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SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines Pharmacovigilance and Committees Division

## Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 05-08 March 2018

Chair: June Raine – Vice-Chair: Almath Spooner

05 March 2018, 13:00 – 19:30, room 3/A

06 March 2018, 08:30 – 19:30, room 3/A

07 March 2018, 08:30 – 19:30, room 3/A

08 March 2018, 08:30 – 16:00, room 3/A

Organisational, regulatory and methodological matters (ORGAM)

22 March 2018, 09:00-12:00, room 9/B, via teleconference

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

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Of note, this agenda is a working document primarily designed for PRAC members and the work the Committee undertakes.

### Note on access to documents

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



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## **1. Introduction**

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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the PRAC plenary session to be held 05-08 March 2018. See March 2018 PRAC minutes (to be published post April 2018 PRAC meeting).

### **1.2. Agenda of the meeting on 05-08 March 2018**

**Action:** For adoption

### **1.3. Minutes of the previous meeting on 05-08 February 2018**

**Action:** For adoption

## **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

### **2.4. Planned public hearings**

None

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

### 3.1. Newly triggered procedures

#### 3.1.1. Daclizumab – ZINBRYTA (CAP) – EMEA/H/A-20/1462

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: To be appointed; PRAC Co-rapporteur: To be appointed

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

**Action:** For adoption of a list of questions (LoQ)

### 3.2. Ongoing procedures

#### 3.2.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452

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Applicant(s): Raptor Pharmaceuticals Europe BV (Quinsair), various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Martin Huber

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

**Action:** For discussion

#### 3.2.2. Radium (<sup>223</sup>Ra) dichloride - XOFIGO (CAP) - EMEA/H/A-20/1459

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Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Valerie Strassmann

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

**Action:** For adoption of a list of outstanding issues (LoOI)

#### 3.2.3. Ulipristal acetate - ESMYA (CAP) - EMEA/H/A-20/1460

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga; 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 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

**Action:** For adoption of a list of outstanding issues (LoOI)

### 3.3. Procedures for finalisation

None

### 3.4. Re-examination procedures<sup>1</sup>

#### 3.4.1. Retinoids: acitretin (NAP); adapalene (NAP); alitretinoin - PANRETIN (CAP); bexarotene – TARGRETIN (CAP); isotretinoin (NAP); tazarotene (NAP); tretinoin (NAP) - EMEA/H/A-31/1446

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Applicant(s): Eisai Ltd (Panretin, Targretin), various

PRAC Rapporteur: To be appointed; PRAC Co-rapporteur: To be appointed

Scope: Request for re-examination of the review of the benefit-risk balance following notification by United Kingdom of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

**Action:** For discussion

### 3.5. Others

None

## 4. Signals assessment and prioritisation<sup>2</sup>

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

#### 4.1.1. Amitriptyline (NAP)

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Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of dry eye

**Action:** For adoption of PRAC recommendation

EPITT 19173 – New signal

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<sup>1</sup> Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

<sup>2</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



Lead Member State: GR

4.1.2. Clopidogrel – CLOPIDOGREL APOTEX (CAP), CLOPIDOGREL BGR (CAP), CLOPIDOGREL HCS (CAP), CLOPIDOGREL KRKA (CAP), CLOPIDOGREL KRKA D.D. (CAP), CLOPIDOGREL MYLAN (CAP), CLOPIDOGREL RATIOPHARM (CAP), CLOPIDOGREL RATIOPHARM GMBH (CAP), CLOPIDOGREL TAD (CAP), CLOPIDOGREL TEVA (CAP), CLOPIDOGREL ZENTIVA (CAP), GREPID (CAP), ISCOVER (CAP), PLAVIX (CAP), ZYLLT (CAP); NAP  
Clopidogrel, acetylsalicylic acid - CLOPIDOGREL/ACETYLSALICYLIC ACID ZENTIVA (CAP), DUOPLAVIN (CAP); NAP

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Applicant(s): Apotex Europe BV (Clopidogrel Apotex), Archie Samuel s.r.o. (Clopidogrel ratiopharm GmbH), HCS bvba (Clopidogrel HCS), Laboratoires Biogaran (Clopidogrel BGR), Krka, d.d. (Clopidogrel Krka , Clopidogrel Krka d.d., Zyllt), Mylan S.A.S. (Clopidogrel Mylan), Pharmathen S.A. (Grepid), Sanofi-aventis groupe (Clopidogrel Zentiva, Clopidogrel/Acetylsalicylic acid Zentiva), Sanofi Clir SNC (Duoplavin, Plavix), TAD Pharma GmbH (Clopidogrel TAD), Teva B.V. (Clopidogrel ratiopharm, Clopidogrel Teva), various

PRAC Rapporteur: To be appointed

Scope: Signal of insulin autoimmune syndrome

**Action:** For adoption of PRAC recommendation

EPITT 19155 – New signal

Lead Member State: PT

4.1.3. Norepinephrine (NAP)

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Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of stress cardiomyopathy

**Action:** For adoption of PRAC recommendation

EPITT 19172 – New signal

Lead Member State: IE

4.1.4. Pembrolizumab – KEYTRUDA (CAP)

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Applicant(s): Merck Sharp & Dohme

PRAC Rapporteur: Sabine Straus

Scope: Signal of cholangitis sclerosing

**Action:** For adoption of PRAC recommendation

EPITT 19154 – New signal

Lead Member State: NL

## 4.2. New signals detected from other sources

None

## 4.3. Signals follow-up and prioritisation

### 4.3.1. Cefalexin<sup>3</sup> (NAP)

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Applicant(s): various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

**Action:** For adoption of PRAC recommendation

EPITT 18911 – Follow-up to September 2017

### 4.3.2. Efavirenz - STOCRIN (CAP) - EMEA/H/C/000250/SDA/072, SUSTIVA (CAP) - EMEA/H/C/000249/SDA/083; efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/SDA/043; emtricitabine - EMTRIVA (CAP) - EMEA/H/C/000533/SDA/052; tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/SDA/275

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Applicant(s): Bristol-Myers Squibb Pharma EEIG (Atripla, Sustiva), Gilead Sciences International Limited (Emtriva, Viread), Merck Sharp & Dohme Limited (Stocrin)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of autoimmune hepatitis

**Action:** For adoption of PRAC recommendation

EPITT 18956 – Follow-up to November 2017

### 4.3.3. Hormonal contraceptives:

Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol<sup>4</sup> (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, norgestimate acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene<sup>5</sup> (NAP); ethinylestradiol, gestodene<sup>6</sup> (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol<sup>7</sup> (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP)

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Applicant(s): Teva B.V (Zoely), Janssen-Cilag International NV (Evra), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal related to a known association between hormonal contraceptives and a small

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<sup>3</sup> First-generation cephalosporin

<sup>4</sup> Contraception indication

<sup>5</sup> All route of administrations except transdermal

<sup>6</sup> Transdermal application

<sup>7</sup> Combination pack

increase in breast cancer following a recent publication

**Action:** For adoption of PRAC recommendation

EPITT 19143 – Follow up to January 2018

## 5. Risk management plans (RMPs)

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

#### 5.1.1. Brexpiprazole - EMEA/H/C/003841

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Scope: Treatment of schizophrenia

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.1.2. Tezacaftor, ivacaftor - EMEA/H/C/004682, Orphan

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Applicant: Vertex Pharmaceuticals (Europe) Ltd.

Scope: Treatment of cystic fibrosis

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.1.3. Tisagenlecleucel - EMEA/H/C/004090, Orphan

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Applicant: Novartis Europharm Limited, ATMP<sup>8</sup>

Scope (accelerated assessment): Treatment of B cell acute lymphoblastic leukaemia (ALL) and diffuse large B cell lymphoma (DLBCL)

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CAT and CHMP

#### 5.1.4. Vonicog alfa - EMEA/H/C/004454, Orphan

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Applicant: Baxalta Innovations GmbH

Scope: Treatment of von Willebrand disease (VWD)

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

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

#### 5.2.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0018, Orphan

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Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

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<sup>8</sup> Advanced therapy medicinal product

Scope: Updated RMP (version 8.0) to address the requests made in the conclusion of procedure IB/14, including updates from pre-approval information to post-marketing information, an update of the number of patients treated in clinical trials, special access schemes and commercial distribution, change in the development of the custom-made device, postponement of pharmacokinetic (PK) study CUV052 (study on the PK profile in erythropoietic protoporphyria (EPP) patients after administration of implant 1 on day 1 and implant 2 on day 60), update on timelines for safety extension study CUV037 from Q1 2013 to Q12018, update on timelines for on-going and planned pharmacovigilance studies, key elements of educational and training programme, replacement of 'pigmentary lesions' by 'pigmentary expressions' and general update of safety information

