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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 February 2018

Chair: June Raine – Vice-Chair: Almath Spooner

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

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

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

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

Organisational, regulatory and methodological matters (ORGAM)

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

### Health and safety information

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.

### Disclaimers

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

Of note, 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](#)).



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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 February 2018. See February 2018 PRAC minutes (to be published post March 2018 PRAC meeting).

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

**Action:** For adoption

### 1.3. Minutes of the previous meeting on 08-11 January 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

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

### 3.1. Newly triggered procedures

None

## 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
- 

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 adoption of a list of outstanding issues (LoOI)

### 3.2.2. Flupirtine (NAP) - EMEA/H/A-31/1458

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Applicant(s): various

PRAC Rapporteur: Ana Sofia Diniz Martins; 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 adoption of a list of outstanding issues (LoOI) (or adoption of a recommendation to CMDh)

### 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 discussion

## 3.3. Procedures for finalisation

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

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

PRAC Rapporteur: Ana Sofia Diniz Martins; PRAC Co-rapporteur: Julie Williams

Scope: 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 adoption of a recommendation to CHMP

### 3.3.2. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide (NAP) - EMEA/H/A-31/1454

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Applicant(s): Sanofi-aventis, various

PRAC Rapporteur: Sabine Straus; PRAC Co-rapporteur: Jean-Michel Dogné

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

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

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

None

### 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. Biotin (NAP)

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Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of interference with clinical laboratory tests

**Action:** For adoption of PRAC recommendation

EPITT 19156 – New signal

Lead Member State: DE

### 4.2. New signals detected from other sources

#### 4.2.1. Human coagulation(plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP) Recombinant factor VIII: antihemophilic factor (recombinant) (NAP); efmoroctocog alfa – ELOCTA (CAP); lonoctocog alfa – AFSTYLA (CAP); moroctocog alfa – REFACTO AF (CAP); octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY (CAP); simoctocog alfa – NUWIQ (CAP), VIHUMA (CAP); susoctocog alfa – OBIZUR (CAP); turoctocog alfa – NOVOEIGHT (CAP); NAP

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Applicant(s): Baxalta Innovations GmbH (Obizur), Baxter AG (Advate), Bayer AG (Helixate)

<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

Nexgen, Iblis, Kogenate Bayer, Kovaltry), CSL Behring GmbH (Afstyla, Voncento), Novo Nordisk A/S (NovoEight), Octapharma AB (Nuwiq, Vihuma), Pfizer Limited (ReFacto AF), Swedish Orphan Biovitrum AB (publ) (Elocta), various

PRAC Rapporteur: To be appointed

Scope: Signal of inhibitor development in previously untreated patients (PUPs) with haemophilia A treated with plasma-derived vs recombinant coagulation factor VIII concentrates

**Action:** For adoption of PRAC recommendation

EPITT 18701 – Related to signal recommendation dated July 2016

Lead Member State: DE

#### 4.2.2. Varenicline – CHAMPIX (CAP)

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Applicant(s): Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Signal of loss of consciousness

**Action:** For adoption of PRAC recommendation

EPITT 19146 – New signal

Lead Member State: DK

#### 4.2.3. Paracetamol (NAP)

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Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus

**Action:** For adoption of PRAC recommendation

EPITT 17796 – Related to signal recommendation dated January 2017

Lead Member State: BE

### 4.3. Signals follow-up and prioritisation

#### 4.3.1. Apixaban – ELIQUIS (CAP) - EMEA/H/C/002148/SDA/026; dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/SDA/048; edoxaban – LIXIANA (CAP) - EMEA/H/C/002629/SDA/009; rivaroxaban – XARELTO (CAP) - EMEA/H/C/000944/SDA/041

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Applicant(s): Bayer AG (Xarelto), Boehringer Ingelheim International GmbH (Pradaxa), Bristol-Myers Squibb- Pfizer EEIG (Eliquis), Daiichi Sankyo Europe GmbH (Lixiana)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of cholesterol embolisms

**Action:** For adoption of PRAC recommendation

EPITT 19078 – Follow-up to October 2017

#### 4.3.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/SDA/007

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Applicant(s): Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Signal of pneumonia

**Action:** For adoption of PRAC recommendation

EPITT 18950 – Follow-up to October 2017

#### 4.3.3. Filgrastim - ACCOFIL (CAP) - EMEA/H/C/003956/SDA/002, FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/SDA/020, GRASTOFIL (CAP) - EMEA/H/C/002150/SDA/003, NIVESTIM (CAP) - EMEA/H/C/001142/SDA/016, RATIOGRASTIM (CAP) - EMEA/H/C/000825/SDA/021, TEVAGRASTIM (CAP) - EMEA/H/C/000827/SDA/021, ZARZIO (CAP) - EMEA/H/C/000917/SDA/020, NAP; lenograstim (NAP); lipegfilgrastim – LONQUEx (CAP) - EMEA/H/C/002556/SDA/013; pegfilgrastim – NEULASTA (CAP) - EMEA/H/C/000420/SDA/058

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Applicant(s): Accord Healthcare Limited (Accofil), Amgen Europe B.V. (Neulasta), Apotex Europe BV (Grastofil), Hexal AG (Filgrastim Hexal), Hospira UK Limited (Nivestim), Ratiopharm GmbH (Ratiograstim), Sandoz GmbH (Tevagrastim), Sicor Biotech UAB (Lonquex), Teva GmbH; various

PRAC Rapporteur: Patrick Batty

Scope: Signal of aortitis

**Action:** For adoption of PRAC recommendation

EPITT 18940 – Follow-up to September 2017

#### 4.3.4. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/SDA/033, NAP

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Applicant(s): Addmedica, various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of cutaneous lupus erythematosus

**Action:** For adoption of PRAC recommendation

EPITT 18939 – Follow-up to September 2017

#### 4.3.5. Ritonavir - NORVIR (CAP) - EMEA/H/C/000127/SDA/050; lopinavir, ritonavir – KALETRA (CAP) – EMEA/H/C/000368/SDA/120; levothyroxine (NAP)

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Applicant(s): AbbVie Ltd. (Kaletra, Norvir), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism

**Action:** For adoption of PRAC recommendation

EPITT 18896 – Follow-up to December 2017



## 5. Risk management plans (RMPs)

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

#### 5.1.1. Adalimumab - EMEA/H/C/004866

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Scope: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, uveitis, paediatric uveitis

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

#### 5.1.2. Adalimumab - EMEA/H/C/004865

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Scope: Treatment of juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, uveitis, paediatric uveitis

