocellular carcinoma (HCC) recurrence in patients

<sup>35</sup> In accordance with Article 107n of Directive 2001/83/EC

treated with a DAAV and to establish whether any measures are necessary to minimise these risks. The benefit-risk balance of Epclusa (sofosbuvir/velpatasvir), Exviera (dasabuvir), Harvoni (ledipasvir/sofosbuvir), Maviret (glecaprevir/ pibrentasvir), Sovaldi (sofosbuvir), Viekirax (ombitasvir/periteprevir/ritonavir), Vosevi (sofosbuvir/velpatasvir/voxilaprevir) and Zepatier (elbasvir/grazoprevir) was considered to remain favourable subject to amendments to the product information and to [conditions](#). As a condition, in order to evaluate the risk of early recurrence of HCC associated with DAAV, the MAHs shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. For further background, see [PRAC minutes December 2016](#), [PRAC minutes January 2018](#) and [PRAC minutes March 2020](#).

A substantial amendment for a joint protocol previously agreed in June 2018 for a prospective, non-interventional study evaluating the risk of early recurrence of HCC in HCV-infected patients after DAAV therapy compared to HCV-infected patients without previous DAAV therapy during routine clinical care with previous successfully treated HCC, was presented for further review by the PRAC.

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

- Having considered protocol version 4.1 in accordance with Article 107o of Directive 2001/83/EC, the PRAC considered that the study is non-interventional and the substantial amendments to the PASS protocol can be endorsed.
- Additionally, the PRAC recommended that the consortium of MAHs should perform a systematic review of all publicly available data regarding HCC recurrence, with a Cochrane-type methodology and if the data allow, a meta-analysis of the main outcomes should be performed. The systematic review and the meta-analysis should be submitted together with the final report of the PASS.
- The PRAC recommended that the MAH submit to EMA a variation procedure to update the RMP and Annex II-D accordingly.

## **7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>36</sup>**

See Annex I 17.2.

## **7.3. Results of PASS imposed in the marketing authorisation(s)<sup>37</sup>**

None

## **7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>38</sup>**

See also Annex I 17.4.

### **7.4.1. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0072/G**

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Applicant: Amgen Europe B.V.

<sup>36</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>37</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>38</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: Grouped variations consisting of the submission of the final reports for: 1) study 20101363 (listed as a category 3 study in the RMP): a non-interventional pharmacovigilance study of osteonecrosis of the jaw and infection leading to hospitalisation among patients with cancer treated with Xgeva (denosumab) or zoledronic acid in Sweden, Denmark and Norway; 2) study 20170728 (listed as a category 3 study in the RMP): a retrospective cohort study on incidence of new primary malignancies among patients with bone metastases from breast, prostate, or lung cancer treated with Xgeva (denosumab) or intravenous zoledronic acid. The RMP (version 35.0) is updated accordingly. In addition, the RMP is brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

### **Background**

Denosumab is a human monoclonal antibody (IgG2) indicated, as Xgeva, for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

As stated in the RMP of Xgeva (denosumab), the MAH conducted non-imposed non-interventional PASS studies including study 20101363: a non-interventional pharmacovigilance study of osteonecrosis of the jaw and infection leading to hospitalisation among patients with cancer treated with Xgeva (denosumab) or zoledronic acid in Sweden, Denmark and Norway; and study 20170728: a retrospective cohort study on incidence of new primary malignancies among patients with bone metastases from breast, prostate, or lung cancer treated with Xgeva (denosumab) or intravenous zoledronic acid to assess the risks of Xgeva (denosumab). The Rapporteur assessed the MAH's final study report.

### **Summary of advice**

- Based on the available data and the Rapporteur's review, the PRAC agreed that the product information should be updated<sup>39</sup> to include information about the incidence of osteonecrosis of the jaw in patients treated with Xgeva (denosumab) or zoledronic acid.

7.4.2. [Duloxetine - CYMBALTA \(CAP\) - EMEA/H/C/000572/WS1755/0083; DULOXETINE LILLY \(CAP\) - EMEA/H/C/004000/WS1755/0020; XERISTAR \(CAP\) - EMEA/H/C/000573/WS1755/0086; YENTREVE \(CAP\) EMEA/H/C/000545/WS1755/0068](#)

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study FIJ-MC-B059: an observational study to assess foetal outcomes following maternal exposure to duloxetine and the revised final report from study F1J-MC-B057: an observational study to assess maternal and foetal outcomes following exposure to duloxetine

### **Background**

Duloxetine is an antidepressant which is a combined serotonin (5-HT) and noradrenaline

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<sup>39</sup> Update of SmPC section 4.8

(NA) reuptake inhibitor. It is indicated, as Cymbalta, Duloxetine Lilly, Xeristar and Yentreve centrally authorised medicines, for the treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder. Yentreve (duloxetine) is also indicated for women for the treatment of moderate to severe stress urinary incontinence.

As stated in the RMP of Cymbalta, Duloxetine Lilly, Xeristar and Yentreve (duloxetine), the MAH conducted non-interventional PASS studies FIJ-MC-B059: an observational study to assess foetal outcomes following maternal exposure to duloxetine and study F1J-MC-B057: an observational study to assess maternal and foetal outcomes following exposure to duloxetine. The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see [PRAC minutes January 2020](#).

#### **Summary of advice**

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC agreed that the product information of duloxetine-containing products should be updated<sup>40</sup> to reflect the available knowledge with regard to the use of duloxetine during pregnancy.

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

See Annex I 17.1.

### **7.6. Others**

See Annex I 17.6.

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

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

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

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

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

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

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<sup>40</sup> Update of SmPC section 4.6. The package leaflet is updated accordingly

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

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

See Annex I 18.1.

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

See Annex I 18.2.

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

See 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**

None

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

None

### **10.3. Other requests**

None

## 10.4. Scientific Advice

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

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

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

None

### 11.2. Other requests

None

## 12. Organisational, regulatory and methodological matters

### 12.1. Mandate and organisation of the PRAC

#### 12.1.1. Pandemic - monthly summary safety reports - process for submission and assessment

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In the context of the coronavirus (COVID-19) pandemic, the EMA secretariat informed the PRAC of the process for submission of monthly summary safety reports to EMA, in order to rapidly detect trends in safety, and raise signals for medicinal products with an indication in COVID 19 treatment receiving a positive opinion for compassionate use and/or a positive opinion for marketing authorisation(s). The PRAC supported the way forward and requested to review the process once experience is gained.

#### 12.1.2. Pandemic - monthly summary safety reports – assessment report template

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Further to the explanations provided on the process for submission and assessment of monthly summary safety reports (see under 12.1.1. ), the EMA secretariat presented to PRAC the draft assessment report template for the submission of monthly summary safety reports to EMA. The PRAC adopted the template.