**Action:** For adoption of PRAC Assessment Report

#### 5.2.2. [Anidulafungin - ECALTA \(CAP\) - EMEA/H/C/000788/II/0036](#)

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Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Updated RMP (version 12.1) in order to include new safety information: an update of incidence and prevalence of hepatotoxicity categorised as an important identified risk and a re-categorisation of convulsions from an important potential risk to important identified risk based on ongoing study A8851008: a prospective, open-label study to assess the pharmacokinetics, safety and efficacy of anidulafungin when used to treat children with invasive candidiasis, including candidemia, PASS A8851030: a retrospective cohort study of the risk of severe hepatic injury in hospitalised patients treated with echinocandins for candida infections, the 'global antifungal surveillance programme' and the MAH's review and analysis of cumulative exposure data up to the data lock point (DLP) of 31 August 2017

**Action:** For adoption of PRAC Assessment Report

#### 5.2.3. [Apremilast - OTEZLA \(CAP\) - EMEA/H/C/003746/II/0018](#)

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Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: Updated RMP (version 10.0) in order to introduce changes in the pharmacovigilance activities related to the use of apremilast in pregnancy and to remove 'use in patients of different racial origin' from the safety concerns

**Action:** For adoption of PRAC Assessment Report

#### 5.2.4. [Ceftaroline fosamil - ZINFORO \(CAP\) - EMEA/H/C/002252/II/0036](#)

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Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Julie Williams

Scope: Updated RMP (version 16) to include the new population (children from the age of 2 months) as approved in variation II/22. In addition, to amend the statement concerning additional monitoring following renewal procedure in which the black triangle symbol was removed from the product information. Furthermore, the updated RMP includes a re-categorisation of the following important identified risk as not important:

hypersensitivity/anaphylaxis and *C. difficile*-associated diarrhea

**Action:** For adoption of PRAC Assessment Report

#### 5.2.5. [Cetorelix - CETROTIDE \(CAP\) - EMEA/H/C/000233/II/0064](#)

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Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Updated RMP (version 5.0) in order to update the list of important identified risks by adding 'ovarian hyperstimulation syndrome' (OHSS) and removing injection site reactions (ISR). In addition, further minor RMP updates were introduced

**Action:** For adoption of PRAC Assessment Report

#### 5.2.6. [Darunavir - PREZISTA \(CAP\) - EMEA/H/C/000707/WS1355/0094;](#) [Darunavir, cobicistat - REZOLSTA \(CAP\) - EMEA/H/C/002819/WS1355/0024](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Amelia Cupelli

Scope: Updated RMP (version 25.4 for Prezista, version 4.4 for Rezolsta) in order to amend the due date for the final report for study GS-US-216-0128: 'a phase 2/3, multicentre, multicohort, two-part study evaluating pharmacokinetics (PK), safety, and efficacy of cobicistat-boosted atazanavir (ATV/co) or cobicistat-boosted darunavir (DRV/co), administered with background regimen (BR) in human immunodeficiency virus-1 (HIV-1) infected, treatment-experienced, virologically suppressed paediatric subjects' from Q1 2022 to Q1 2024

**Action:** For adoption of PRAC Assessment Report

#### 5.2.7. [Ibrutinib - IMBRUVICA \(CAP\) - EMEA/H/C/003791/II/0040/G, Orphan](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of an updated RMP (version 9.1) in order to: 1) include a feasibility assessment of experiments and/or studies to further understand the effect of ibrutinib on various components and functions of the adaptive and humoral immune system; 2) include the completed non-clinical in vitro rabbit ventricular and atrial wedge study (under review in procedure IB/0039) in the table of completed studies in the RMP annex; 3) include a targeted follow-up questionnaire for cardiac arrhythmias as part of routine pharmacovigilance activities; 4) update the text for clarification purposes, to modify the important potential risk of 'infections (excluding progressive multifocal leukoencephalopathy (PML))' to 'infections (including viral reactivation)' (PML is already listed as a separate important potential risk); 5) replace the three post-authorisation measures (PAMs) for study PCYC-1103-CA: 'a long term safety study of Bruton's tyrosine kinase (Btk) inhibitor ibrutinib in B cell lymphoma and chronic lymphocytic leukaemia', study PCI32765CAN3001: 'a phase 3b, multicentre, open-label, ibrutinib long term extension study' and study PCYC-1116-CA: 'an open label extension study in patients 65 years or older with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma

(SLL) who participated in study PCYC-1115-CA (ibrutinib version chlorambucil)', all related to long-term safety (> 2 years) of ibrutinib, with a single long-term safety PAM for study 3038-1: a long term study to characterize the safety of long term exposure to ibrutinib based on data and pooled analyses from trials of patients with mantle cell lymphoma and CLL

**Action:** For adoption of PRAC Assessment Report

#### 5.2.8. [Telbivudine - SEBIVO \(CAP\) - EMEA/H/C/000713/II/0048](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Caroline Laborde

Scope: Updated RMP (version 11.0) in order to reclassify the risk of lactic acidosis from an important potential risk to an important identified risk and to include a targeted questionnaire for fatal cases as additional risk minimisation measure as requested by the PRAC as part of the assessment of PSUSA/00002880/201608 adopted in April 2017

**Action:** For adoption of PRAC Assessment Report

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

#### 5.3.1. [Blinatumomab - BLINCYTO \(CAP\) - EMEA/H/C/003731/II/0018, Orphan](#)

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include children aged one month and older to the authorised population for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to include the new population, update the posology and the safety information. The package leaflet and the RMP (version 6.0) are updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.2. [Bortezomib - BORTEZOMIB ACCORD \(CAP\) - EMEA/H/C/003984/X/0008](#)

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Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Line extension application to add a new strength of powder for solution for injection (1 mg) to the currently approved strength (3.5 mg) of Bortezomib Accord. The RMP (version 6.0) is updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.3. [Brivaracetam - BRIVIACT \(CAP\) - EMEA/H/C/003898/II/0010/G](#)

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Applicant: UCB Pharma S.A.



PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped application consisting of: 1) extension of indication to include adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy 4 years of age and older. As a consequence, sections 4.1, 4.2, 4.7, 5.1 and 5.2 of the SmPC are updated; 2) submission of a 5mL oral syringe and adaptor for the paediatric population. The package leaflet, labelling and the RMP (version 6.1) are updated accordingly. The submission also includes a final environmental risk assessment (ERA) for the inclusion of the paediatric population in accordance with the new proposed indication

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.4. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0003

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include for the treatment of advanced renal cell carcinoma the 'treatment-naïve adults with intermediate or poor risk per International Metastatic Renal Carcinoma Database (IMDC) criteria'. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add a warning on dose reductions and dose interruptions and to update the safety information. The final report of study A031203: a randomized phase 2 study comparing cabozantinib with commercially supplied sunitinib in patients with previously untreated locally advanced or metastatic renal cell carcinoma is submitted in support of this application. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes in the product information

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.5. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0065

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of plaque psoriasis in adult patients. 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 13) are updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.6. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0011, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include the combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.1) are

updated accordingly. In addition, the MAH took the opportunity to update the contact details of the Lithuanian and Slovenian local representatives in the package leaflet

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.7. [Darunavir - PREZISTA \(CAP\) - EMEA/H/C/000707/WS1312/0093;](#)  
[Darunavir, cobicistat - REZOLSTA \(CAP\) - EMEA/H/C/002819/WS1312/0023;](#)  
[Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA \(CAP\) - EMEA/H/C/004391/WS1312/0005](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4, 4.6, 5.1 and 5.2 of the SmPCs for Prezista, Rezolsta and Symtuza to reflect the data of study TMC114HIV3015 (listed as a category 3 study in the RMP): a single arm, open label study to assess the pharmacokinetics of darunavir and ritonavir, darunavir and cobicistat, etravirine, and rilpivirine in human immunodeficiency virus-1 (HIV-1) infected pregnant women. The package leaflet of Symtuza and the RMPs (version 25.3 for Prezista, version 4.3 for Rezolsta and version 2.1 for Symtuza) are updated accordingly. In addition, the MAH took the opportunity to implement RMP template (version 2) for the Prezista and Rezolsta RMPs, the removal of the fulfilled category 4 data collection on adverse events of anti-HIV drugs (D:A:D) study from the Prezista and Rezolsta RMPs, removal of observational study on growth in children and 'growth abnormalities in the paediatric population' as an important potential risk in the Prezista RMP as well as the addition of the missing information 'safety in patients with cardiac conduction disorders' in the Rezolsta RMP (alignment with Tybost (cobicistat) RMP)

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.8. [Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA \(CAP\) - EMEA/H/C/004391/II/0002/G](#)

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of: 1) submission of the results of study GS-US-311-1089: a phase 3, randomized, double-blind, switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in human immunodeficiency virus 1 (HIV-1) positive subjects who are virologically suppressed on regimens containing emtricitabine/tenofovir disoproxil fumarate (FTC/TDF). The RMP (version 5.0) is updated accordingly; 2) update of the RMP to remove pancreatitis, convulsion, and cardiac conduction abnormalities as risks in the RMP in alignment with the RMPs for Prezista (darunavir) and Rezolsta (darunavir/cobicistat)