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

#### 5.1.3. Adalimumab - EMEA/H/C/004320

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Scope: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis, paediatric uveitis

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

#### 5.1.4. Beclometasone dipropionate anhydrous, formoterol fumarate – EMEA/H/C/004836

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Scope: Symptomatic treatment and reduction of exacerbations in adult patients with chronic obstructive pulmonary disease (COPD) with airflow limitation and who are at risk of exacerbations

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

#### 5.1.5. Beclometasone dipropionate anhydrous, formoterol fumarate – EMEA/H/C/004702

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Scope: Symptomatic treatment and reduction of exacerbations in adult patients with chronic obstructive pulmonary disease (COPD) with airflow limitation and who are at risk of exacerbations

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

#### 5.1.6. Bictegravir, emtricitabine, tenofovir alafenamide – EMEA/H/C/004449

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Scope: treatment of adults infected with human immunodeficiency virus-1 (HIV-1)

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

#### 5.1.7. Daunorubicin, cytarabine – EMEA/H/C/004282, Orphan

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Applicant: Jazz Pharmaceuticals Ireland Limited

Scope (accelerated assessment): Treatment of adults with high-risk acute myeloid leukaemia (AML)

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

#### 5.1.8. Erenumab – EMEA/H/C/004447

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Scope: Prophylaxis of migraine in adults

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

#### 5.1.9. Infliximab – EMEA/H/C/004647

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Scope: Treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis

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

#### 5.1.10. Inotersen – EMEA/H/C/004782, Orphan

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Applicant: Ionis USA Ltd

Scope (accelerated assessment): Treatment of adult patients with hereditary transthyretin amyloidosis (hATTR)

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

#### 5.1.11. Naldemedine – EMEA/H/C/004256

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Scope: Treatment of opioid-induced constipation (OIC) in adult patients

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

#### 5.1.12. Nitisinone – EMEA/H/C/004582

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Scope: Treatment of hereditary tyrosinemia type 1

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

#### 5.1.13. Sodium benzoate – EMEA/H/C/004150, Orphan

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Applicant: Lucane Pharma

Scope: Treatment of non ketotic hyperglycinemia, urea cycle disorders including carbamoyl-phosphate synthase-1 deficiency, ornithine transcarbamylase deficiency, citrullinaemia type 1, argininosuccinic aciduria, hyperargininaemia, N-acetylglutamate synthase deficiency, ornithine translocase deficiency and lysinuric protein intolerance

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

#### 5.1.14. Sufentanil – EMEA/H/C/004335

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Scope: Management of acute moderate to severe pain

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

### 5.1.15. Vestronidase alfa – EMEA/H/C/004438, Orphan

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Applicant: Ultragenyx Germany GmbH

Scope: Treatment of mucopolysaccharidosis VII (MPS VII; Sly syndrome) for patients of all ages

**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. Albiglutide - EPERZAN (CAP) - EMEA/H/C/002735/II/0029/G

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

Scope: Grouped variations to: 1) update the RMP to amend the category 3 study 201805: an observational study of the risk of common malignant neoplasms and malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide compared to those prescribed other antidiabetic agents, in order to use a different database to study the risk of neoplasms in association with albiglutide exposure; 2) update the RMP to add a new category 3 study as an additional pharmacovigilance activity study 207351: an observational study to assess maternal and foetal outcomes following exposure to albiglutide during pregnancy

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

### 5.2.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0027, Orphan

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Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Updated RMP (version 4.0) in order to re-classify an imposed non-interventional PASS listed as a category 2 study in the RMP (specific obligation) to a study listed as a category 3 in the RMP (required additional pharmacovigilance activities). This study is an observational registry (DF-VOD2013-03-REG) aiming at recording safety and outcome data in patients diagnosed with severe veno-occlusive disease (VOD) following haematopoietic stem cell transplantation (HSCT) treated or not with Defitelio. Annex II of the product information is updated accordingly

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

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

### 5.3.1. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0010

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Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update information on effect of hepatic impairment on pharmacokinetic (PK) of alectinib based on final results from study NP29783: a multicentre, open label study following single oral dosing of alectinib to subjects with hepatic impairment and matched healthy subjects with normal hepatic function. The

Package Leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest EC guidance regarding warning statements on sodium

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

#### 5.3.2. [Anakinra - KINERET \(CAP\) - EMEA/H/C/000363/II/0056](#)

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include a new indication for Kineret 100 mg/0.67 mL solution for injection in pre-filled syringe for the treatment of active Still's disease, including systemic juvenile idiopathic arthritis and adult-onset Still's disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the SmPC and package leaflet

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

#### 5.3.3. [Ataluren - TRANSLARNA \(CAP\) - EMEA/H/C/002720/II/0037, Orphan](#)

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Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include a new population: children from 2 to less than 5 years of age. 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 7.1) are updated accordingly

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

#### 5.3.4. [Atazanavir, cobicistat - EVOTAZ \(CAP\) - EMEA/H/C/003904/WS1292/0019;](#) [Atazanavir, atazanavir sulfate - REYATAZ \(CAP\) - EMEA/H/C/000494/WS1292/0114](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: Update of section 4.3 and 4.5 of the SmPC in order to add a contraindication with lurasidone to reflect this interaction based on literature data. The Package Leaflet and the RMP (version 14 for Reyataz; version 6 for Evotaz) are updated accordingly

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

#### 5.3.5. [Atezolizumab - TECENTRIQ \(CAP\) - EMEA/H/C/004143/II/0002/G](#)

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Applicant: Roche Registration Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 4.8 of the SmPC in order to add myocarditis as a new adverse reaction based on the results of a cumulative review of cases of suspected myocarditis. As a consequence, the information regarding the posology and special warnings have been updated. Annex II, the Package Leaflet and the RMP (version 2.0) have been updated accordingly; 2) update of the RMP to add haemolytic

anaemia as a new important identified potential risk

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

#### 5.3.6. [Bosutinib - BOSULIF \(CAP\) - EMEA/H/C/002373/II/0025/G, Orphan](#)

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Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of an extension of indication to include treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic phase (CP) chronic myelogenous leukaemia (CML) for Bosulif based on study AV001: a multicentre phase 3 randomized, open-label study of bosutinib versus imatinib in adult patients with newly diagnosed CP CML. In addition, the MAH updated the SmPC with safety and efficacy data from study B1871006: a phase 1/2 study of bosutinib in Ph+ leukaemias, and study B1871008: a phase 3 randomized, open-label study of bosutinib versus imatinib in subjects with newly diagnosed CP Ph+ CML. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly. Furthermore, Annex IIIA is 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