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

#### 12.2.1. Committee for Medicinal Products for Human Use (CHMP) - PRAC collaboration group – proposals for improvements

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PRAC lead: Martin Huber, Adrien Inoubli, Ulla Wandel-Liminga

Following the CHMP-PRAC strategic review and learning meeting (SRLM) held in Helsinki, Finland in October 2019 during the Finnish presidency of the EU, a 'CHMP-PRAC collaboration group' composed of CHMP and PRAC members as well as EMA staff members was set up as part of the agreed actions in order to identify various points where the collaboration between the CHMP and PRAC could be improved. The EMA Secretariat

presented on behalf of the CHMP-PRAC collaboration group proposals to address the identified issues. Further discussion will be scheduled in due course.

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

None

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

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

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

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

None

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

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

### **12.10.3. PSURs repository**

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None

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

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

Post-meeting note: following the PRAC meeting of June 2020, the updated EURD list was adopted by the CHMP and CMDh at their June 2020 meetings and published on the EMA website on 01/07/2020, see:

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

## **12.11. Signal management**

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

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PRAC lead: Menno van der Elst

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

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

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None

### **12.12.2. Additional monitoring**

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None



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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 24/06/2020, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

## **12.13. EudraVigilance database**

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

None

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

### 12.14.1. Risk management systems

None

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

None

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

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

None

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

None

### 12.15.3. COVID-19-vaccine monitoring – ACCESS<sup>41</sup> project - preparation

PRAC lead: Jean Michel Dogne, Brigitte Keller-Stanislawski, Adrien Inoubli

The EMA secretariat provided PRAC with an overview of the [ACCESS project](#) on the EMA contract with the Utrecht University (the Netherlands), to identify a Europe-wide network of data sources and test their utility in monitoring and investigating the coverage, safety and effectiveness of coronavirus (COVID-19) vaccines. The commissioned research will also measure background rates for adverse event of special interest (AESIs) that might need extra consideration in the monitoring of COVID-19 vaccines. Further updates will be given to PRAC in due course.

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<sup>41</sup> vACcine Covid-19 monitoring readinESS

#### 12.15.4. Registry-based studies – guideline - draft

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PRAC lead: Virginie Hivert, Brigitte Keller-Stanislawski, Sabine Straus, Ulla Wändel Liminga

The EMA Secretariat presented to PRAC the draft guideline on registry-based studies prepared by the EMA Cross-Committee Task Force on Registries following the public consultation on the discussion paper on 'use of patient disease registries for regulatory purposes – methodological and operational considerations by the (EMA/763513/2018)'. The guideline is primarily targeted at marketing authorisation applicants/MAHs and includes an Annex with considerations on registries. PRAC members were invited to provide written comments until 31 July 2020.

Post-meeting note: On 24 September 2020, the public consultation on the draft guideline on registry-based studies ([EMA/502388/2020](#)) was published on the EMA website and is open for comments until 31 December 2020.

### 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. Drug-induced hepatotoxicity - PRAC assessors' guide - draft

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PRAC lead: Menno van der Elst, Martin Huber

In line with the [PRAC work plan 2020](#), and as a follow-up to the last discussion (for further background, see [PRAC minutes May 2020](#)), the EMA secretariat presented to PRAC a further updated assessors' guide regarding drug-induced hepatotoxicity after implementation of PRAC comments. This is due for adoption in July 2020.

## 12.20.2. Serious cutaneous adverse reactions (SCARs) - PRAC assessors' guide - update

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PRAC lead: Sabine Straus, Zane Neikena

The drafting group presented to the PRAC the updated version of the assessors' guide which reflects the comments from the PRAC, following discussion in March 2020 and May 2020 PRAC. The PRAC adopted the updated guide.

As a follow-up to the May 2020 discussion (for further background, see [PRAC minutes May 2020](#)), the EMA secretariat presented to the PRAC a further updated assessors' guide regarding severe cutaneous adverse reactions (SCARs) following implementation of PRAC comments. The PRAC adopted the updated guide.

## 13. Any other business

None

## 14. Annex I – Signals assessment and prioritisation<sup>42</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>43</sup>.

#### 14.1.1. Capecitabine – CAPECITABINE ACCORD (CAP), CAPECITABINE MEDAC (CAP), CAPECITABINE TEVA (CAP), ECANSYA (CAP), XELODA (CAP); NAP

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Applicant(s): Accord Healthcare S.L.U.(Capecitabine Accord), Krka, d.d., Novo mesto (Ecansya), Medac Gesellschaft fur klinische Spezialpreparate mbH (Capecitabine Medac); Roche Registration GmbH (Xeloda), Teva B.V. (Capecitabine Teva)

PRAC Rapporteur: Martin Huber

Scope: Signal of anaphylactic reaction

EPITT 19561 – New signal

Lead Member State(s): DE

#### 14.1.2. Cefepime (NAP)

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Applicant(s): various

PRAC Rapporteur: Ana Sofia Diniz Martins

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

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<sup>42</sup> <sup>42</sup> Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

<sup>43</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

EPITT 17866 – New signal

Lead Member State(s): PT

#### 14.1.3. Cladribine - MAVENCLAD (CAP)

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Applicant(s): Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of seizure

EPITT 19573 – New signal

Lead Member State(s): PT

### 14.2. New signals detected from other sources

None

## 15. Annex I – Risk management plans

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

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

#### 15.1.1. Dasatinib - EMEA/H/C/005446

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Scope: Treatment of leukaemia

#### 15.1.2. Dasatinib - EMEA/H/C/005317

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Scope: Treatment of leukaemia

#### 15.1.3. Lenalidomide - EMEA/H/C/005306

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Scope: Treatment of multiple myeloma

#### 15.1.4. Pegfilgrastim - EMEA/H/C/005085

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Scope: Treatment of neutropenia

### 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. [Blinatumomab - BLINCYTO \(CAP\) - EMEA/H/C/003731/II/0033, Orphan](#)

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Submission of an updated RMP (version 11) in line with revision 2 of GVP module V on 'Risk management systems'. The protocol for study 20150136 (listed as a category 1 in the RMP/Annex II): an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices is updated and the enrolment period extended by 1 year. As a consequence, the milestones in the RMP are updated accordingly. In addition, the RMP includes a proposed update to the milestone of study 20180138 (listed as a category 3 study in the RMP): long-term follow-up of patients enrolled in TOWER study: a phase 3, randomized, open label study investigating the efficacy of the bispecific T-cell engager (BiTE) antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukaemia (ALL)

### 15.2.2. [Filgrastim - GRASTOFIL \(CAP\) - EMEA/H/C/002150/II/0030](#)

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP (version 6.0) in order to update the safety concerns and additional pharmacovigilance activities by removing the Severe Chronic Neutropenia International Registry (SCNIR) and the European Society for Blood and Marrow Transplant (EBMT) registries following the conclusion of the SCNIR and EBMT combined analysis report in line with the latest approved RMP (version 4.0) for Accofil (filgrastim) finalised within procedure II/037 concluded in October 2019

### 15.2.3. [Human coagulation factor VIII, human von Willebrand factor - VONCENTO \(CAP\) - EMEA/H/C/002493/II/0042](#)

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Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 7) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and reflect the completion of study CSLCT-BIO-12-83: a post-marketing study (PMS) to collect long-term data on the haemostatic efficacy of human coagulation factor VIII/von Willebrand factor (FVIII/VWF) complex in patients with von Willebrand disease (VWD) who require a VWF product to control a bleeding event or as prophylaxis therapy. In addition, the RMP is updated to request a waiver to study Biostate\_4001 (listed as a category 3 study in the RMP): a low-interventional multicentre PASS for Vocento (FVIII/VWF) for routine prophylaxis, treatment of bleeding events and/or surgery in male patients with haemophilia A due to feasibility reasons