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.9. [Denosumab - XGEVA \(CAP\) - EMEA/H/C/002173/II/0059](#)

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety

information and to revise the special warnings, precautions for use and undesirable effects based on cases of clinically significant hypercalcemia following discontinuation of denosumab in patients with growing skeletons (i.e. adolescent subject with giant-cell tumour of bone (GCTB) in study 20062004: an open label, multicentre, phase 2 study of denosumab in subjects with GCTB) and in post-marketing reports of paediatric patients treated with denosumab for GCTB or for unapproved indications previously determined as an important identified risk. The package leaflet and the RMP (version 30) are updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.10. [Eluxadoline - TRUBERZI \(CAP\) - EMEA/H/C/004098/II/0005/G](#)

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Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) submission of the final report from study ELX-PH-08 (listed as a category 3 study in the RMP). This is an in vitro evaluation study aimed to investigate the effects on treating primary cultures of cryopreserved human hepatocytes with eluxadoline on the expression of cytochrome P450 (CYP) enzymes; 2) submission of the final report from study 3030-102-002 (listed as a category 3 study in the RMP). This is a randomised, open label study aimed to evaluate the effect of eluxadoline as a potential time dependent inhibitor of CYP3A4<sup>9</sup> with the substrate midazolam. The RMP (version 2.0) is updated to refine the important identified risk of 'sphincter of Oddi (SO) spasm' to 'SO spasm (sphincter of Oddi dysfunction, SOD)' and to include pancreatitis as an important identified risk as agreed in the conclusions of PSUSA/00010528/201703 finalised at PRAC/CHMP in October 2017

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.11. [Enoxaparin sodium - INHIXA \(CAP\) - EMEA/H/C/004264/X/0026](#)

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Applicant: Techdow Europe AB

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add two new strengths of 30,000 IU (300 mg)/3 mL and 50,000 IU (500 mg)/5 mL for enoxaparin sodium solution for injection in vial, for subcutaneous, extracorporeal and intravenous administration. The RMP (version 3) is updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.12. [Fingolimod - GILENYA \(CAP\) - EMEA/H/C/002202/X/0044/G](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength of hard capsules (0.25 mg) to the currently approved presentations of Gilenya; 2)

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<sup>9</sup> Cytochrome P 450 3A4

extension of indication to add a new indication for the treatment of paediatric patients of 10 years of age and above with relapsing multiple sclerosis (RMS). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3, 6 and 8 of the SmPC are updated. The package leaflet, labelling and the RMP (version 13.0) are updated accordingly. In addition, Annex II is updated to be brought in line with the latest QRD template (version 10)

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.13. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/II/0047

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final clinical study report (CSR) for study D2399 (listed as a category 3 study in the RMP): a single arm, open-label, multicentre study evaluating the long-term safety and tolerability study of fingolimod 0.5 mg/day administered orally once daily in approximately 5,000 patients with relapsing multiple sclerosis. The RMP (version 14.0) is updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.14. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0085

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of study EPI-HPV-069: a meta-analysis assessing the risk of three autoimmune diseases following vaccination with Cervarix: autoimmune thyroiditis (AIT), Guillain-Barre syndrome (GBS) and inflammatory bowel disease (IBD). The RMP (version 18) is updated accordingly and includes minor updates related to other studies

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

#### 5.3.15. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0008, Orphan

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Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of section 4.5 of the SmPC to include that CYP3A4<sup>10</sup> substrates known to have a narrow therapeutic index should be administered with caution in patients receiving idebenone, based on the final study report for study SNT-I-017: an open-label study to assess the potential for pre-systemic inhibition of cytochrome P450 3A4 (CYP3A) by idebenone in healthy male subjects using midazolam as a substrate'. The package leaflet and the RMP (version 1.5) are updated accordingly. The provision of the study report fulfils MEA 005.1

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

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<sup>10</sup> Cytochrome P450 3A4

### 5.3.16. [Insulin aspart - FIASP \(CAP\) - EMEA/H/C/004046/II/0003/G](#)

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Julie Williams

Scope: Grouped variations to: 1) update the RMP (version 2.0) to reclassify the risk of mix-up between basal and bolus insulin from a potential to an important identified risk; 2) update the secondary packaging material (carton, label, instructions for use (IFU)) design and change colour of selected plastic components from yellow to red. In addition, the MAH submitted as part of this variation a proposal for communication to healthcare professionals (HCPs) and patients (indirectly) regarding similarity between Fiasp and Tresiba (insulin degludec)

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

### 5.3.17. [Lapatinib - TYVERB \(CAP\) - EMEA/H/C/000795/II/0051](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.1 and 5.1 of the SmPC based on results from study EGF114299/LAP016A2307 (listed as a condition (ANX027.4) in Annex II): a phase 3 trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI versus lapatinib plus an AI as first- or second-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received prior trastuzumab and endocrine therapies. Annex II is updated accordingly. In addition, the RMP (version 34.0) is updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

### 5.3.18. [Levetiracetam - KEPRA \(CAP\) - EMEA/H/C/000277/II/0169/G](#)

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC to add the adverse drug reaction (ADR) 'gait disturbance' to address the CHMP recommendation from P46/085; 2) update of section 4.2 of the SmPC to add dysgeusia as a potential experience post administration and update of section 4.5 of the SmPC to remove drug interaction with methotrexate in accordance with the latest levetiracetam company core data sheet; 3) update of section 4.6 to add information on 'women of childbearing potential' and to update the pregnancy section to address the PRAC recommendation from LEG 084.1. The package leaflet and the RMP (version 8) are updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

### 5.3.19. [Liraglutide - SAXENDA \(CAP\) - EMEA/H/C/003780/II/0016](#)

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study NN8022-4192 (listed as a category 3 study in the RMP). This is a randomised, placebo-controlled trial on subjects with obesity or overweight who were otherwise healthy, to compare the effect of liraglutide 3.0 mg with placebo on postprandial gallbladder dynamics after 12 weeks of treatment. This variation fulfils post-authorisation measure MEA 009.2. The RMP (version 29) is updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

### 5.3.20. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0013/G

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of extension of indication to include children and adolescents aged 6 to 17 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC and sections 1, 2, 3, 4 and information for healthcare professionals in the package leaflet are updated accordingly. In addition to the proposed SmPC/package leaflet updates specific to the paediatric indication, the MAH proposed to include some wording to ensure the name and batch number of the administered product should be clearly recorded in the patient file. The RMP (version 3) is updated accordingly; as well as quality variations

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

### 5.3.21. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/II/0002, Orphan

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.5 and 5.2 of the SmPC in order to reflect the results from study R1600721: 'assessment of PKC412 (midostaurin) and its metabolites (CGP052421 and CGP062221) as inhibitors of human bile salt export pump (BSEP)' and study R1701192: 'in vitro assessment of cytochrome P450 3A4 and 3A5 enzyme inhibition by PKC412, CGP52421 and CGP62221', in fulfilment of the post-authorisation measures MEA 011 and REC 014. In addition, the MAH took the opportunity to update section 5.2 of the SmPC to correct figures as per study A2107 (amendment 02), an open label study on absorption, distribution, metabolism and excretion (ADME) already assessed and to make editorial changes in the SmPC. The RMP (version 2.0) is updated accordingly. In addition, the search criteria for the important identified risk pulmonary toxicity (including pleural effusion and interstitial lung disease) was updated to include the MedDRA PT<sup>11</sup> 'pleural effusion'

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

### 5.3.22. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0018/G, Orphan

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped variations consisting of: 1) update of section 4.4 in order to remove the

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<sup>11</sup> Medical dictionary for regulatory activities – Preferred term



current warning on co-administration with pirfenidone and update of section 5.1 to include the results of study 1199.222: a phase 4, 12 week, open label, randomised, parallel group study to evaluate the safety, tolerability and pharmacokinetic (PK) of oral nintedanib in combination with oral pirfenidone in comparison with nintedanib alone in patients with idiopathic pulmonary fibrosis (IPF); 2) update of section 5.2 of the SmPC in order to include the results of study 1199.229 (listed as a category 3 study in the RMP): a phase 4, open label, multidose, 2 groups study to investigate the drug-drug interaction (DDI) between nintedanib and pirfenidone in patients with IPF. The RMP (version 5.0) is updated accordingly. In addition, the MAH took the opportunity to implement some corrections to the French and Swedish translations

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

### 5.3.23. Nitric oxide - INOMAX (CAP) - EMEA/H/C/000337/II/0051

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Applicant: Linde Healthcare AB