#### 5.3.7. [Trametinib - MEKINIST \(CAP\) - EMEA/H/C/002643/WS1274/0023;](#) [Dabrafenib - TAFINLAR \(CAP\) - EMEA/H/C/002604/WS1274/0031](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the combination adjuvant treatment with trametinib and dabrafenib of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the Mekinist and Tafinlar SmPCs are updated. The Package Leaflet and the RMP (version 14.0 for Mekinist and version 9.0 for Tafinlar) are updated accordingly. In addition, the MAH took the opportunity to correct some typos throughout the Mekinist and Tafinlar product information, to include a cross reference to the Mekinist SmPC in section 4.6 of the Tafinlar SmPC regarding fertility as well as to update the list of local representatives for Bulgaria, Hungary, Estonia, Latvia and Lithuania in the Package Leaflet of both products

**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/0003/G](#)

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to reflect the week-48 results from two studies listed as category 3 studies in the RMP, namely study TMC114FD2HTX3001: evaluation of the efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed-dose combination regimen versus a regimen consisting of darunavir/cobicistat (DRV/COBI) fixed

dose combination (FDC) co-administered with emtricitabine/tenofovir alafenamide (FTC/TDF) FDC in antiretroviral (ARV) treatment-naïve human immunodeficiency virus 1 (HIV-1) infected subjects; and TMC114IFD3013: evaluation of switching to a D/C/F/TAF once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor combined with FTC/TDF in virologically-suppressed, HIV-1 infected subjects. The RMP (version 2.0) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to make minor editorial revision in the product information

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

#### 5.3.9. [Dasatinib - SPRYCEL \(CAP\) - EMEA/H/C/000709/X/0056/G](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Grouped application consisting of: 1) extension application (line extension) to introduce a new pharmaceutical form (powder for oral suspension) associated with a new strength (10 mg/mL); 2) extension of indication to include the treatment of children and adolescents aged 1 year to 18 years with Ph+ chronic phase in chronic myeloid leukaemia (CML). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, to add a warning on effects on growth and development in the paediatric population and to update the safety information. The Package Leaflet and the RMP (version 15.0) are updated accordingly

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

#### 5.3.10. [Defibrotide - DEFITELIO \(CAP\) - EMEA/H/C/002393/II/0026, Orphan](#)

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Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the frequencies of adverse reactions included in the tabulated list of adverse reactions and to update the clinical efficacy and safety information based on the results from study 2006-05 (listed as category 3 in the RMP): a phase 3, open-label expanded access study designed to provide access to defibrotide as an investigational new drug to patients with severe hepatic veno-occlusive disease. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to bring the SmPC in line with the latest QRD template (version 10), to update the list of local representatives in the package leaflet and to correct a translation error in the Polish, Finnish, Danish and Latvian versions

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

#### 5.3.11. [Denosumab - XGEVA \(CAP\) - EMEA/H/C/002173/II/0055](#)

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with multiple myeloma and in adults with bone metastases from solid tumours for

Xgeva. 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 24.0) are updated accordingly

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

#### 5.3.12. [Dimethyl fumarate - TECFIDERA \(CAP\) - EMEA/H/C/002601/II/0037](#)

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of a clinical study report (CSR) for study 109MS307: an open-label study to assess the immune response to vaccination in Tecfidera-treated versus interferon-treated subjects with relapsing forms of multiple sclerosis (category 3). As a consequence, section 4.5 of the SmPC is updated. The Package Leaflet and the RMP (version 9.0) are updated accordingly

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

#### 5.3.13. [Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA \(CAP\) - EMEA/H/C/000797/II/0127/G](#)

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Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of sections 4.3, 4.4, 4.5 and 5.1 of the SmPC to include the results of the final study report for study AI266959: an interventional study to determine the concentration-electrocardiographic effects of efavirenz in healthy subjects enriched for CYP2B6<sup>3</sup> polymorphism, as requested by PRAC in the recommendation for PSUSA procedure (PSUSA/00001200/201604) on Stocrin/Sustiva (efavirenz) finalised in November 2016; 2) update of sections 4.4 and 4.8 of the SmPC to add catatonia as a psychiatric symptom following an assessment of catatonia cases reported in the literature and the US FDA adverse event reporting system (FAERS); 3) the RMP (version 17) is updated to remove malignant neoplasms as a potential risk. The MAH took the opportunity to implement minor editorial changes in the product information and minor linguistic amendments to the following languages: Danish, German, Finnish, French Hungarian, Icelandic, Maltese, Norwegian, Portuguese, Spanish and Swedish

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

#### 5.3.14. [Eliglustat - CERDELGA \(CAP\) - EMEA/H/C/003724/II/0015/G, Orphan](#)

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variations consisting of an update of sections 4.2, 4.3, 4.4, 4.5 and 5.2 of the SmPC based on the final data from: 1) study POP13777: an open-label pharmacokinetic and tolerability study of eliglustat tartrate given as a single dose in subjects with mild and moderate hepatic impairment, and in matched subjects with normal hepatic function (MEA003.3) and; 2) study POP13778: an open-label two-stage pharmacokinetic and tolerability study of eliglustat tartrate given as a single dose in subjects with mild, moderate and severe renal impairment, and in matched subjects with normal renal function

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<sup>3</sup> Cytochrome P450, family 2, subfamily B, polypeptide 6



(MEA004.3). Annex II D, the package leaflet and the RMP (version 5.0) are updated accordingly