### 15.2.4. [Ibrutinib - IMBRUVICA \(CAP\) - EMEA/H/C/003791/II/0061, Orphan](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Submission of an updated RMP (version 16.2) in order to introduce changes to safety concerns following the conclusions of renewal procedure R/049 finalised in April 2019. The MAH took the opportunity to include additional changes related to two post-authorisation measures, namely the postponement of the completion date of study PCI-32765MCL3002 (listed as a category 3 study in the RMP): a randomized, double-blind, placebo-controlled phase 3 study of the Bruton's tyrosine kinase (BTK) inhibitor, PCI-32765 (ibrutinib), in combination with bendamustine and rituximab (BR) in subjects with newly diagnosed mantle cell lymphoma and the removal of study 54179060CLL1017 on DDI in line with the conclusions of variation II/058 finalised in April 2020

#### 15.2.5. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0019/G, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) submission of the final report from study NSMM-5001 (listed as a specific obligation (SOB) in Annex II-E on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation): a global, prospective, non-interventional, observational efficacy study in multiple myeloma patients. Annex II and the RMP (version 5.0) are updated accordingly; 2) submission of an updated RMP (version 5.0) in order to extend the due date of post-authorisation efficacy study (PAES) C16010 (listed in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product': provision of an interim report of overall survival (OS) at the time of the third interim analysis and provision of a final report for the final analysis of OS from the phase 3, randomized, double-blind study C16010 in adult patients with relapsed and/or refractory multiple myeloma. The MAH took the opportunity to correct a typographical error in Annex II

#### 15.2.6. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0103

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 22.0) to include 'growth retardation' as an important identified risk as per the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002162/201901) finalised in September 2019, and to add study CAMN107A2203: a multicentre, open label, non-controlled phase 2 study to evaluate efficacy and safety of oral nilotinib in paediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in chronic phase (CP) or with Ph+ CML in CP or accelerated phase (AP) resistant or intolerant to either imatinib or dasatinib as an additional pharmacovigilance activity in relation to the important identified risk of 'growth retardation' to the pharmacovigilance plan. In addition, the additional pharmacovigilance activity of collection of gene signature data in patients who relapse on treatment-free remission (TFR) compared to patients who relapse on treatment is deleted from the RMP in line with the conclusions of MEA 051.1 concluded in October 2019. The MAH took the opportunity to revise the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'

15.2.7. Pioglitazone - GLIDIPION (CAP) - EMEA/H/C/002558/WS1791/0013;  
PIOGLITAZONE ACTAVIS (CAP) - EMEA/H/C/002324/WS1791/0014;  
PIOGLITAZONE TEVA (CAP) - EMEA/H/C/002297/WS1791/0023; PIOGLITAZONE  
TEVA PHARMA (CAP) - EMEA/H/C/002410/WS1791/0023

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Applicant(s): Actavis Group PTC ehf (Glipidion, Pioglitazone Actavis), Teva B.V.  
(Pioglitazone Teva, Pioglitazone Teva Pharma)

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of the RMP (version 4.0) in order to amend the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and in line with the RMP of the originator product containing pioglitazone. In addition, the educational pack for healthcare professionals (HCPs) and the prescriber guide are removed as additional risk minimisation measures (aRMMs) in line with the conclusions of the PSUR single assessment (PSUSA) procedure for pioglitazone and pioglitazone/glimepiride (PSUSA/00002417/201807) finalised in March 2019

15.2.8. Telotristat ethyl - XERMELO (CAP) - EMEA/H/C/003937/II/0021, Orphan

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Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

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

### 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. Albutrepenonacog alfa - IDELVION (CAP) - EMEA/H/C/003955/X/0035, Orphan

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Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add a new strength of 3,500 IU (700 IU/mL) for albutrepenonacog alfa powder and solvent for solution for injection. The RMP (version 3.1) is updated accordingly

15.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0042

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include in combination with platinum-based chemotherapy first-line treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC). As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 14.0) are updated accordingly

### 15.3.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0076

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information based on the final results from study BEL115467 (listed as an imposed PASS in Annex II): a randomized, double-blind, placebo-controlled 52-week study to assess adverse events of special interest in adults with active, autoantibody-positive systemic lupus erythematosus receiving belimumab. The package leaflet is updated accordingly. The RMP (version 36) is updated in accordance and also includes minor updates. In addition, the MAH took the opportunity to introduce minor editorial changes to Annex II and the labelling

### 15.3.4. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0030, Orphan

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the treatment of Philadelphia chromosome positive CD19<sup>44</sup> positive B-cell precursor acute lymphoblastic leukaemia (ALL) in adult and paediatric patients with relapsed or refractory ALL and adult patients in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. 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 10.0) are updated accordingly

### 15.3.5. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/II/0014

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Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.4 and 4.8 of the SmPC to reflect a signal of anaphylactic reaction detected in post marketing setting. The package leaflet and the RMP (version 1.2) are updated accordingly. The MAH took the opportunity to introduce minor updates throughout the product information

### 15.3.6. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0010/G, Orphan

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of an extension of indication to include the treatment of adults with X-linked hypophosphataemia (XLH), and modification of the currently approved indication in children and adolescents, by removing the qualification 'with growing skeletons', in order to include the treatment in all children with radiographic evidence of bone disease. The application provides new week-48 data from study UX023-CL304: a randomized, double-blind, placebo-controlled, phase 3 study with open-label extension to assess the efficacy and safety of burosumab (KRN23) in adults with XLH. 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

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<sup>44</sup> Cluster of differentiation 19



the RMP (version 2.0) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.7. [Certolizumab pegol - CIMZIA \(CAP\) - EMEA/H/C/001037/II/0087](#)

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to introduce a change in posology for axial spondyloarthritis (aSpA) and to update the safety and efficacy information based on the results of study AS0005 (C-OPTIMISE) (listed as a category 3 study in the RMP): a multicentre, open-label (part A) followed by a randomised, double-blind, parallel-group, placebo-controlled study (part B) to evaluate maintenance of remission in subjects with active aSpA receiving either certolizumab pegol 200mg once every 2 weeks (q2w) or 200mg once every 4 weeks (q4w) as compared to placebo. The package leaflet and the RMP (version 17.0) are updated accordingly. In addition, the interim study reports for studies AS0006 and AS0007 are submitted to include additional pooled safety data in the SmPC. Study AS0006 is a phase 3, multicentre, randomised, placebo-controlled, double-blind study to evaluate efficacy and safety of certolizumab pegol in subjects with active aSpA without x-ray evidence of ankylosing spondylitis and objective signs of inflammation. Study AS0007 is a multicentre, open-label study to assess the effects of certolizumab pegol on the reduction of anterior uveitis flares in aSpA subjects with a history of anterior uveitis (C-VIEW)