PRAC Rapporteur: Julie Williams

Scope: Quality variation to introduce an additional container closure system. The RMP (version 6.0) is updated to reflect post-authorisation experience with the new cylinder closure system

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

### 5.3.24. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0047

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on the nivolumab use in patients who have previously undergone allogeneic hematopoietic stem cell transplantation (HSCT) and the increased risk of rapid onset and severe graft versus host disease (GVHD) based on evidence from spontaneous case reports, literature case reports, and from 2 multicentre case series. Annex II.D and the package leaflet are updated accordingly. The RMP (version 7.8) is also updated to include the 'risk of GVHD with nivolumab after allogeneic HSCT' as an important potential risk based on the RMP template (revision 2). In addition, the MAH took the opportunity to make some minor editorial corrections to the product information

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

### 5.3.25. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0027, Orphan

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Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.2, 4.4, and 4.8 of the SmPC in order to add new adverse drug reactions (ADR): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) following a review of reports on severe skin reactions. The package leaflet and the RMP (version 12.0) are updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.26. [Rituximab - BLITZIMA \(CAP\) - EMEA/H/C/004723/WS1333/0007; RITEMVIA \(CAP\) - EMEA/H/C/004725/WS1333/0007; RITUZENA \(CAP\) - EMEA/H/C/004724/WS1333/0008; TRUXIMA \(CAP\) - EMEA/H/C/004112/WS1333/0008](#)

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Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Doris Stenver

Scope: Submission of the clinical study report (CSR) of final results (up to 76 weeks) of study CT-P10 3.2: 'a randomised, controlled, double-blind, parallel-group, phase 3 study to compare the pharmacokinetics, efficacy, and safety between CT-P10 (rituximab), Rituxan and MabThera in patients with rheumatoid arthritis'. In addition, results up to week 24 of study CT-P10 3.3: 'a phase 3, randomised, parallel-group, active-controlled, double-blind study to demonstrate equivalence of pharmacokinetics and non-inferiority of efficacy for CT-P10 (rituximab) in comparison with Rituxan each administered in combination with cyclophosphamide, vincristine, and prednisone (CVP) in patients with advanced follicular lymphoma' are updated in this variation. The RMP (version 9.0) is updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.27. [Trastuzumab - HERCEPTIN \(CAP\) - EMEA/H/C/000278/II/0140](#)

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Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC for Herceptin 150mg powder for concentrate for solution for infusion and sections 4.4, 4.8 and 5.1 of the SmPC for Herceptin 600mg solution for injection in vial, in order to update the safety information based on the final results from study BO22227 (Hannah) (listed as a category 3 study in the RMP): a phase 3, randomised, open-label study to compare pharmacokinetics, efficacy and safety of subcutaneous (SC) Herceptin with intravenous (IV) Herceptin administered in women with HER2 positive early breast cancer (EBC). The RMP (version 19.0) is updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

## 6. Periodic safety update reports (PSURs)

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

6.1.1. [Aflibercept<sup>12</sup> - ZALTRAP \(CAP\) - PSUSA/00010019/201708](#)

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Ulla Wändel Liminga

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<sup>12</sup> Oncological indication(s) only

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.2. [Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor \( \$\Delta\$ LNGFR\) and the herpes simplex I virus thymidine kinase \(HSV-TK Mut2\) - ZALMOXIS \(CAP\) - PSUSA/00010530/201708 \(with RMP\)](#)

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Applicant: MolMed SpA, ATMP<sup>13</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CAT and CHMP

6.1.3. [Asenapine - SYCREST \(CAP\) - PSUSA/00000256/201708](#)

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Applicant: N.V. Organon

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.4. [Baricitinib - OLUMIANT \(CAP\) - PSUSA/00010578/201708](#)

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.5. [Brimonidine<sup>14</sup> - MIRVASO \(CAP\) - PSUSA/00010093/201708](#)

---

Applicant: Galderma International

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.6. [Caffeine<sup>15</sup> - PEYONA \(CAP\) - PSUSA/00010615/201707](#)

---

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Daniela Philadelphia

Scope: Evaluation of a PSUSA procedure

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

<sup>14</sup> Centrally authorised product(s) only

<sup>15</sup> Indicated in premature apnoea of premature newborns, centrally authorised product(s) only

**Action:** For adoption of recommendation to CHMP

#### 6.1.7. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/201708

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.8. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/201708

Applicant: Actelion Registration Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.9. Cobicistat - TYBOST (CAP) - PSUSA/00010081/201708

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.10. Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - PSUSA/00010082/201708

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.11. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/201708

Applicant: Roche Registration Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.12. Copper (<sup>64</sup>Cu) chloride - CUPRYMINA (CAP) - PSUSA/00010040/201708

Applicant: Sparkle S.r.l.

PRAC Rapporteur: Patrick Batty  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.13. [Corifollitropin alfa - ELONVA \(CAP\) - PSUSA/00000875/201707](#)

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Applicant: Merck Sharp & Dohme Limited  
PRAC Rapporteur: Menno van der Elst  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.14. [Crizotinib - XALKORI \(CAP\) - PSUSA/00010042/201708](#)

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Applicant: Pfizer Limited  
PRAC Rapporteur: Ghania Chamouni  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.15. [Dabrafenib - TAFINLAR \(CAP\) - PSUSA/00010084/201708](#)

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Applicant: Novartis Europharm Limited  
PRAC Rapporteur: Ulla Wändel Liminga  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.16. [Diphtheria, tetanus, pertussis \(acellular, component\), hepatitis B \(rDNA\), poliomyelitis \(inactivated\), haemophilus type b conjugate vaccine \(adsorbed\) - VAXELIS \(CAP\) - PSUSA/00010469/201708](#)

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Applicant: MCM Vaccine B.V.  
PRAC Rapporteur: Brigitte Keller-Stanislawski  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.17. [Eliglustat - CERDELGA \(CAP\) - PSUSA/00010351/201708](#)

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Applicant: Genzyme Europe BV  
PRAC Rapporteur: Dolores Montero Corominas  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

6.1.18. [Emtricitabine, rilpivirine, tenofovir disoproxil - EVIPLERA \(CAP\) - PSUSA/00009142/201708](#)

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Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.19. [Enzalutamide - XTANDI \(CAP\) - PSUSA/00010095/201708](#)

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.20. [Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR \(CAP\) - PSUSA/00010352/201708](#)

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Applicant: Chiesi Farmaceutici S.p.A., ATMP<sup>16</sup>

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CAT and CHMP

6.1.21. [Ferric maltol - FERACCRU \(CAP\) - PSUSA/00010476/201708](#)

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Applicant: Shield TX (UK) Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.22. [Fluticasone, salmeterol<sup>17</sup> - AERIVIO SPIROMAX \(CAP\), AIREXAR SPIROMAX \(CAP\) - PSUSA/00010531/201708](#)

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Applicant: Teva B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

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<sup>16</sup> Advanced therapy medicinal product

<sup>17</sup> Centrally authorised product(s) only

6.1.23. Human alpha<sub>1</sub>-proteinase inhibitor<sup>18</sup> - RESPREEZA (CAP) - PSUSA/00010410/201708

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Applicant: CSL Behring GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.24. Human coagulation factor VIII, human von Willebrand factor<sup>19</sup> - VONCENTO (CAP) - PSUSA/00010102/201708

---

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.25. Ibuprofen<sup>20</sup> - PEDEA (CAP) - PSUSA/00001712/201707

---

Applicant: Orphan Europe SARL

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.26. Ioflupane (<sup>123</sup>I) - DATSCAN (CAP) - PSUSA/00001767/201707

---

Applicant: GE Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

6.1.27. Lenvatinib - KISPLYX (CAP), LENVIMA (CAP) - PSUSA/00010380/201708

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Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

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<sup>18</sup> Centrally authorised product(s) only

<sup>19</sup> Centrally authorised product(s) only

<sup>20</sup> Indicated in ductus arteriosus only

#### 6.1.28. Linacotide - CONSTELLA (CAP) - PSUSA/00010025/201708 (with RMP)

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Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.29. Loxapine<sup>21</sup> - ADASUVE (CAP) - PSUSA/00010113/201708

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Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.30. Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - PSUSA/00002017/201707

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Applicant: Roche Registration Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.31. Natalizumab - TYSABRI (CAP) - PSUSA/00002127/201708

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.32. Nonacog alfa - BENEFIX (CAP) - PSUSA/00002183/201708

---

Applicant: Pfizer Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.33. Ospemifene - SENSHIO (CAP) - PSUSA/00010340/201708

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Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

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<sup>21</sup> Pre-dispensed inhalation powder only



Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

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#### 6.1.34. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/201708

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

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#### 6.1.35. Pyronaridine, artesunate - PYRAMAX (Art 58<sup>22</sup>) - EMEA/H/W/002319/PSUV/0017

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Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUR procedure

**Action:** For adoption of recommendation to CHMP

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#### 6.1.36. Reslizumab - CINQAERO (CAP) - PSUSA/00010523/201708