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

#### 5.3.15. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0017/G

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped variations consisting of an extension of indication to include the reduction of atherosclerotic cardiovascular disease risk in adults with high cardiovascular risk based on the results from study 20110118: a double-blind, randomised, placebo-controlled, multicentre study assessing the impact of additional low-density lipoprotein (LDL)-cholesterol reduction on major cardiovascular events when evolocumab (AMG 145) is used in combination with statin therapy in patients with clinically evident cardiovascular disease (category 3 pharmacovigilance activity in the RMP, MEA 004). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update section 5.1 of the SmPC to include important mechanistic information for healthcare professionals based on study 20120153 (a double-blind, randomised, multicentre, placebo-controlled, parallel group study to determine the effects of evolocumab (AMG 145) treatment on atherosclerotic disease burden as measured by intravascular ultrasound in subjects undergoing coronary catheterisation, a category 3 pharmacovigilance activity, MEA 006). The RMP (version 2.0) is also updated in order to add two category 3 studies in the RMP (study 20160250: a multicentre, open-label, single-arm, extension study to assess long-term safety of evolocumab therapy in subjects with clinically evident cardiovascular disease in selected European countries and study 20150338: a multicentre, controlled, open-label extension (OLE) study to assess the long-term safety and efficacy of evolocumab (AMG 145)) as well as to update the milestones of five category 3 studies (study 20110110: multicentre, controlled, OLE study to assess the long-term safety and efficacy of evolocumab; study 20110271: multicentre, open-label study to assess the long-term safety, tolerability, and efficacy of evolocumab on low-density lipoprotein cholesterol (LDL-C) in subjects with severe familial hypercholesterolaemia (including homozygous familial hypercholesterolemia (HoFH)); study 20120138: a multicentre, controlled, OLE study to assess the long-term safety and efficacy of evolocumab; study 20130286: a double blind, randomised, placebo controlled, multicentre study to evaluate safety, tolerability, and efficacy on LDL-C of evolocumab in human immunodeficiency virus (HIV) positive patients with hyperlipidemia and mixed dyslipidemia; and study 20130295 a multicentre, OLE study to assess long-term safety and efficacy of evolocumab therapy in patients with clinically evident cardiovascular disease (FOURIER-OLE))

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

#### 5.3.16. Ferric maltol - FERACCRU (CAP) - EMEA/H/C/002733/II/0010

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Applicant: Shield TX (UK) Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to widen the indication from 'the treatment in adults with iron deficiency anaemia' in patients with inflammatory bowel disease (IBD) to 'the treatment of

adults with iron deficiency'. As a consequence, sections 4.1, 4.4, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

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

#### 5.3.17. Florbetapir (<sup>18</sup>F) - AMYVID (CAP) - EMEA/H/C/002422/II/0029

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Update of section 4.4. of the SmPC following the final report from study I6E-MC-AVBF (listed as a category 3 study in the RMP): a non-interventional category 3 study, a European drug usage survey to assess the usage pattern of Amyvid in the EU. The RMP (version 3.1) is updated accordingly

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

#### 5.3.18. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/X/0037, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Extension application to introduce a new pharmaceutical form (film-coated tablets) associated with new strengths (140 mg, 280 mg, 420 mg and 560 mg). The RMP (version 8.0) is updated accordingly

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

#### 5.3.19. Insulin degludec, liraglutide - XULTOPHY (CAP) - EMEA/H/C/002647/II/0023

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information based on cardiovascular outcomes studies conducted for each of the monocomponents of Xultophy, namely: study LEADER (liraglutide cardiovascular outcomes trial): a long term, multicentre, randomised double-blind placebo-controlled trial to determine liraglutide effects on cardiovascular events, and study DEVOTE (Insulin degludec cardiovascular outcomes trial): a trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events. The MAH also proposed to reorganise parts of section 5.1 to improve the reader friendliness and to remove Xultophy from the list of medicines under additional monitoring. The Package Leaflet and the RMP (version 7.0) are updated accordingly

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

#### 5.3.20. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS1278/0042; ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS1278/0053

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Opdivo and Yervoy SmPCs are updated. The Package Leaflet and the RMP (version 19.0 for Yervoy and version 13.0 for Opdivo) are updated accordingly. In addition, the MAH took the opportunity to correct some typos throughout the Yervoy and Opdivo product information

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

#### 5.3.21. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/II/0064

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of section 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the safety and efficacy information based on interim results from study GS-US-334-0154 (listed as a category 3 study in the RMP): a study to evaluate the safety, efficacy and pharmacokinetics in patients treated with ledipasvir/sofosbuvir fixed-dose combination for 12 weeks in genotype 1 or 4 HCV-infected subjects with renal insufficiency. The Package Leaflet and the RMP (version 3.2) are updated accordingly

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

#### 5.3.22. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0011/G, Orphan

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of hepatocellular carcinoma (HCC) based on pivotal study 304: a multicentre, randomized, open-label, phase 3 trial to compare the efficacy and safety of lenvatinib versus sorafenib in first-line treatment of subjects with unresectable HCC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 10) are updated accordingly; 2) section 4.2 of the SmPC is updated to add that the medicinal product can be administered as a suspension in water or apple juice. In addition, the labelling is updated to include a unique identifier

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

#### 5.3.23. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0004, Orphan

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.8 of the SmPC to include new safety information related to hydrocephalus. The Package Leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to correct some typographical errors in section 5.1 of the SmPC

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

#### 5.3.24. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/X/0016/G, Orphan

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Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Grouped application consisting of: 1) extension application (line extension) to add a new pharmaceutical form (film-coated tablets) associated with a new strength (100 mg and 150 mg); 2) alignment of the Product Information (PI) for the approved capsule presentation with the PI proposed for the tablet presentation. The RMP (version 15) is updated accordingly

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

#### 5.3.25. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0128

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Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.6 of the SmPC in order to reflect the final study results from a non-interventional safety study BV29684, which assessed the safety of oseltamivir exposure in pregnant women (listed as a category 3 study in the RMP (MEA099)). The RMP (version 15.0) is updated accordingly

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

#### 5.3.26. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0019

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Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations, based on data from the FLAURA study (D5160C00007): a phase 3, double-blind, randomised study to assess the efficacy and safety of osimertinib versus a standard of care epidermal growth factor receptor-tyrosine kinase inhibitor as first-line treatment in patients with epidermal growth factor receptor mutation-positive, locally-advanced or metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 8) are updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and Package Leaflet. As part of this application, the MAH requested an additional year of market protection

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

#### 5.3.27. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0093/G

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of: 1) addition of a new device: the on-body injector (Onpro kit) to be used with Neulasta, 6mg solution for injection, pre-filled syringe; 2) change the fill volume for Neulasta, 6 mg, solution for injection pre-filled syringe co-packed

with the on-body injector (Onpro kit). In addition, the MAH took the opportunity to introduce editorial changes regarding the container closure system. As a consequence, sections 3, 4.2, 5.1, 6.4, 6.5, 6.6 and 8 of the SmPC are updated. The Labelling, Package Leaflet and the RMP (version 4.2) are updated accordingly. In addition the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to include some editorial changes and correct some typos throughout the product information. Finally, the MAH brought the product information in line with the latest QRD template (version 10)