#### 15.3.8. [Clopidogrel - ISCOVER \(CAP\) - EMEA/H/C/000175/WS1820/0142; PLAVIX \(CAP\) - EMEA/H/C/000174/WS1820/0140](#)

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

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

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

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

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

### 15.3.10. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0039, Orphan

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of section 5.1 of the SmPC in order to amend information regarding immunogenicity following completion of post-authorisation commitments in variation II/030 (finalised in December 2019), variation II/032 (finalised in April 2020) on re-analysis of all anti-daratumumab antibodies (ADA) samples taken from previously submitted clinical studies, namely: 1) study MMY1001: an open-label, multicentre, phase 1b study of JNJ-54767414 (daratumumab) in combination with backbone regimens for the treatment of subjects with multiple myeloma; 2) study MMY3003: a phase 3, randomised trial comparing daratumumab, lenalidomide, and dexamethasone vs lenalidomide-dexamethasone in subjects with relapsed or refractory multiple myeloma; 3) study MMY3004: a phase 3, randomised trial comparing daratumumab, bortezomib, and dexamethasone vs bortezomib and dexamethasone in subjects with relapsed or refractory multiple myeloma; 4) study SMM2001: a randomised phase 2 trial to evaluate 3 daratumumab dose schedules in smoldering multiple myeloma; 5) study MMY1004: an open-label, multicentre, dose escalation phase 1b study to assess the safety and pharmacokinetics of subcutaneous delivery of daratumumab with the addition of recombinant human hyaluronidase (rHuPH20) for the treatment of subjects with relapsed or refractory multiple myeloma; 6) study MMY1008: a phase 1 study of subcutaneous delivery of JNJ-54767414 (daratumumab) in Japanese participants with relapsed or refractory multiple myeloma; 7) study MMY2040: a multicentre phase 2 study to evaluate subcutaneous daratumumab in combination with standard multiple myeloma treatment regimens; 8) study MMY3012: a phase 3 randomized, multicentre study of subcutaneous vs. intravenous administration of daratumumab in subjects with relapsed or refractory multiple myeloma; using the enhanced DT method (previously developed as a result of MEA 005). As a result, immunogenicity is removed from the RMP as an important potential risk considering the additional pharmacovigilance activity of 'investigation of a new method for detecting antidrug antibodies' as completed. The RMP (version 6.5) is updated accordingly

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

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

PRAC Rapporteur: Željana Margan Koletić

Scope: Extension of indication to include treatment of community acquired pneumonia (CAP) for Quofenix (delafloxacin) 450 mg tablets and 300 mg powder for concentrate for solution for infusion. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 2.0) are updated in accordance

### 15.3.12. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA<sup>45</sup>), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine - HEXACIMA (CAP) - EMEA/H/C/002702/WS1792/0099/G; HEXAXIM (Art 58<sup>46</sup>) -

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<sup>45</sup> Ribosomal deoxyribonucleic acid

<sup>46</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)

Applicant(s): Sanofi Pasteur (Hexaxim, Hexacima), Sanofi Pasteur Europe (Hexyon)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 5.1 of the SmPC in order to revise the existing warning regarding preterm infants and to add new information on immunogenicity in preterm infants and in infants born from women vaccinated during pregnancy based on the final results from study A3L00053-EXT: an observational cohort study conducted by the 'Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute (CEV) of University of Antwerp' with diphtheria, tetanus, pertussis, hepatitis b, poliomyelitis and haemophilus type b conjugate (DTaP-IPV-HB-PRP-T) vaccine, aimed to describe the concentrations of immunoglobulin G (IgG) against different antigens. The RMP (version 12.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'; 2) update of sections 2 and 4.4 of the SmPC in order to add a warning for the following excipients with known effects: phenylalanine, potassium and sodium in line with the Annex to the European Commission (EC) guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The package leaflet is updated accordingly. In addition, the MAH/Scientific opinion holder (SOH) took the opportunity to introduce editorial changes in sections 4.2, 4.4 and 4.5 of the SmPC and to update the list of local representatives in the package leaflet

#### 15.3.13. Eftrenonacog alfa - ALPROLIX (CAP) - EMA/H/C/004142/II/0029, Orphan

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

#### 15.3.14. Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP) - EMA/H/C/004781/X/0014/G

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (184mcg/55mcg/22mcg); 2) extension of indication to add maintenance treatment in adult patients with asthma. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 2.2) are updated in accordance

15.3.15. [Fluticasone furoate, umeclidinium, vilanterol - TEMYBRIC ELLIPTA \(CAP\) - EMEA/H/C/005254/X/0004/G](#)

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (184mcg/55mcg/22mcg); 2) extension of indication to add maintenance treatment in adult patients with asthma. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 2.2) are updated in accordance

15.3.16. [Fluticasone furoate, umeclidinium, vilanterol - TRELEGY ELLIPTA \(CAP\) - EMEA/H/C/004363/X/0012/G](#)

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (184mcg/55mcg/22mcg); 2) extension of indication to add maintenance treatment in adult patients with asthma. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 2.2) are updated in accordance

15.3.17. [Guselkumab - TREMFYA \(CAP\) - EMEA/H/C/004271/II/0017](#)

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. 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 5.1) are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.18. [Influenza vaccine surface antigen inactivated prepared in cell cultures - FLUCELVAX TETRA \(CAP\) - EMEA/H/C/004814/II/0013](#)

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Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to amend the existing indication on prophylaxis of influenza, from the currently approved age range 'adults and children from 9 years of age' to 'adults and children from 2 years of age'. 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 2.1) are updated in accordance

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

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults with no epidermal growth factor receptor (EGFR) or anaplastic large-cell lymphoma kinase (ALK) positive tumour mutations for combination of Odivo (nivolumab) and Yervoy (ipilimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. The RMPs (version 17.0 for Odivo (nivolumab), version 27.0 for Yervoy (ipilimumab)) are updated accordingly

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

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Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kimmo Jaakkola

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

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

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

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

### 15.3.22. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/II/0029

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Applicant: Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to add the treatment of schizophrenia in adolescent from 13 to less than 18 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the product information in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and to update the list of local representatives in the package leaflet

#### 15.3.23. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0035

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include the use of Lynparza (olaparib) tablets in combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO<sup>47</sup> stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy with bevacizumab. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 19.0) are updated accordingly. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza (olaparib) hard capsules are revised based on updated safety data analysis. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.24. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0036

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include the use of Lynparza (olaparib) tablets as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene mutations (germline and/or somatic) who have progressed following a prior new hormonal agent. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 20) are updated accordingly. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza (olaparib) hard capsules are revised based on updated safety data analysis

#### 15.3.25. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/II/0101

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include treatment of nasal polyps in adult patients with inadequate response to intranasal corticosteroids. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 16.0) are updated in accordance. In addition, the MAH took the opportunity to introduce minor editorial changes in section 4.2 of the SmPC and in the package leaflet and to update

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<sup>47</sup> International Federation of Gynaecology and Obstetrics

the details of the Dutch local representative. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

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

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

#### **15.3.27. Pemetrexed - PEMETREXED ACCORD (CAP) - EMEA/H/C/004072/X/0010**

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Adrien Inoubli

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (25 mg/mL solution for infusion). The RMP (version 1.0) is updated accordingly