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Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

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#### 6.1.37. Safinamide - XADAGO (CAP) - PSUSA/00010356/201708

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Applicant: Zambon S.p.A.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

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#### 6.1.38. Saxagliptin - ONGLYZA (CAP) - PSUSA/00002685/201707

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

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<sup>22</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)

#### 6.1.39. [Sebelipase alfa - KANUMA \(CAP\) - PSUSA/00010422/201708](#)

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.40. [Sitagliptin - JANUVIA \(CAP\), RISTABEN \(CAP\), TESAVEL \(CAP\), XELEVIA \(CAP\) - PSUSA/00002711/201708](#)

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.41. [Sitagliptin, metformin hydrochloride - EFFICIB \(CAP\), JANUMET \(CAP\), RISTFOR \(CAP\), VELMETIA \(CAP\) - PSUSA/00002003/201708](#)

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.42. [Teduglutide - REVESTIVE \(CAP\) - PSUSA/00009305/201708](#)

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

#### 6.1.43. [Vemurafenib - ZELBORAF \(CAP\) - PSUSA/00009329/201708](#)

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Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

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

### 6.2.1. Catridecacog - NOVOTHIRTEEN (CAP); NAP - PSUSA/00010034/201707

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Applicants: Novo Nordisk A/S (NovoThirteen), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

### 6.2.2. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP); NAP - PSUSA/00002014/201706

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Applicants: Therakind Limited (Jylamvo), Nordic Group B.V. (Nordimet), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

### 6.2.3. Oxybutynin - KENTERA (CAP); NAP - PSUSA/00002253/201707

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Applicants: Nicobrand Limited (Kentera), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

### 6.2.4. Ribavirin<sup>23</sup> - REBETOL (CAP); NAP - PSUSA/00010007/201707

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Applicants: Merck Sharp & Dohme Limited (Rebetol), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CHMP

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

### 6.3.1. Almotriptan (NAP) - PSUSA/00000101/201706

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Applicant(s): various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

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<sup>23</sup> Oral formulations only

**Action:** For adoption of recommendation to CMDh

#### 6.3.2. Amorphine (NAP) - PSUSA/00000185/201706

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.3. Caffeine<sup>24</sup> (NAP) - PSUSA/00000482/201707

Applicant(s): various

PRAC Lead: Daniela Philadelphly

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.4. Carbetocin (NAP) - PSUSA/00000546/201706

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.5. Cefadroxil (NAP) - PSUSA/00000584/201707

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.6. Ceftibuten (NAP) - PSUSA/00000611/201707

Applicant(s): various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.7. Delapril, manidipine (NAP); delapril, indapamide (NAP) - PSUSA/00010496/201706

Applicant(s): various

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<sup>24</sup> Indicated in apnoea, non-centrally authorised product(s) only

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.8. Demeclocycline, triamcinolone (NAP) - PSUSA/00010415/201707

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.9. Diclofenac, misoprostol (NAP) - PSUSA/00001040/201707

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.10. Enalapril, hydrochlorothiazide (NAP) - PSUSA/00001212/201707

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.11. Epirubicin (NAP) - PSUSA/00001234/201706

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.12. Ezetimibe, rosuvastatin (NAP) - PSUSA/00010271/201707

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

### 6.3.13. [Flecainide \(NAP\) - PSUSA/00001396/201706](#)

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Applicant(s): various

PRAC Lead: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

### 6.3.14. [Fluticasone propionate, formoterol fumarate dihydrate \(NAP\) - PSUSA/00010339/201707](#)

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Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

### 6.3.15. [Human coagulation factor XIII \(NAP\) - PSUSA/00001622/201706](#)

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Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

### 6.3.16. [Hydrochlorothiazide, moexipril \(NAP\) - PSUSA/00002082/201706](#)

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Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

### 6.3.17. [Ketorolac<sup>25</sup> \(NAP\) - PSUSA/00001810/201707](#)

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Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

### 6.3.18. [Ketorolac<sup>26</sup> \(NAP\) - PSUSA/00001811/201707](#)

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Applicant(s): various

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<sup>25</sup> Ophthalmic formulations only

<sup>26</sup> Systemic formulations only

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.19. [Ketotifen<sup>27</sup> \(NAP\) - PSUSA/00001812/201706](#)

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.20. [Landiolol \(NAP\) - PSUSA/00010570/201708](#)

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.21. [Levocetirizine \(NAP\) - PSUSA/00001850/201707](#)

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.22. [Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide \(NAP\) - PSUSA/00010390/201707](#)

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Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.23. [Magnesium sulfate, sodium sulfate, potassium sulfate \(NAP\) - PSUSA/00010239/201708](#)

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Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

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<sup>27</sup> Ophthalmic formulations only

#### 6.3.24. Methylaminolevulinate (NAP) - PSUSA/00002019/201706

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.25. Octreotide (NAP) - PSUSA/00002201/201706

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Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.26. Oxytocin (NAP) - PSUSA/00002263/201706

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Applicant(s): various

PRAC Lead: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.27. Theophylline (NAP) - PSUSA/00002921/201706

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Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.28. Triamcinolone<sup>28</sup> (NAP) - PSUSA/00003017/201707

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Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.29. Trimetazidine (NAP) - PSUSA/00003043/201708

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Applicant(s): various

PRAC Lead: Carmela Macchiarulo

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<sup>28</sup> Topical and nasal formulations only



Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

#### 6.3.30. Typhoid vaccine (live, attenuated) (NAP) - PSUSA/00003067/201707

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**Action:** For adoption of recommendation to CMDh

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

#### 6.4.1. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/LEG 035

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Review of cases of T cell-lymphoma reported in the post marketing setting including a discussion on the potential dechallenge effect, as requested in the conclusions of PSUSA/00001393/201702 adopted by PRAC at its October 2017 meeting

**Action:** For adoption of advice to CHMP

#### 6.4.2. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/LEG 036

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Review of cases of tumefactive lesions reported in the literature and in post marketing setting, as requested in the conclusions of PSUSA/00001393/201702 adopted by PRAC at its October 2017 meeting

**Action:** For adoption of advice to CHMP

#### 6.4.3. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/LEG 004

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Analysis of all available data relating to myocardial infarction, including a review of all post-marketing cases, as requested in the conclusions of PSUSA/00010319/201704 adopted by PRAC at its November 2017 meeting

**Action:** For adoption of advice to CHMP

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

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>29</sup>

#### 7.1.1. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/PSA/S/0026

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Applicant: Shire Pharmaceuticals

PRAC Rapporteur: Almath Spooner

Scope: Amended PASS protocol for registry PARADIGM on subjects with chronic hypoparathyroidism to explore physicians advancing disease knowledge in hypoparathyroidism including an amended statistical analysis plan (SAP), to the protocol previously agreed at the December 2017 PRAC meeting (PSP/S/0058.1)

**Action:** For adoption of PRAC Assessment Report, PRAC outcome letter

#### 7.1.2. Telavancin - VIBATIV (CAP) - EMEA/H/C/PSA/S/0027

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Applicant: Theravance Biopharma Ireland Ltd

PRAC Rapporteur: Julie Williams

Scope: Amended protocol (version 4.0) for a non-interventional imposed PASS: a multicentre, multinational, post-marketing, retrospective chart review on the use of intravenous Vibativ (telavancin) in clinical settings to the protocol previously agreed in June 2014 (MEA 006.3); including a request to extend the submission of the final results and/or a PASS study review to 31 December 2020 due to the extremely low usage of the product and difficulties in patient enrolment

**Action:** For adoption of PRAC Assessment Report, PRAC outcome letter

### 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>30</sup>

#### 7.2.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 008.3

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 008.2 [assessment of a protocol for a retrospective, observational new user cohort study, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with medicines containing sodium-glucose co-transporter-2 (SGLT2) inhibitors or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

**Action:** For adoption of advice to CHMP

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<sup>29</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>30</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

### 7.2.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 007.3

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.2 [assessment of a protocol for a retrospective, observational new user cohort study, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with medicines containing sodium-glucose co-transporter-2 (SGLT2) inhibitors or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

**Action:** For adoption of advice to CHMP

### 7.2.3. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/MEA 002.3

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.2 [PASS protocol for a multiple sclerosis (MS) pregnancy exposure registry study 109MS402 (listed as a category 3 in the RMP) aiming at evaluating prospectively pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product] as per the request for supplementary information (RSI) adopted the November 2017 PRAC meeting

**Action:** For adoption of advice to CHMP

### 7.2.4. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001

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Applicant: Almirall S.A

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study M-41008-40: a PASS in European psoriasis registries (listed as a category 3 in the RMP) to evaluate the long-term safety of Skilarence (dimethyl fumarate) used for the treatment of patients with moderate to severe psoriasis [future due date(s): end of data collection: Q1 2027; study report: within a year of availability of the final data set] (from initial MAA/opinion)