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

#### 5.3.28. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0037/G

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Grouped variations consisting of an update of sections 4.4 and 4.8 of the SmPC to add information regarding the risks of encephalitis, sarcoidosis and graft versus host disease (GVHD) that have been reported in patients treated with pembrolizumab. The package leaflet, the 'additional risk minimisation measures' section (educational material) in Annex II and the RMP (version 13.0) are updated accordingly. In addition, the MAH implemented minor changes in the SmPC section 5.1 and editorial changes in the package leaflet

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

#### 5.3.29. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0064/G

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of: 1) extension of indication for Isentress 100 mg granules for oral suspension to include the treatment of human immunodeficiency virus type 1 (HIV-1) in exposed full-term neonates under the age of 4 weeks based on safety and pharmacokinetic (PK) data from a pivotal phase 1 study IMPAACT P1110 (protocol 080) conducted in a total of 42 HIV-1 exposed full-term infants (defined as  $\geq 37$  weeks gestational age and  $\geq 2,000$  g), who received either 2 single doses of oral suspension within 48 hours of birth and day 7-10 of age (cohort I), or a multiple-dose regimen of raltegravir over the first 6 weeks of age (cohort II). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. The provision of the results of IMPAACT P1110 study addresses the final paediatric investigation plan (PIP) measure, i.e. study 4, conducted to generate PK, safety, and tolerability data in HIV exposed neonates and infants <6 weeks of age born to HIV infected mothers; 2) update of the suspension volume from 5 mL to 10 mL for a final suspension concentration of 10 mg/mL to facilitate accurate measurements of the smaller doses required for neonates. As a consequence, the 5 mL syringe supplied in the current commercial kit is replaced with 3 new oral dosing syringes, and sizes (1 mL, 3 mL, and 10 mL) from a different (new) supplier. As a consequence, sections 6.5 and 6.6 of the SmPC are updated. The labelling, the instructions for use in 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

### 5.3.30. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0058

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Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include the prevention of stroke, myocardial infarction and cardiovascular death, and for the prevention of acute limb ischaemia and mortality in adult patients with coronary artery disease (CAD) or peripheral artery disease (PAD) for Xarelto 2.5 mg co-administered with acetylsalicylic acid. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet, Labelling and the RMP (version 11.1) are updated accordingly. In addition, section 4.8 of the SmPC is updated for all other dose strengths (10/15/20 mg) of Xarelto with relevant exposure information based on the provided clinical data

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

### 5.3.31. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/X/0035

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Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension application to add a new strength of 250 µg in a polyvinyl chloride (PVC)/polyvinylidene chloride (PVDC)/aluminium (Alu) blister of 28 tablets. The RMP (version 18) is updated accordingly

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

### 5.3.32. Sevelamer carbonate - SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/X/0011

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Extension application to add a new strength of 0.8 g powder for oral suspension. The RMP (version 9.0) is updated accordingly

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

### 5.3.33. Sevelamer carbonate - RENVELA (CAP) - EMEA/H/C/000993/X/0039

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Extension application to add a new strength of 0.8 g powder for oral suspension. The RMP (version 9.0) is updated accordingly

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

### 5.3.34. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/II/0065

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Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on study A6181109: 'a randomized double-blind phase 3 study of adjuvant sunitinib vs. placebo in subjects at high risk of recurrent RCC'. The Package Leaflet and the RMP (version 16) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC and Package Leaflet. This procedure fulfils PAM (FU2 22.5). Furthermore, the product information (PI) is 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

#### 5.3.35. [Telotristat ethyl - XERMELO \(CAP\) - EMEA/H/C/003937/II/0002/G, Orphan](#)

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Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) Submission of the final report for study LX301 (pivotal phase 3 study, listed as category 3 studies in the RMP): a randomised, multicentre, double-blind, placebo-controlled study evaluating the efficacy and safety of telotristat etiprate in patients with carcinoid syndrome not adequately controlled by somatostatin analogue (SSA) therapy; 2) Submission of the final report for study LX303 (pivotal phase 3 study, listed as category 3 studies in the RMP): a randomised, multicentre, double-blind, placebo-controlled study evaluating the safety and efficacy of telotristat etiprate in patients with carcinoid syndrome. The MAH also took the opportunity to provide updated safety data from the long-term extension study LX302: a phase 3, multicentre, open-label study to further evaluate the safety and tolerability of telotristat. As a consequence, the RMP (version 3.0) is updated

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

#### 5.3.36. [Tivozanib - FOTIVDA \(CAP\) - EMEA/H/C/004131/II/0002](#)

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Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Update of the section 5.2 of the SmPC with additional information on transporter proteins based on the results of an in vitro interaction transporter study. The updated RMP (version 2.0) is updated accordingly

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

#### 5.3.37. [Tocilizumab - ROACTEMRA \(CAP\) - EMEA/H/C/000955/II/0072](#)

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Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of juvenile idiopathic polyarthritis (pJIA) rheumatoid factor positive or negative and extended oligoarthritis in patients of 2 years of age and older, who have responded inadequately to previous therapy with methotrexate. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 23.0) are 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. Aclidinium bromide - BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP) - PSUSA/00009005/201707

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.2. Albutrepenonacog alfa - IDELVION (CAP) - PSUSA/00010497/201707

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Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.3. Antithrombin alfa - ATRYN (CAP) - PSUSA/00000224/201707

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Applicant: Laboratoire Francais du Fractionnement et des Biotechnologies

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.4. Asparaginase<sup>4</sup> - SPECTRILA (CAP) - PSUSA/00010445/201707

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Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.5. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/201707

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Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

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<sup>4</sup> Centrally authorised product(s) only

#### 6.1.6. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/201707

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.7. Birch bark extract<sup>5</sup> - EPISALVAN (CAP) - PSUSA/00010446/201707

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Applicant: Amryt AG

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.8. Botulinum B toxin - NEUROBLOC (CAP) - PSUSA/00000428/201706 (with RMP)

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Applicant: Eisai Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.9. Brivaracetam - BRIVIACT (CAP) - PSUSA/00010447/201707

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.10. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/201707

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.11. Dapagliflozin, metformin - EBYMECT (CAP), XIGDUO (CAP) - PSUSA/00010294/201707

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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<sup>5</sup> Centrally authorised product(s) only

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

#### 6.1.12. Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/201707

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.13. Etanercept<sup>6</sup> - BENEPALI (CAP) - PSUSA/00010452/201707

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.14. Evolocumab - REPATHA (CAP) - PSUSA/00010405/201707

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.15. Icatibant - FIRAZYR (CAP) - PSUSA/00001714/201707

Applicant: Shire Orphan Therapies GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.16. Idelalisib - ZYDELIG (CAP) - PSUSA/00010303/201707