#### **15.3.28. Prucalopride - RESOLOR (CAP) - EMEA/H/C/001012/II/0051**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of Section 4.4 of the SmPC with suicidal ideation and behaviour and to add 'suicidal ideation and behaviour' to the list of safety concerns as an important potential risk in the RMP based on post-marketing reports. The package leaflet and the RMP (version 16.0) are updated accordingly. The MAH took to opportunity to introduce editorial changes to the RMP and SmPC

#### **15.3.29. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS1830/0032; NEPARVIS (CAP) - EMEA/H/C/004343/WS1830/0029**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study CLCZ696D2301 (PARAGON HF) (listed as a category 3 study in the RMP): a multicentre, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 (sacubitril/valsartan) compared to valsartan, on morbidity and mortality in heart failure patients (NYHA<sup>48</sup> class II-IV) with preserved ejection fraction to evaluate cognitive function. The RMP (version 2.0) is updated accordingly

#### **15.3.30. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/X/0043/G**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

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<sup>48</sup> New York Heart Association

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength (200/50 mg film-coated tablets). The new formulation is indicated for the treatment of chronic hepatitis C (CHC) in patients aged 6 years and older; 2) inclusion of paediatric use in patients aged 6 to <18 years who weigh greater than or equal to 35 kg to the existing presentation (400/100 mg film-coated tablets). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 5.1) are updated in accordance

#### **15.3.31. Tacrolimus - PROTOPIC (CAP) - EMEA/H/C/000374/II/0083/G**

Applicant: LEO Pharma A/S

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC following results from two non-interventional PASS, namely: 1) JOELLE study (listed as a category 3 study in the RMP): a joint European longitudinal lymphoma and skin cancer evaluation; 2) APPLES study (listed as a category 3 study in the RMP): a prospective paediatric longitudinal evaluation to assess the long-term safety of tacrolimus ointment for the treatment of atopic dermatitis. The package leaflet and the RMP (version 15.1) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

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

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

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

## **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. Acridinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201911**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

### **16.1.2. 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/00010505/201911**

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Applicant: Orchard Therapeutics (Netherlands) BV, ATMP<sup>49</sup>

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### **16.1.3. Avatrombopag - DOPTLET (CAP) - PSUSA/00010779/201911**

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Applicant: Dova Pharmaceuticals Ireland Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

### **16.1.4. Bazedoxifene - CONBRIZA (CAP) - PSUSA/00000302/201910**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

### **16.1.5. Benralizumab - FASENRA (CAP) - PSUSA/00010661/201911**

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Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

### **16.1.6. Buprenorphine<sup>50</sup> - SIXMO (CAP) - PSUSA/00010778/201911**

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Applicant: L. Molteni & C. dei Fratelli Alitti Societa di Esercizio S.p.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

<sup>50</sup> Implant(s) only

**16.1.7. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/201911**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

**16.1.8. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/201911**

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Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

**16.1.9. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/201911**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

**16.1.10. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/201911**

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Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.11. Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/201911**

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Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

**16.1.12. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/201911**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

**16.1.13. Empagliflozin, linagliptin - GLYXAMBI (CAP) - PSUSA/00010539/201911**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### 16.1.14. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/201911

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

#### 16.1.15. Gemtuzumab ozogamicin - MYLOTARG (CAP) - PSUSA/00010688/201911

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

#### 16.1.16. Glibenclamide<sup>51</sup> - AMGLIDIA (CAP) - PSUSA/00010690/201911

Applicant: Ammtek

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### 16.1.17. Hydrocortisone<sup>52</sup> - PLENADREN (CAP) - PSUSA/00009176/201911

Applicant: Shire Services BVBA

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### 16.1.18. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/201911

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.19. Ketoconazole<sup>53</sup> - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201911

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

#### 16.1.20. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/201911

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

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<sup>51</sup> Centrally authorised product(s) only

<sup>52</sup> Treatment of adrenal insufficiency, modified-release tablets only

<sup>53</sup> Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

#### 16.1.21. Letermovir - PREVYMIS (CAP) - PSUSA/00010660/201911

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.1.22. Necitumumab - PORTRAZZA (CAP) - PSUSA/00010471/201911

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

#### 16.1.23. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/201911

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.24. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/201911

Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

#### 16.1.25. Pegvaliase - PALYNZIQ (CAP) - PSUSA/00010761/201911

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.26. Prasterone<sup>54</sup> - INTRAROSA (CAP) - PSUSA/00010672/201911

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.27. Prucalopride - RESOLOR (CAP) - PSUSA/00002568/201910

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

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<sup>54</sup> Pessary, vaginal use only

Scope: Evaluation of a PSUSA procedure

**16.1.28. Rituximab - BLITZIMA (CAP); MABTHERA (CAP); RITEMVIA (CAP); RIXATHON (CAP); RIXIMYO (CAP); TRUXIMA (CAP) - PSUSA/00002652/201911**

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

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

**16.1.29. Ruriococog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/201911**

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.1.30. Stiripentol - DIACOMIT (CAP) - PSUSA/00002789/201911**

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Applicant: Biocodex

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

**16.1.31. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/201911**

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.32. Tofacitinib - XELJANZ (CAP) - PSUSA/00010588/201911**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

**16.1.33. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/201911**

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Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

**16.1.34. Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/201911**

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

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/00000425/201911**

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

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

### **16.2.2. Tadalafil - ADCIRCA (CAP); CIALIS (CAP); TADALAFIL LILLY (CAP); NAP - PSUSA/00002841/201910**

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Applicants: Eli Lilly Nederland B.V. (Adcirca, Cialis, Tadalafil Lilly), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

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

### **16.3.1. Calcium salts, colecalciferol (NAP) - PSUSA/00010386/201910**

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### **16.3.2. Clevidipine (NAP) - PSUSA/00010288/201911**

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### **16.3.3. Corticorelin (NAP) - PSUSA/00000876/201910**

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### **16.3.4. Fluticasone, salmeterol<sup>55</sup> (NAP) - PSUSA/00001455/201910**

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Applicant(s): various

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<sup>55</sup> For nationally approved product(s) only

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### **16.3.5. Human coagulation factor VII (NAP) - PSUSA/00001619/201910**

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Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

#### **16.3.6. Isoflurane (NAP) - PSUSA/00001786/201910**

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

#### **16.3.7. Isoniazid (NAP) - PSUSA/00001789/201911**

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### **16.3.8. Methoxyflurane (NAP) - PSUSA/00010484/201911**

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### **16.3.9. Ozenoxacin (NAP) - PSUSA/00010651/201911**

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Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### **16.3.10. 1-propanol, 2-propanol, orthophenylphenol (NAP) - PSUSA/00010406/201910**

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Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### **16.3.11. Tetrabenazine (NAP) - PSUSA/00002911/201910**

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Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

#### **16.3.12. Timolol<sup>56</sup> (NAP) - PSUSA/00010432/201910**

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Applicant(s): various

PRAC Lead: Jana Lukačšínová

Scope: Evaluation of a PSUSA procedure

#### **16.3.13. Tixocortol (NAP); chlorhexidine gluconate, tixocortol pivalate (NAP) - PSUSA/00010333/201911**

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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**