**Action:** For adoption of advice to CHMP

### 7.2.5. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 002

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Applicant: Almirall S.A

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study M-41008-44: a PASS retrospective chart review to assess the effectiveness of Skilarence (dimethyl fumarate) risk minimisation activities in daily practice (from initial MAA/opinion)

**Action:** For adoption of advice to CHMP

#### 7.2.6. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/MEA 006.3

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised protocol for drug utilisation study (DUS) ELIGL C06912 conducted in the US population using the MarketScan database to assess adherence to the labelling with regard to drug-drug interactions (DDI) and to genotyping assessment prior to the initiation of eliglustat therapy. The aim of the protocol revision is to propose a new additional database: the 'International Collaborative Gaucher Group' (ICGG) Gaucher registry database to achieve the first study objective 'to estimate the proportion of patients in the U.S. who have been genotyped for CYP2D6<sup>31</sup> prior to the initiation of eliglustat therapy'

**Action:** For adoption of advice to CHMP

#### 7.2.7. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 045.4

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Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 045.2 [PASS protocol for study GS-EU-276-4027, a drug utilisation study (DUS) to characterize: 1) prescribers' level of knowledge about the key risks of Truvada for a pre-exposure prophylaxis (PrEP) indication and assess the effectiveness of risk minimisation measures; 2) prescribing practices in routine clinical practice of Truvada for PrEP by describing the demographics of human immunodeficiency virus 1 (HIV-1) uninfected individuals who were prescribed Truvada for PrEP, and the prescribed dosing schedule for Truvada for PrEP as reported by the prescriber, as a result of variation II/126 finalised at CHMP/PRAC in July 2016 to extend the indication to PrEP] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

**Action:** For adoption of advice to CHMP

#### 7.2.8. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.4

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second progress report for study MRK-2859: ulcerative colitis (UC) Nordic registry: a non-interventional observational longitudinal PASS of Simponi (golimumab) in the treatment of UC using Nordic national health registries, including the MAH's response to MEA 026.3 [first progress report for study MRK-2859] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

**Action:** For adoption of advice to CHMP

#### 7.2.9. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 002.1

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Applicant: Sanofi-aventis groupe

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<sup>31</sup> Cytochrome P450 2D6

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 002 [protocol for a study/survey (listed as a category 3 study in the RMP): a cross-sectional multinational, multichannel survey conducted among healthcare professionals and patients to measure the effectiveness of Suliqa (insulin glargine/lixisenatide) educational materials set up to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

**Action:** For adoption of advice to CHMP

#### **7.2.10. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 001.5**

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Updated protocol for study 178-CL-114 (version 10.0): a long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (individual and composite outcomes) in patients administered mirabegron, following FDA's request for supplementary information

**Action:** For adoption of advice to CHMP

#### **7.2.11. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: PASS protocol for a 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)) (from initial MAA/opinion)

**Action:** For adoption of advice to CHMP

### **7.3. Results of PASS imposed in the marketing authorisation(s)<sup>32</sup>**

#### **7.3.1. Domperidone (NAP) - EMEA/H/N/PSR/J/0010**

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Applicant: Janssen Pharmaceutical

PRAC Rapporteur: Caroline Laborde

Scope: Results for a PASS assessing the effectiveness of the risk minimisation measures of domperidone to characterise prescribers' knowledge, understanding and extent of

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<sup>32</sup> In accordance with Article 107p-q of Directive 2001/83/EC

awareness regarding new safety information for domperidone following the change in SmPC and the distribution of a direct healthcare professional communication (DHPC), as imposed in the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2013, as per the request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

**Action:** For adoption of recommendation to CMDh (or request for supplementary information (RSI))

### 7.3.2. Domperidone (NAP) - EMEA/H/N/PSR/J/0015

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Applicant: Janssen Pharmaceutical

PRAC Rapporteur: Caroline Laborde

Scope: Results of a drug utilisation study (DUS) of domperidone in Europe using databases to investigate the effectiveness of risk minimisation measures and to describe the prescribing patterns before and after the changes to the domperidone label in routine clinical practice in selected European countries, as required in the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2013

**Action:** For adoption of recommendation to CMDh (or request for supplementary information (RSI))

### 7.3.3. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/PSR/S/0014

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Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Results of an observational study to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis (CF), the frequency and outcomes of pregnancy in ivacaftor-treated patients, drug utilisation of ivacaftor and evaluate CF disease progression in ivacaftor-treated patients

**Action:** For adoption of recommendation to CHMP (or request for supplementary information (RSI))

### 7.3.4. Strontium ranelate - OSSEOR (CAP), PROTELOS (CAP) - EMEA/H/C/PSR/S/0013

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Results for a European programme of PASS for Protelos/Osseor through EU-ADR Alliance<sup>33</sup> exploring the effectiveness of the newly established risk minimisation measures (RMM) by characterising utilisation patterns of strontium ranelate, as imposed in the conclusions of a referral procedure (EMEA/H/A20/1371) under Article 20 of Regulation (EC) No 726/2004 finalised in 2014

**Action:** For adoption of recommendation to CHMP (or request for supplementary information (RSI))

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<sup>33</sup> Federated collaborative framework for drug safety studies

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

### 7.4.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0173

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Applicant: AbbVie Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study BSRBR-RA (British Society for Rheumatology Biologics Registers Rheumatoid Arthritis): a registry in the UK, evaluating the influence of tumour necrosis factor (TNF) inhibitor treatment on cancer incidence in rheumatoid arthritis (RA) patients with a history of malignancy. No changes to the product information are proposed

**Action:** For adoption of PRAC Assessment Report

### 7.4.2. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/II/0037

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Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of the final report from PASS CLE-20098-094 study on agomelatine and the risk of hospitalisation for acute liver injury. This is a large, multinational, retrospective longitudinal cohort and nested case-control study to compares the risk of acute liver injury (ALI) in patients initiating treatment with agomelatine and other antidepressants with the risk in patients initiating treatment with citalopram

**Action:** For adoption of PRAC Assessment Report

### 7.4.3. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/II/0038

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of the final report from PASS CLE-20098-094 study of agomelatine and the risk of hospitalisation for acute liver injury. This is a large, multinational, retrospective longitudinal cohort and nested case-control study to compares the risk of acute liver injury (ALI) in patients initiating treatment with agomelatine and other antidepressants with the risk in patients initiating treatment with citalopram

**Action:** For adoption of PRAC Assessment Report

### 7.4.4. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0052

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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report for study HGS1006-C1074 (BEL112234) (listed as a category 3 study in the RMP, in fulfilment of a MEA 012): 'a multicentre, continuation trial of

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<sup>34</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

belimumab in subjects with systemic lupus erythematosus (SLE) who completed the phase 3 protocol HGS1006-C1056 or HGS1006-C1057'. The RMP (version 26.0) is updated accordingly. In addition, the MAH took the opportunity to update the RMP regarding study BEL116027: an open-label, non-randomized, 52-week study to evaluate treatment holidays and rebound phenomenon after treatment with belimumab 10 mg/kg in SLE subjects for the due date of the final study report and introduction of protocol changes (reduced study sample size), already agreed in the conclusions of recent procedures MEA 006.4 and MEA 006.5

**Action:** For adoption of PRAC Assessment Report

7.4.5. [Emtricitabine, tenofovir disoproxil - TRUVADA \(CAP\) - EMEA/H/C/000594/WS1326/0145;](#)  
[Tenofovir disoproxil - VIREAD \(CAP\) - EMEA/H/C/000419/WS1326/0184](#)

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Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Caroline Laborde

Scope: Submission of the final report from study GS-EU-104-0433 (listed as a category 3 study in the RMP). This is an observational, drug utilisation study (DUS) of Viread in children and adolescents with human immunodeficiency virus-1 (HIV-1) infection, in fulfilment of a post-authorisation measure (PAM) for Viread (MEA 46) and Truvada (MEA 276)

**Action:** For adoption of PRAC Assessment Report

7.4.6. [Fluticasone furoate, vilanterol - RELVAR ELLIPTA \(CAP\) - EMEA/H/C/002673/WS1283/0035; REVINTY ELLIPTA \(CAP\) - EMEA/H/C/002745/WS1283/0031](#)

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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final report for study 205052 (PRJ2214): a drug utilisation study (DUS) to identify the extent of any off-label prescribing fluticasone furoate/vilanterol (FF/VI) in any dose in children less than 12 years of age; and prescribing of FF/VI 200/25 mcg in patients with a diagnosis of chronic obstructive pulmonary disease (COPD) considering the presence of a concurrent diagnosis of asthma. The RMP (version 9.1) is updated accordingly

**Action:** For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

**Action:** For adoption of PRAC Assessment Report

7.4.7. [Pneumococcal polysaccharide conjugate vaccine \(adsorbed\) - SYNFLORIX \(CAP\) - EMEA/H/C/000973/II/0124/G](#)