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.17. Idursulfase - ELAPRASE (CAP) - PSUSA/00001722/201707

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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<sup>6</sup> For biosimilar Benepali only

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

**6.1.18. [Ingenol mebutate - PICATO \(CAP\) - PSUSA/00010035/201707](#)**

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Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

**6.1.19. [Insulin glargine, lixisenatide - SULIQUA \(CAP\) - PSUSA/00010577/201707](#)**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

**6.1.20. [Lipegfilgrastim - LONQUEx \(CAP\) - PSUSA/00010111/201707](#)**

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Applicant: Sicor Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

**6.1.21. [Lomitapide - LOJUXTA \(CAP\) - PSUSA/00010112/201707](#)**

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Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

**6.1.22. [Mercaptamine<sup>7</sup> - CYSTADROPS \(CAP\) - PSUSA/00010574/201707](#)**

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Applicant: Orphan Europe SARL

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

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

**6.1.23. [Modified vaccinia Ankara virus - IMVANEX \(CAP\) - PSUSA/00010119/201707 \(with RMP\)](#)**

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Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

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<sup>7</sup> Indicated in the treatment of corneal cystine crystal deposits

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.24. Nateglinide - STARLIX (CAP) - PSUSA/00002128/201706

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.25. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/201708

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.26. Palivizumab - SYNAGIS (CAP) - PSUSA/00002267/201706

Applicant: AbbVie Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.27. Pegaspargase<sup>8</sup> - ONCASPAR (CAP) - PSUSA/00010457/201707

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.28. Peginterferon alfa-2a - PEGASYS (CAP) - PSUSA/00009254/201707

Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.29. Peginterferon beta-1a - PLEGRIDY (CAP) - PSUSA/00010275/201707

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Julie Williams

<sup>8</sup> Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

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

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6.1.30. [Perampanel - FYCOMPA \(CAP\) - PSUSA/00009255/201707](#)

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Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

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6.1.31. [Phenylephrine, ketorolac - OMIDRIA \(CAP\) - PSUSA/00010419/201707](#)

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Applicant: Omeros London Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

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6.1.32. [Rotavirus vaccine monovalent \(live, oral\) - ROTARIX \(CAP\) - PSUSA/00002665/201707](#)

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Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

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

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6.1.33. [Sacubitril, valsartan - ENTRESTO \(CAP\), NEPARVIS \(CAP\) - PSUSA/00010438/201707](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

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6.1.34. [Saxagliptin, dapagliflozin - QTERN \(CAP\) - PSUSA/00010520/201707](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

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6.1.35. [Temozolomide - TEMODAL \(CAP\) - PSUSA/00002886/201707](#)

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.36. Tocofersolan - VEDROP (CAP) - PSUSA/00002981/201707

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Applicant: Orphan Europe SARL

PRAC Rapporteur: Patrick Batty

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. Aripiprazole - ABILIFY (CAP), ABILIFY MAINTENA (CAP), ARIPIPRAZOLE SANDOZ (CAP); NAP - PSUSA/00000234/201707

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Applicants: Otsuka Pharmaceutical Europe Ltd (Abilify, Abilify Maintena), Sandoz GmbH (Aripiprazole Sandoz), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

#### 6.2.2. Fentanyl<sup>9</sup> - EFFENTORA (CAP), INSTANYL (CAP), PECFENT (CAP); NAP - PSUSA/00001369/201704

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Applicants: Teva B.V. (Effentora), Takeda Pharma A/S (Instanyl), Archimedes Development Limited (PecFent), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

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

#### 6.2.3. Nitric oxide - INOMAX (CAP); NAP - PSUSA/00002172/201706

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Applicants: Linde Healthcare AB (INOMax), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

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<sup>9</sup> Transmucosal route of administration only



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

#### 6.3.1. Amikacin (NAP) - PSUSA/00000143/201706

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Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.2. Benserazide, levodopa (NAP) - PSUSA/00000330/201706

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Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.3. Cilastatin, imipenem (NAP) - PSUSA/00000748/201706

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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

#### 6.3.4. Hepatitis A (inactivated), typhoid polysaccharide vaccine (adsorbed) (NAP) - PSUSA/00001594/201706

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Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.5. Latanoprost, timolol (NAP) - PSUSA/00001833/201706

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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

#### 6.3.6. Pentamidine (NAP) - PSUSA/00002338/201706

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Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.7. Solifenacin (NAP) - PSUSA/00002769/201706

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.8. Interferon alfa-2a (NAP) - PSUSA/00009197/201706

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.9. Pitavastatin (NAP) - PSUSA/00010502/201707

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.10. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/201707

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.11. Sulfamethizole (NAP) - PSUSA/00010561/201706

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.12. Nitrous oxide (NAP); nitrous oxide, oxygen (NAP) - PSUSA/00010572/201706

Applicant(s): various

PRAC Lead: Amy Tanti

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.13. Levonorgestrel/ethinylestradiol, ethinylestradiol<sup>10</sup> (NAP) - PSUSA/00010442/201707

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.14. Technetium (<sup>99m</sup>Tc) sestamibi (NAP) - PSUSA/00002868/201706

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.15. Misoprostol<sup>11</sup> (NAP) - PSUSA/00010291/201706

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

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

#### 6.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/LEG 057

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of a cumulative review of cases on *Pneumocystis jirovecii* infections as requested in the conclusions of PSUSA/00000013/201612 adopted in September 2017

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

#### 6.4.2. Alendronic acid, colecalciferol - ADROVANCE (CAP) - EMEA/H/C/000759/LEG 015

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of a detailed review on cases of osteonecrosis other than the jaw and external auditory canal, including information on diagnostic criteria applied and results of diagnostic tests, discussion on potential influence of local anatomy and discussion on underlying pathophysiological mechanism and possible risk factors as requested for bisphosphonate-containing products following the conclusions of PSUSA/00003149/201608

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<sup>10</sup> Combination pack

<sup>11</sup> Gastrointestinal indication only

for zoledronic acid (indicated in the treatment of cancer and fractures) adopted in April 2017

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

#### 6.4.3. Alendronic acid, colecalciferol - FOSAVANCE (CAP) - EMEA/H/C/000619/LEG 016

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of a detailed review on cases of osteonecrosis other than the jaw and external auditory canal, including information on diagnostic criteria applied and results of diagnostic tests, discussion on potential influence of local anatomy and discussion on underlying pathophysiological mechanism and possible risk factors as requested for bisphosphonate-containing products following the conclusions of PSUSA/00003149/201608 for zoledronic acid (indicated in the treatment of cancer and fractures) adopted in April 2017