#### **16.4.1. Octocog alfa - ADVATE (CAP) - EMEA/H/C/000520/LEG 100**

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Applicant: Takeda Manufacturing Austria AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Review of cases with a fatal outcome and updated information on reports indicative of factor VIII (FVIII) inhibition, following the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00002200/201908) adopted in April 2020

#### **16.4.2. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/LEG 062.1**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 062 [cumulative review of severe cutaneous skin reactions (SCARs) following the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00002326/201901) adopted in September 2019] as per the request for supplementary information (RSI) adopted in January 2020

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

#### **16.5.1. Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/II/0066/G, Orphan**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on drug-induced liver injury (DILI) as requested in the conclusions of LEG 015 concluded in February 2020, assessing a review of cases of serious

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<sup>56</sup> For systemic use only



hepatic reactions and cases of hyponatremia and adequacy of the risk minimisation measures (RMM) of the product information requested in the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00002435/201902) adopted in September 2019. The package leaflet and the RMP (version 10.0) are updated accordingly. In addition, the MAH took the opportunity to amend the package leaflet to reflect information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' as well as minor changes; 2) update of sections 4.4 and 4.8 of the SmPC in order to add a warning on hyponatraemia and to add hyponatraemia to the list undesirable effects as requested in the conclusions of LEG 015 assessing a review of cases of hyponatremia requested in the conclusions of PSUSA procedure (PSUSA/00002435/201902)

## **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. Buprenorphine – SIXMO (CAP) - EMEA/H/C/PSP/S/0086.1**

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Applicant: L. Molteni & C. dei Fratelli Alitti Societa di Esercizio S.p.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to PSP/S/0086 [protocol for study MOLTeNI-2019-01: a prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in the routine clinical care] as per the request for supplementary information (RSI) adopted in February 2020

#### **17.1.2. Dinutuximab beta – QARZIBA (CAP) - EMEA/H/C/PSA/S/0047.1**

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Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0047 [substantial amendment to a previously agreed protocol (PSP/S/0065) in July 2018: a registry of patients with high-risk neuroblastoma being treated with Qarziba (dinutuximab beta) to assess: 1) pain severity and use of analgesics during treatment; 2) incidence of neurotoxicity, visual impairment, capillary leak syndrome, cardiovascular events and hypersensitivity reactions; 3) long term safety] as per the request for supplementary information (RSI) adopted in February 2020

#### **17.1.3. Eliglustat – CERDELGA (CAP) - EMEA/H/C/PSA/S/0054**

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Applicant: Genzyme Europe BV

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

PRAC Rapporteur: Eva Segovia

Scope: Substantial amendment to a protocol previously agreed in December 2018 (PSA/S/0035) for a prospective multicentre observational post authorisation safety sub-registry to characterize the long-term safety profile of commercial use of Cerdelga (eliglustat) in adult patients with Gaucher disease

#### **17.1.4. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064.4**

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Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0064.3 [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 2020

#### **17.1.5. Parathyroid hormone – NATPAR (CAP) - EMEA/H/C/PSA/S/0053**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Substantial amendment to a protocol previously agreed in March 2018 (PSA/S/0026) for study PARADIGHM (physicians advancing disease knowledge in hypoparathyroidism): a registry for subjects with chronic hypoparathyroidism to explore physicians advancing disease knowledge in hypoparathyroidism

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

#### **17.2.1. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 053.3**

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 053.2 [amendment to a previously agreed protocol for study M07-001: a prospective registry for an observational, multicentre, multinational study of patients with paroxysmal nocturnal haemoglobinuria (PNH)] as per the request for supplementary information (RSI) adopted in February 2020

#### **17.2.2. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/MEA 005.4**

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Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 005.3 [amendment to a previously agreed protocol (version 2.0) for study EVM-19596-00-001 (listed as a category 3 study in the RMP): a drug

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

utilisation study (DUS) using relevant healthcare databases at two different time periods in order to define the compliance to contraindications over time and the number of subjects diagnosed with pancreatitis after eluxadoline treatment] as per the request for supplementary information (RSI) adopted in February 2020

#### 17.2.3. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/MEA 027.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 027 [protocol for study EXCEED (listed as a category 3 study in the RMP): a pan-European PASS to assess the risk of pancreatic cancer among type 2 diabetes mellitus (T2DM) patients who initiated exenatide as compared with those who initiated other non-glucagon-like peptide 1 receptor agonists based glucose lowering drugs] as per the request for supplementary information (RSI) adopted in January 2020

#### 17.2.4. Exenatide - BYETTA (CAP) - EMEA/H/C/000698/MEA 047.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 027 [protocol for study EXCEED (listed as a category 3 study in the RMP): a pan-European PASS to assess the risk of pancreatic cancer among type 2 diabetes mellitus (T2DM) patients who initiated exenatide as compared with those who initiated other non-glucagon-like peptide 1 receptor agonists based glucose lowering drugs] as per the request for supplementary information (RSI) adopted in January 2020

#### 17.2.5. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/MEA 009.1

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: MAH's response to MEA 009 [protocol for study EPI-ZOSTER-030 VS (targeted safety study): a non-interventional/observational prospective cohort study to evaluate the safety of Shingrix (herpes zoster vaccine) in older adults ( $\geq 50$  year of age) in the United States [final clinical study report (CSR) expected in March 2025] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in March 2020

#### 17.2.6. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/MEA 020.1

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: MAH's response to MEA 020 [protocol for study EPI-ZOSTER-032 VS: a non-interventional/observational targeted safety study to evaluate the safety of Shingrix (herpes zoster vaccine) in the Medicare population (65 years old or older) in the United States [final clinical study report (CSR) expected in June 2027]] as per the request for supplementary

information (RSI) adopted in March 2020

#### [17.2.7. Siponimod - MAYZENT \(CAP\) - EMEA/H/C/004712/MEA 002](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Protocol for a study (listed as a category 3 study in the RMP) on pregnancy outcomes intensive monitoring (PRIM) in order to prospectively collect and evaluate safety data on pregnancy outcomes and congenital malformations related to siponimod exposure immediately before and during pregnancy [final clinical study report (CSR) expected in 2030] (from initial opinion/marketing authorisation(s) (MA))

#### [17.2.8. Siponimod - MAYZENT \(CAP\) - EMEA/H/C/004712/MEA 004](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Protocol for a survey study (listed as a category 3 study in the RMP) among healthcare professionals (HCPs) and patients/caregivers in selected European countries in order to evaluate whether HCPs and patients/caregivers receive the educational materials and to capture their knowledge and behaviour around specific siponimod safety measures (from initial opinion/marketing authorisation(s) (MA))

#### [17.2.9. Tafamidis - VYNDAQEL \(CAP\) - EMEA/H/C/002294/MEA 016](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Amendment to a protocol previously agreed by CHMP for study B3461001: a sub-analysis of 'transthyretin amyloidosis outcomes survey (THAOS)': a global, multicentre, longitudinal, observational survey of patients with documented transthyretin (TTR) gene mutations or wild-type ATTR amyloidosis, in order to evaluate the effects of tafamidis in non-V30M patients