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations consisting of the submission of the final study reports from two 5-year invasive pneumococcal disease (IPD) post-marketing surveillance (PMS) studies: 1) 'monitoring the population effectiveness of pneumococcal conjugate vaccination in the



Finnish national vaccination programme' (MEA 019); 2) 'epidemiology of invasive pneumococcal disease in the Netherlands' (MEA 020), addressing the potential risks of 'possible serotype replacement of disease isolates' and 'possible breakthrough infections/vaccine failure'. The MAH also provided data from IPD surveillance from 5 other European countries (Austria, Bulgaria, Cyprus, Iceland and Sweden) and 6-year update results from a 5-year PMS in Kenya (pneumococcal conjugate vaccine impact study (PCVIS), MEA 021). The RMP (version 17) is updated accordingly

**Action:** For adoption of PRAC Assessment Report

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

### **7.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 053.5**

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Caroline Laborde

Scope: Second interim study report for PASS study ALGMYC07390 evaluating the prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions, including MAH's response to MEA 053.4 on first interim report as per the request for supplementary information adopted in July 2017 [final clinical study report (CSR): due 31 August 2019]

**Action:** For adoption of advice to CHMP

### **7.5.2. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.9**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

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

**Action:** For adoption of advice to CHMP

### **7.5.3. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/MEA 006.2**

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Second interim report for drug utilisation study (DUS) ELIGL C06912 conducted in the US population using the MarketScan database to assess adherence to the labelling with regard to drug-drug interactions (DDI) and to genotyping assessment prior to the initiation of eliglustat therapy

**Action:** For adoption of advice to CHMP

#### 7.5.4. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 005

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: First interim report for an enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMEA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR): Q4/2021]

**Action:** For adoption of advice to CHMP

#### 7.5.5. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 005

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: First interim report for an enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMEA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR): Q4/2021]

**Action:** For adoption of advice to CHMP

#### 7.5.6. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 002

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: First interim report for an enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMEA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR): Q4/2021]

**Action:** For adoption of advice to CHMP

#### 7.5.7. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 045.3

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Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Enrolment progress report for study GS-EU-276-4027: a cross-sectional PASS to assess healthcare provider's level of awareness of risk minimisation materials for Truvada (emtricitabine/tenofovir disoproxil) for pre-exposure prophylaxis (PrEP) in the European

Union

**Action:** For adoption of advice to CHMP

#### 7.5.8. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.7

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Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.6 [second interim study report for a US category 3, non-interventional PASS (B2311060 study): active surveillance of conjugated oestrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data] as per the request for supplementary information (RSI) adopted in November 2017

**Action:** For adoption of advice to CHMP

#### 7.5.9. Florbetaben (<sup>18</sup>F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 005.1

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Applicant: Piramal Imaging Limited

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 005 [interim results for PASS study FBB-01\_02\_13: a prospective observational study to assess the effectiveness of the training and risk minimisation measures recommended for the usage of the diagnostic agent Neuraceq in post-authorisation clinical settings [final clinical study report (CSR): Q1/2019]] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

**Action:** For adoption of advice to CHMP

#### 7.5.10. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 027.5

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual progress report of the ENEIDA registry (study MK-8259-042): a long-term, non-interventional observational study of patients with inflammatory bowel disease (IBD) in Spain to evaluate whether the use of golimumab is associated with a risk of colectomy for intractable disease, advanced neoplasia (colorectal cancer or high grade dysplasia), and hepatosplenic T-cell lymphoma (HSTCL) in patients with ulcerative colitis (UC) as compared with alternative therapies for similar severity of disease

**Action:** For adoption of advice to CHMP

#### 7.5.11. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/LEG 188.5

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Annual report for 2017 on a review of second primary malignancies (SPM), including a data analysis plan, in order to compare incidence rates of SPM among patients treated

with Glivec (imatinib) with expected incidence based on the rates among the general population

**Action:** For adoption of advice to CHMP

#### 7.5.12. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/ANX 191.6

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Fourth progress report for study CSTI571I2201: a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Philadelphia positive (Ph+) acute lymphoblastic leukaemia (ALL) patients treated with chemotherapy + imatinib ± hematopoietic stem cell treatment (±HSCT)

**Action:** For adoption of advice to CHMP

#### 7.5.13. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 133.12

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Tenth annual paediatric inflammatory bowel disease (IBD) registry (DEVELOP) report on long-term safety and efficacy of infliximab and other therapies, safety and efficacy of variable infliximab dosing intervals, episodic therapy, monotherapy (initiated de novo or following discontinuation of concomitant immunomodulators), combined infliximab and immunomodulator therapy (azathioprine/6-mercaptopurine (AZA/6-MP) or methotrexate (MTX))

**Action:** For adoption of advice to CHMP

#### 7.5.14. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 005

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Julie Williams

Scope: First annual progress report for a patient registry of lixisenatide use in adult patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and databases in Italy and Belgium [due date: final report due in December 2020] (from initial MAA/opinion)

**Action:** For adoption of advice to CHMP

#### 7.5.15. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 013.4

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Annual interim results for study GS-EU-337-1820: a prospective observational drug

utilisation study (DUS) of ledipasvir/sofosbuvir (LDV/SOF) in adults with hepatitis C virus/human immunodeficiency virus (HCV/HIV) coinfection [final clinical study report (CSR): Q3/Q4 2019]

**Action:** For adoption of advice to CHMP

#### 7.5.16. Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/MEA 008.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: First annual progress report for a patient registry of lixisenatide use in adult patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and databases in Italy and Belgium

**Action:** For adoption of advice to CHMP

#### 7.5.17. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/001252/ANX 002.10

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Eighth interim report of the observational safety study on Bronchitol (inhaled mannitol) using the UK cystic fibrosis (CF) Trust registry aiming at comparing the rate of identified and potential risks for Bronchitol in patients with CF between Bronchitol-exposed patients vs. an unexposed patient group matched (via propensity score modelling) for age, disease severity, concomitant medications and presence of chronic *Pseudomonas*

**Action:** For adoption of advice to CHMP

#### 7.5.18. Nalmefene - SELINCRO (CAP) - EMEA/H/C/002583/MEA 001.3

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Interim baseline study report for PASS 14910A (EUPAS5678): a non-interventional multi-country prospective cohort study investigating patterns of use of Selincro (nalmefene) and frequency of adverse drug reactions in routine clinical practice

**Action:** For adoption of advice to CHMP

#### 7.5.19. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 002.3

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Study progress report (EVM-17123, November 2017, version 2.0) for PASS D3820R00006 (previously D2288R00081): a post-marketing observational drug utilisation

study (DUS) of Moventig (naloxegol) conducted in selected European populations in order to describe demographic, clinical, and treatment characteristics in the baseline of patients treated with naloxegol as well as to describe treatment pattern characteristics of naloxegol utilisation at initiation and follow-up (from initial MAA/opinion)

**Action:** For adoption of advice to CHMP

#### 7.5.20. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/LEG 087.5

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Fifth annual review on pregnancy cases, including cumulative data up to September 2017

**Action:** For adoption of advice to CHMP

#### 7.5.21. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/MEA 004.7

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Complementary data to the annual interim analysis for PASS study E2007-G000-402: a post-marketing observational safety study to evaluate the long-term safety and tolerability of Fycompa (perampanel) as add-on therapy in epilepsy patients

**Action:** For adoption of advice to CHMP

#### 7.5.22. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/ANX 033.2

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Second interim report on drug utilisation studies evaluating rivaroxaban use and potential adverse outcomes, namely study 16159 (EUPAS11145) – namely study 16159 (EUPAS11145) in routine clinical practice in Germany; study 16646 (EUPAS11141) in routine clinical practice in the Netherlands; study 16647 (EUPAS11299) in routine clinical practice in the UK; study 17543 (EUPAS9895) in routine clinical practice in Sweden

**Action:** For adoption of advice to CHMP

#### 7.5.23. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/ANX 034.1

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report on study SN 17452 (EUPAS9977): an observational post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of Xarelto (rivaroxaban) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales

**Action:** For adoption of advice to CHMP

#### **7.5.24. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/ANX 043**

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Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Interim report on a post-authorisation programme addressing the safety of rivaroxaban in the secondary prevention of acute coronary syndrome outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all population and particularly in patients at increased risk of bleeding. The report includes findings from the drug utilisation and specific outcome studies (ANX033), Specialist cohort event monitoring study (ANX 034); modified prescription event monitoring study (ANX 035)

**Action:** For adoption of advice to CHMP

### **7.6. Others**

#### **7.6.1. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/MEA 024**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to SDA 043.1 [signal of incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia, EPITT 18688] to review the instructions for use (IFU) for Bydureon (exenatide) and propose improvements of the IFU as applicable, as per the request for information adopted by PRAC in July 2017