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

#### 6.4.4. Alendronic acid, colecalciferol - VANTAVO (CAP) - EMEA/H/C/001180/LEG 008

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of a detailed review on cases of osteonecrosis other than the jaw and external auditory canal, including information on diagnostic criteria applied and results of diagnostic tests, discussion on potential influence of local anatomy and discussion on underlying pathophysiological mechanism and possible risk factors as requested for bisphosphonate-containing products following the conclusions of PSUSA/00003149/201608 for zoledronic acid (indicated in the treatment of cancer and fractures) adopted in April 2017

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

#### 6.4.5. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/LEG 010

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Caroline Laborde

Scope: Submission of an overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the effectiveness of each measure in place to minimise any risk (including educational material and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017

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

#### 6.4.6. Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/LEG 086

Applicant: Actelion Registration Limited

PRAC Rapporteur: Caroline Laborde

Scope: Submission of an overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the effectiveness of each measure in place to minimise any risk (including educational material

and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017

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

#### 6.4.7. Sorafenib - NEXAVAR (CAP) - EMEA/H/C/000690/LEG 038

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Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated cumulative review on hypoglycaemia as requested in the conclusions of PSUSA/00002773/201612 adopted in September 2017

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

#### 6.4.8. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 035.1

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Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 035 [Review of cases of posterior reversible encephalopathy syndrome (PRES) as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

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

#### 6.4.9. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 036.1

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Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 036 [Review of cases of sarcoidosis as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

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

#### 6.4.10. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 037.1

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Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 037 [Review of cases of lymphopenia as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC 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>12</sup>

#### 7.1.1. Chenodeoxycholic acid – CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/PSP/S/0057

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Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol for a cerebrotendinous xanthomatosis registry: a long term non-interventional follow-up of safety and effectiveness of Chenodeoxycholic acid Leadiant (chenodeoxycholic acid)

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

#### 7.1.2. Glycerol phenylbutyrate – RAVICTI (CAP) - EMEA/H/C/PSA/S/0025

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Applicant: Horizon Pharma Ireland Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Protocol for a European post-authorisation registry for Ravicti (glycerol phenylbutyrate) oral liquid in partnership with the European Registry and network for intoxication type

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

#### 7.1.3. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0020.2

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Applicant: Bayer Pharma AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to PSA/S/0020.1 [Amended protocol for EURAS-LCS12 study: a European active surveillance study of LCS-12 (levonorgestrel intrauterine contraceptive system releasing 12 mcg levonorgestrel/24h in vitro), an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to investigate whether LCS-12 is associated with an increased risk of unintended pregnancy compared to Mirena and to copper IUDs] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

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

#### 7.1.4. Valproate (NAP) - EMEA/H/N/PSA/J/0015.2

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Applicant: Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to PSA/J/0015.1 [Protocol for a joint drug utilisation study (DUS) using EU databases to study the effectiveness of the imposed risk minimisation measures following the conclusion of the referral procedure under Article 31 of Directive 2001/83/EC completed in 2014 (EMEA/H/A-31/1387) and to further characterise the prescribing patterns

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<sup>12</sup> In accordance with Article 107n of Directive 2001/83/EC

for valproate] as per the request for supplementary information (RSI) adopted at the September 2017 PRAC meeting

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

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>13</sup>

### 7.2.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 012.2

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 012.1 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as requested in the request for supplementary information (RSI) adopted in September 2017

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

### 7.2.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 013.1

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 013 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as requested in the request for supplementary information (RSI) adopted in September 2017

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

### 7.2.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 011.2

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 011.1 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as requested in the request for supplementary information (RSI) adopted in September 2017

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

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<sup>13</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



#### 7.2.4. [Canagliflozin, metformin - VOKANAMET \(CAP\) - EMEA/H/C/002656/MEA 012.1](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 012 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as requested in the request for supplementary information (RSI) adopted in September 2017

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

#### 7.2.5. [Cladribine - MAVENCLAD \(CAP\) - EMEA/H/C/004230/MEA 003](#)

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Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Protocol for a PASS focusing on pregnancy aimed at assessing the occurrence of major congenital abnormalities (MCA), estimating proportions of pregnancy outcomes, proportions of alterations in foetal growth and pre-term births in pregnant women exposed to oral cladribine and in pregnancies fathered by male partner exposed to oral cladribine, and comparison of study outcomes with pregnant women with multiple sclerosis (MS) not exposed to any disease modifying drugs (DMDs) (from initial opinion/MA) [final study report due date: Q1/2028]

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

#### 7.2.6. [Cobimetinib - COTELLIC \(CAP\) - EMEA/H/C/003960/MEA 003.1](#)

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Applicant: Roche Registration Limited

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 003 [Protocol for study ML939302 (COVENIS): a non-interventional study to investigate the effectiveness, safety and utilisation of cobimetinib and vemurafenib in patients with and without brain metastasis with BRAF V600 mutant melanoma under real world conditions (final clinical study report (CSR) due date: December 2022)]

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

#### 7.2.7. [Lidocaine, prilocaine - FORTACIN \(CAP\) - EMEA/H/C/002693/MEA 004.1](#)

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Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 004 [Protocol for a drug utilisation study (DUS) in Europe for Fortacin (lidocaine, prilocaine) (listed as a category 3 study in RMP): a retrospective cohort study using electronic medical records database aiming at characterising the population of patients who are prescribed the medicinal product and at describing the real-life prescribing

patterns] as per the request for supplementary information (RSI) adopted in September 2017

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

#### 7.2.8. [Mercaptamine - CYSTADROPS \(CAP\) - EMEA/H/C/003769/MEA 001](#)

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Applicant: Orphan Europe SARL

PRAC Rapporteur: Dolores Montero Corominas

Scope: PASS protocol for study CYT-DS-001 (listed as a category 3 study in the RMP): an open-label longitudinal PASS to assess the safety of Cystadrops (mercaptamine) in paediatric and adult cystinosis patients in long term use [final clinical study report (CSR) due date: by 2021] (from initial opinion/MA)

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

#### 7.2.9. [Sodium oxybate - XYREM \(CAP\) - EMEA/H/C/000593/MEA 019.2](#)

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Applicant: UCB Pharma Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 019.1 [Protocol for study NA0001 (EU PAS register EUPAS15024): a non-interventional PASS on the effectiveness of the educational materials] as per the request for supplementary information (RSI) adopted in September 2017