#### [17.2.10. Upadacitinib - RINVOQ \(CAP\) - EMEA/H/C/004760/MEA 003](#)

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study P19-150: a long-term post-authorisation safety study (PASS) of upadacitinib use in rheumatoid arthritis (RA) patients in Europe to evaluate the safety of upadacitinib among patients with RA receiving routine clinical care (from initial opinion/marketing authorisation(s) (MA)) [final study report expected in March 2030]

#### [17.2.11. Upadacitinib - RINVOQ \(CAP\) - EMEA/H/C/004760/MEA 004](#)

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study P19-141: a long-term post-authorisation safety study (PASS) of upadacitinib use in rheumatoid arthritis (RA) patients in the US in order to: 1) compare the incidence of malignancy, non-melanoma skin cancer (NMSC), major adverse cardiovascular events (MACE), venous thromboembolism (VTE) and serious infection events in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA; 2) describe the incidence rates of herpes zoster, opportunistic infections and evidence of drug-induced liver injury (DILI); 3) describe the incidence of the above outcomes in very elderly patients (aged  $\geq$  75 years); 4) characterise VTE clinical risk factors and baseline biomarkers in a sub-study of new initiators of upadacitinib and comparator biologic therapies (from initial opinion/marketing authorisation(s) (MA)) [final study report expected in March 2033]

#### **17.2.12. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 005**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study P20-199: a drug utilisation study (DUS) to evaluate the effectiveness of the additional risk minimisation measures (aRMM) in place to describe the baseline characteristics of new users of upadacitinib, and in a similar manner, to describe new users of a biological disease-modifying antirheumatic drugs (bDMARD) for comparison (from initial opinion/marketing authorisation(s) (MA)) [final study report expected in September 2024]

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

None

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

#### **17.4.1. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/II/0033**

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final study report for study 178-CL-114: an evaluation of cardiovascular events in users of mirabegron and other treatments for overactive bladder

#### **17.4.2. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0023**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from study A3921205 (listed as a category 3 study in the RMP): an observational, PASS within the Consortium of Rheumatology Researchers of North America (CORRONA) registry comparing rates of malignancy, cardiovascular and

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

<sup>60</sup> In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

serious infection outcomes among patients treated for moderately to severely active rheumatoid arthritis. The RMP (version 10.1) is updated accordingly

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

### **17.5.1. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.14**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Seventh annual interim report for study BEL116543/HGS1006-C1124 (SABLE): a long-term controlled safety registry evaluating the incidence of all-cause mortality and adverse events of special interest (AESIs) in patients with systemic lupus erythematosus followed for a minimum of 5 years

### **17.5.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 013.5**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 013.4 [interim report for study BEL114256/ HGS1006-C1101: a pregnancy register collecting information on pregnancy and live birth outcomes, and following infants for serious infections during the first year of life [final report submission extended from April 2019 to April 2022]] as per the request for supplementary information (RSI) adopted in January 2020

### **17.5.3. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.7**

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Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: 5-year interim results for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation, in light of available data [final clinical study report (CSR) expected in December 2024]

### **17.5.4. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.7**

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Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year interim results for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation, in light of available data [final clinical study report (CSR) expected in December 2024]

#### **17.5.5. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 041.3**

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Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Fourth interim report for the Insuman (insulin human) 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

#### **17.5.6. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/ANX 041.8**

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Applicant: Celgene Europe BV

PRAC Rapporteur: Adrien Inoubli

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

#### **17.5.7. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/MEA 036.6**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Annual report (covering the period from 01 February 2019 to 31 January 2020) for a drug utilisation study (DUS) on the effectiveness of risk minimisation measures (RMM) for multiple patch use

#### **17.5.8. Rivastigmine - PROMETAX (CAP) - EMEA/H/C/000255/MEA 037.6**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Annual report (covering the period from 01 February 2019 to 31 January 2020) for a drug utilisation study (DUS) on the effectiveness of risk minimisation measures (RMM) for multiple patch use

#### **17.5.9. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.5**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Third 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]

#### 17.5.10. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.7

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Third 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]

#### 17.5.11. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002.2

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Third 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 - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Third 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. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002.4

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Interim report for safety surveillance programme using existing EU rheumatoid arthritis (RA) registries conducted in four countries: Germany (German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (OBS15180)), Spain (Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER) (6R88-RA-1720)), Sweden (Register for Antirheumatic Therapies in Sweden (ARTIS) (OBS15220)) and UK (British Society for Rheumatology Biologicals Register (BSRBR) (6R88-RA-1634))

#### 17.5.14. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.5

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli



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

#### **17.5.15. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018.3**

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Fourth 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]

#### **17.5.16. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.7**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Second 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. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/MEA 013.3**

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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

#### **17.6.2. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/LEG 028.1**

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adrien Inoubli

Scope: Second six-monthly update on the development of multi-dose nasal spray DoseGuard as requested in the conclusions of procedure R/0049 finalised in April 2019

### **17.6.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/MEA 062.2**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to MEA 062 [feasibility report for an international, exploratory, retrospective non-interventional study to collect long-term safety data including malignancies in children with growth failure who have received at least 3 years of Increlex (mecasermin) therapy and followed at least 5 years after the end of Increlex (mecasermin) treatment (from variation II/60 concluded in November 2019)] as per the request for supplementary information (RSI) adopted in March 2020

## **17.7. New Scientific Advice**

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

## **17.8. Ongoing Scientific Advice**

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

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

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

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

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

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

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

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Applicant: SERB SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

#### **18.1.2. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0068 (without RMP)**

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Annual reassessment of the marketing authorisation

#### **18.1.3. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0028 (without RMP)**

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

#### **18.1.4. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/S/0011 (without 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. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0006 (without RMP)**

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Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Conditional renewal of the marketing authorisation

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

#### **18.3.1. Asparaginase - SPECTRILA (CAP) - EMEA/H/C/002661/R/0018 (without RMP)**

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Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

#### **18.3.2. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/R/0034 (with RMP)**

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Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: 5-year renewal of the marketing authorisation

#### **18.3.3. Duloxetine - DULOXETINE ZENTIVA (CAP) - EMEA/H/C/003935/R/0009 (with RMP)**

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Applicant: Zentiva k.s.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

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**18.3.4. Efmoroctocog alfa - ELOCTA (CAP) - EMEA/H/C/003964/R/0036 (with RMP)**

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Sonja Hrabcik

Scope: 5-year renewal of the marketing authorisation

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

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

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**18.3.6. Glycerol phenylbutyrate - RAVICTI (CAP) - EMEA/H/C/003822/R/0034 (without RMP)**

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Applicant: Immedica Pharma AB

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

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**18.3.7. Pemetrexed - ARMISARTE (CAP) - EMEA/H/C/004109/R/0022 (with RMP)**

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Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

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**18.3.8. Pemetrexed - PEMETREXED HOSPIRA (CAP) - EMEA/H/C/003970/R/0022 (without RMP)**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

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**18.3.9. Pemetrexed - PEMETREXED MEDAC (CAP) - EMEA/H/C/003905/R/0008 (with RMP)**

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Applicant: medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

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**18.3.10. Pemetrexed - PEMETREXED SANDOZ (CAP) - EMEA/H/C/004011/R/0008 (without RMP)**

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Applicant: Sandoz GmbH

## 19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 08-11 June 2020 meeting (marked as <sup>1</sup>) and for the 18 June 2020 extraordinary meeting (marked as <sup>2</sup>).