**Action:** For adoption of advice to CHMP

#### **7.6.2. Exenatide - BYETTA (CAP) - EMEA/H/C/000698/MEA 044**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to to SDA 043.1 [signal of incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia, EPITT 18688] to review the instructions for use (IFU) for Byetta (exenatide) and propose improvements of the IFU as applicable, as per the request for information adopted by PRAC in July 2017

**Action:** For adoption of advice to CHMP

#### **7.6.3. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/MEA 102.4**

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Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Annual report for study NV20234: a double-blind, randomized, stratified multicentre trial evaluating conventional and double dose oseltamivir in the treatment of

immunocompromised patients with influenza exploring the safety and efficacy of oseltamivir in immunocompromised patients (final clinical study report (CSR): by end of November 2018)

**Action:** For adoption of advice to CHMP

#### **7.6.4. Palonosetron - PALONOSETRON ACCORD (CAP) - EMEA/H/C/004129/LEG 002.2**

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Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Almath Spooner

Scope: MAH's response to LEG 002.1 [six-monthly cumulative review of cases of injection site reactions classified as an important potential risk (1 October 2016-31 March 2017) as requested at the time of the opinion for marketing authorisation(s) for Palonosetron Accord 250 micrograms solution for injection until further market experience is acquired] as per the request for supplementary information (RSI) adopted in September 2017

**Action:** For adoption of advice to CHMP

#### **7.6.5. Padeliporfin - TOOKAD (CAP) - EMEA/H/C/004182/REC 004**

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Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Submission of the outcome of the requested user testing for the patient information guide for Tookad (padeliporfin)

**Action:** For adoption of advice to CHMP

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

None

### **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)**

None



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

### 8.1. Annual reassessments of the marketing authorisation

#### 8.1.1. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0025 (without RMP)

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Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

**Action:** For adoption of advice to CHMP

#### 8.1.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0029 (without RMP)

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Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

**Action:** For adoption of advice to CHMP

#### 8.1.3. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0044 (without RMP)

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Applicant: Pfizer Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.2. Conditional renewals of the marketing authorisation

None

### 8.3. Renewals of the marketing authorisation

#### 8.3.1. Afatinib - GIOTRIF (CAP) - EMEA/H/C/002280/R/0026 (without RMP)

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.3.2. [Alemtuzumab - LEMTRADA \(CAP\) - EMEA/H/C/003718/R/0020 \(with RMP\)](#)

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Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.3.3. [Alogliptin - VIPIDIA \(CAP\) - EMEA/H/C/002182/R/0019 \(without RMP\)](#)

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.3.4. [Alogliptin, metformin - VIPDOMET \(CAP\) - EMEA/H/C/002654/R/0024 \(without RMP\)](#)

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.3.5. [Alogliptin, pioglitazone - INCRESYNC \(CAP\) - EMEA/H/C/002178/R/0023 \(without RMP\)](#)

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.3.6. [Atosiban - ATOSIBAN SUN \(CAP\) - EMEA/H/C/002329/R/0012 \(with RMP\)](#)

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Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.3.7. [Cobicistat - TYBOST \(CAP\) - EMEA/H/C/002572/R/0041 \(with RMP\)](#)

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Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

8.3.8. Fenofibrate, simvastatin - CHOLIB (CAP) - EMEA/H/C/002559/R/0017 (without RMP)

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Applicant: Mylan Products Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

8.3.9. Follitropin alfa - OVALEAP (CAP) - EMEA/H/C/002608/R/0023 (without RMP)

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Applicant: Teva B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

8.3.10. Indacaterol, glycopyrronium - ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/R/0024 (without RMP)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

8.3.11. Indacaterol, glycopyrronium - XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/R/0027 (without RMP)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

8.3.12. Matrix applied characterised autologous cultured chondrocytes - MACI (CAP) - EMEA/H/C/002522/R/0017 (with RMP)

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Applicant: Vericel Denmark ApS, ATMP<sup>35</sup>

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CAT and CHMP

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<sup>35</sup> Advanced therapy medicinal product

### 8.3.13. Mercaptamine - PROCYSBI (CAP) - EMEA/H/C/002465/R/0019 (with RMP)

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Applicant: Chiesi Orphan B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.3.14. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/R/0025 (without RMP)

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Applicant: Bayer AG

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.3.15. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/R/0060 (without RMP)

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Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

### 8.3.16. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/R/0016 (without RMP)

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

## 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 agenda.

### 9.3. Others

None

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

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

#### 10.1.1. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0085

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: PRAC consultation on a variation consisting of the evaluation of the results of study EPI-HPV-069: a meta-analysis assessing the risk of three autoimmune diseases following vaccination with Cervarix: autoimmune thyroiditis (AIT), Guillain-Barre syndrome (GBS) and inflammatory bowel disease (IBD). The RMP (version 18) is updated accordingly and includes minor updates related to other studies

**Action:** For adoption of advice to CHMP

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

None

### 10.3. Other requests

None

### 10.4. Scientific Advice

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

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

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

None

## 11.2. Other requests

### 11.2.1. Thiocolchicoside (NAP) - EMEA/H/N/PSA/J/0010

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Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: PRAC consultation on the evaluation of a progress report for a non-interventional imposed PASS: a drug utilisation study assessing the effectiveness of risk minimisation measures (routine and additional) and further characterising the prescribing patterns for thiocolchicoside-containing medicinal products for systemic use, following the conclusions of a referral procedure under Article 31 of Directive 2001/83/EC finalised in 2014, on request of Italy

**Action:** For adoption of advice to Member States

## 12. Organisational, regulatory and methodological matters

### 12.1. Mandate and organisation of the PRAC

None

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

None

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

#### 12.3.1. Healthcare Professionals' Working Party (HCPWP) – Consultation feedback on how best to cascade the information on the product information updates as well as to consider additional communication and risk minimisation tools to be used

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PRAC lead: Doris Stenver

**Action:** For discussion

#### 12.3.2. Scientific Advice Working Party (SAWP) – Survey on scientific advice procedures with PRAC consultation

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PRAC lead: Martin Huber, Brigitte Keller-Stanislawski

**Action:** For discussion

## 12.4. Cooperation within the EU regulatory network

### 12.4.1. European Network Training Centre (EU NTC) - Operation of Pharmacovigilance in the EU (EU PVOP) - Training curriculum (TC) – Implementation plan for 2018

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PRAC lead: Dolores Montero Corominas

**Action:** For adoption

### 12.4.2. PRAC strategic review and learning meeting, Prague, Czech Republic, 19-20 April 2018

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PRAC lead: Eva Jirsová

**Action:** For discussion

## 12.5. Cooperation with International Regulators

None

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

None

## 12.7. PRAC work plan

None

## 12.8. Planning and reporting

### 12.8.1. PRAC workload statistics – Q4 2017 and overview

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**Action:** For discussion

## 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 – template for sharing assessor's information

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**Action:** For adoption

### 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

**Action:** For discussion

### 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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**Action:** For adoption

## 12.11. Signal management

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

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PRAC lead: Sabine Straus

**Action:** For discussion

## 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 – experience analysis

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**Action:** For discussion



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

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**Action:** For adoption

**12.13. EudraVigilance database**

12.13.1. Activities related to the confirmation of full functionality

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None

12.13.2. EudraVigilance – annual report 2017

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**Action:** For information

12.13.3. EudraVigilance operational plan – milestones 2018 to 2020

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**Action:** For discussion

12.13.4. EudraVigilance (EV) - processing large volumes of cases made available through EV to MAHs

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**Action:** For discussion

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

12.14.1. Risk management systems

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None

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

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None

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

12.15.1. Post-authorisation Safety Studies – imposed PASS

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None

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

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None

## **12.16. Community procedures**

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

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None

### **12.16.2. Referral road map project – call for interest**

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**Action:** For discussion

## **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

### **12.18.3. Policy on scientific publication and representation For EMA’s scientific committees and their members**

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**Action:** For discussion

## **12.19. Continuous pharmacovigilance**

### **12.19.1. Incident management**

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None

## **12.20. Others**

### **12.20.1. Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population-specific considerations IV: ‘Paediatric pharmacovigilance’**

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**Action:** For adoption

12.20.2. Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population-specific considerations V: ‘Medicines used by the older population’

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**Action:** For discussion

12.20.3. Public hearing – outcome report

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**Action:** For discussion

12.20.4. Scientific meeting on long-term pregnancy outcomes, EMA, London, 28-29 June 2018 - Agenda

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Action: For discussion

## 13. Any other business

Next meeting on: 09-12 April 2018

## 14. Explanatory notes

The Notes give a brief explanation of relevant agenda items and should be read in conjunction with the agenda.

### **EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures** (Items 2 and 3 of the PRAC agenda)

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 agenda)

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 agenda)

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 agenda)

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 agenda)

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 agenda)

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: [www.ema.europa.eu/](http://www.ema.europa.eu/)