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus <sup>1,2</sup>	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser <sup>1</sup>	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik <sup>1,2</sup>	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné <sup>1</sup>	Member	Belgium	No interests declared	Full involvement
Laurence de Fays <sup>1,2</sup>	Alternate	Belgium	No restrictions applicable to this meeting	Full involvement
Maria Popova-Kiradjieva <sup>1,2</sup>	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce <sup>1</sup>	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić <sup>1,2</sup>	Alternate	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou <sup>1</sup>	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras <sup>1</sup>	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová <sup>1,2</sup>	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinová <sup>1,2</sup>	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark <sup>1,2</sup>	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted <sup>1,2</sup>	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla <sup>1,2</sup>	Member	Estonia	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Kirsti Villikka <sup>1,2</sup>	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola <sup>1</sup>	Alternate	Finland	No interests declared	Full involvement
Adrien Inoubli <sup>1,2</sup>	Alternate	France	No interests declared	Full involvement
Martin Huber <sup>1,2</sup>	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislowski <sup>1</sup>	Alternate	Germany	No interests declared	Full involvement
Agni Kapou <sup>1</sup>	Member	Greece	No interests declared	Full involvement
Julia Pallos <sup>1,2</sup>	Member	Hungary	No participation in final deliberations and voting on:	14.1.1 - Cefepime (NAP)
Guðrún Stefánsdóttir <sup>1,2</sup>	Member	Iceland	No restrictions applicable to this meeting	Full involvement
Rhea Fitzgerald <sup>1,2</sup>	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes <sup>1,2</sup>	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli <sup>1,2</sup>	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli <sup>1,2</sup>	Alternate	Italy	No interests declared	Full involvement
Zane Neikena <sup>1,2</sup>	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene <sup>1,2</sup>	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch <sup>2</sup>	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg <sup>1</sup>	Member	Malta	No interests declared	Full involvement
Menno van der Elst <sup>1,2</sup>	Member	Netherlands	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Liana Gross-Martirosyan <sup>1,2</sup>	Alternate	Netherlands	No interests declared	Full involvement
David Olsen <sup>1,2</sup>	Member	Norway	No participation in final deliberations and voting on:	4.1.1 - Chloroquine (NAP); hydroxychloroquine (NAP) 16.1.19 - Larotrectinib - VITRAKVI (CAP) 18.2.1 - Larotrectinib - VITRAKVI (CAP)
Karen Pernille Harg <sup>1,2</sup>	Alternate	Norway	No interests declared	Full involvement
Katarzyna Ziolkowska <sup>1,2</sup>	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins <sup>1</sup>	Member	Portugal	No interests declared	Full involvement
Marcia Silva <sup>1,2</sup>	Alternate	Portugal	No interests declared	Full involvement
Alexandra - Maria Spurni <sup>1,2</sup>	Alternate	Romania	No interests declared	Full involvement
Michal Radik <sup>1</sup>	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Marek Juracka <sup>1</sup>	Alternate	Slovakia	No interests declared	Full involvement
Jasmina Klopčič <sup>1,2</sup>	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia <sup>1,2</sup>	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon <sup>1</sup>	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga <sup>1,2</sup>	Member	Sweden	No interests declared	Full involvement
Annika Folin <sup>1</sup>	Alternate	Sweden	No interests declared	Full involvement
Birgitta Grundmark <sup>1,2</sup>	Member	Independent scientific expert	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
Daniel Morales <sup>1,2</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng <sup>1</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente <sup>1</sup>	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stefan Weiler <sup>1,2</sup>	Member	Independent scientific expert	No participation in discussion, final deliberations and voting on:	3.2. Ulipristal acetate – ESMYA (CAP); NAP; 17.5.15 - Ulipristal acetate - ESMYA (CAP)
Raymond Anderson <sup>1</sup>	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini <sup>1,2</sup>	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne <sup>1</sup>	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert <sup>2</sup>	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu <sup>1</sup>	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden <sup>1</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Ivana Bahnik <sup>1</sup>	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Ivana Ljubičić <sup>1</sup>	Expert - via telephone*	Croatia	No restrictions applicable to	Full involvement



Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Petra Kaftanová <sup>2</sup>	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Kristýna Marušáková <sup>2</sup>	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Jana Šípková <sup>2</sup>	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Petra Vacková <sup>2</sup>	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Karin Susanne Erneholm <sup>1</sup>	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg <sup>1</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Josiane Uwera <sup>1</sup>	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Anita Vibsig Neutzsky-Wulff <sup>2</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe <sup>1</sup>	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Krõõt Aab <sup>1</sup>	Expert - via telephone*	Estonia	No interests declared	Full involvement
Katrin Keerma <sup>1</sup>	Expert - via telephone*	Estonia	No interests declared	Full involvement
Anissa Benlazar <sup>1</sup>	Expert - via telephone*	France	No interests declared	Full involvement
Pauline Dayani <sup>1</sup>	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Tiphaine Vaillant <sup>1,2</sup>	Expert - via telephone*	France	No interests declared	Full involvement
Nicole Bick <sup>1</sup>	Expert - via telephone*	Germany	No interests declared	Full involvement
Ines Flügge <sup>2</sup>	Expert - via telephone*	Germany	No interests declared	Full involvement
Anne Kleinau <sup>1</sup>	Expert - via	Germany	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	
Dennis Lex <sup>1</sup>	Expert – via telephone*	Germany	No participation in discussion, final deliberations and voting on:	15.3.26 - Peginterferon beta-1a - PLEGRIDY (CAP)
Ruchika Sharma <sup>2</sup>	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Tiina Asikainen <sup>1</sup>	Expert – via telephone*	Finland	No interests declared	Full involvement
Evelyn Olthof <sup>1</sup>	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Liesbeth van Vlijmen <sup>1</sup>	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Sílvia Duarte <sup>1</sup>	Expert - via telephone*	Portugal	No interests declared	Full involvement
Raquel Granados <sup>1</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Consuelo Mejias <sup>1</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Charlotte Backman <sup>1</sup>	Expert – via telephone*	Sweden	No interests declared	Full involvement
Viveca Odling <sup>1</sup>	Expert – via telephone*	Sweden	No interests declared	Full involvement
Miriam Taekema <sup>1</sup>	Expert – via telephone*	Sweden	No interests declared	Full involvement
Anders Sundström <sup>1</sup>	Expert – via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

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

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

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

## 21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

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

### **Signals assessment and prioritisation**

(Item 4 of the PRAC minutes)

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

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

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

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

(Item 5 of the PRAC minutes)

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

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

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation. PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

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

(Item 7 of the PRAC minutes)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

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

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

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