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

### 7.3. [Results of PASS imposed in the marketing authorisation\(s\)](#)<sup>14</sup>

#### 7.3.1. [Rivaroxaban– XARELTO \(CAP\) - EMEA/H/C/PSR/S/0012](#)

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Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Results of an observational post-authorisation modified prescription-event monitoring safety study to monitor the safety and utilisation of Xarelto (rivaroxaban) for the prevention of stroke in patients with atrial fibrillation (AF), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England, extended to include acute coronary syndrome patients

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

#### 7.3.2. [Thiocolchicoside \(NAP\) - EMEA/H/N/PSR/J/0008](#)

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Applicant: Sanofi

PRAC Rapporteur: Amelia Cupelli

Scope: Results for a joint PASS survey evaluating the effectiveness of risk minimisation

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<sup>14</sup> In accordance with Article 107p-q of Directive 2001/83/EC

measures among healthcare professionals to assess their knowledge and attitudes on prescribing conditions of thiocolchicoside-containing medicinal products for systemic use in France, Greece, Italy and Portugal

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

## 7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>15</sup>

### 7.4.1. Afibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0039

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Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final report for PASS study 16526 (listed as a category 3 study in the RMP): an observational study to evaluate the physician and patient knowledge of safety and safe use information for aflibercept in Europe as stated in the EU educational material of Eylea

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

### 7.4.2. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0045

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report for study 109MS419 (listed as a category 3 study in the RMP): a retrospective, multicentre, observational study aimed to assess the effect of Tecfidera delayed-release capsules on lymphocyte subsets in patients with relapsing forms of multiple sclerosis

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

### 7.4.3. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0049

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study 109MS409 (listed as a category 3 study in the RMP): an observation study aimed to estimate the proportion of dimethyl fumarate use that is prescribed 'on-label' versus 'off-label' in Germany

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

### 7.4.4. Duloxetine - ARICLAIM (CAP) - EMEA/H/C/000552/WS1264/0068; CYMBALTA (CAP) - EMEA/H/C/000572/WS1264/0072; DULOXETINE LILLY (CAP) - EMEA/H/C/004000/WS1264/0008; XERISTAR (CAP) - EMEA/H/C/000573/WS1264/0075; YENTREVE (CAP) - EMEA/H/C/000545/WS1264/0058

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Applicant: Eli Lilly Nederland B.V.

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<sup>15</sup> In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final report from study F1J-MC-B056 (listed as a category 3 study in the RMP): a non-interventional non-imposed study aimed to investigate the association between duloxetine exposure and suicide-related behaviours and ideation in women with stress urinary incontinence (SUI). The RMP (version 12.3) is updated accordingly

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

7.4.5. [Glycopyrronium bromide - ENUREV BREEZHALER \(CAP\) - EMEA/H/C/002691/WS1299/0025](#); [SEEBRI BREEZHALER \(CAP\) - EMEA/H/C/002430/WS1299/0025](#); [TOVANOR BREEZHALER \(CAP\) - EMEA/H/C/002690/WS1299/0028](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final study report for study CNVA237A2402T (a category 1 study in the RMP and marketing authorisations): a multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled glycopyrronium bromide (NVA237) in Europe. As a consequence, Annex II is updated. In addition, the additional monitoring list is to be updated by removing Enurev Breezhaler, Seebri Breezhaler, Tovanor Breezhaler. As a consequence, Annex I and IIIB are updated. The MAH also took this opportunity to update the local representatives. The RMP (version 8) is also updated accordingly

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

7.4.6. [Indacaterol, glycopyrronium - ULTIBRO BREEZHALER \(CAP\) - EMEA/H/C/002679/WS1340/0022](#); [ULUNAR BREEZHALER \(CAP\) - EMEA/H/C/003875/WS1340/0022](#); [XOTERNA BREEZHALER \(CAP\) - EMEA/H/C/003755/WS1340/0025](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report for study CQVA149A2401: a multinational, multi-database drug utilisation study of indacaterol/glycopyrronium bromide (QVA149) in Europe with the objective to estimate the use of QVA149 off-label and in the subpopulations with missing information mentioned in the RMP

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

7.4.7. [Infliximab - INFLECTRA \(CAP\) - EMEA/H/C/002778/II/0054](#)

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Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final study report for a post-marketing surveillance study for Inflectra 100 mg (infliximab) to evaluate its safety and efficacy in Korea: study intended to identify any unexpected adverse events, serious adverse events and frequencies, pattern of occurrence of adverse events under the condition of general clinical practice as well as to determine any factor that may affect the safety and efficacy

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

#### 7.4.8. [Infliximab - REMSIMA \(CAP\) - EMEA/H/C/002576/II/0045](#)

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Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final study report for a post-marketing surveillance study for Remsima 100 mg (infliximab) to evaluate its safety and efficacy in Korea: study intended to identify any unexpected adverse event, serious adverse event and frequencies, pattern of occurrence of adverse events under the condition of general clinical practice as well as determine any factor that may affect the safety and efficacy

**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. [Aclidinium bromide - BRETARIS GENUAIR \(CAP\) - EMEA/H/C/002706/ANX 001.4](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for imposed study D6560R00004: a PASS evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products. The report addresses the all-cause mortality component of the PASS programme

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

#### 7.5.2. [Aclidinium bromide - EKLIRA GENUAIR \(CAP\) - EMEA/H/C/002211/ANX 001.4](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for imposed study D6560R00004: a PASS evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products. The report addresses the all-cause mortality component of the PASS programme

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

#### 7.5.3. [Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR \(CAP\) - EMEA/H/C/003969/ANX 003.1](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for imposed study D6560R00004: a PASS evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products. The report addresses the all-cause mortality component of the PASS programme

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

#### 7.5.4. [Aclidinium bromide, formoterol fumarate dihydrate - DUAKLIR GENUAIR \(CAP\) - EMEA/H/C/003745/ANX 003.1](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for imposed study D6560R00004: a PASS evaluating the risk of cardiovascular endpoints of acclidinium bromide-containing products in new users. The report addresses the all-cause mortality component of the PASS programme

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

#### 7.5.5. [Catridecacog - NOVOTHIRTEEN \(CAP\) - EMEA/H/C/002284/MEA 015.1](#)

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Second interim study report for study NN1841-3868: a multicentre observational study on the use of recombinant factor XIII (FXIII) in the treatment of congenital FXIII deficiency aiming at investigating the incidence of specific adverse drug reactions [final report due date: December 2019]

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

#### 7.5.6. [Certolizumab pegol - CIMZIA \(CAP\) - EMEA/H/C/001037/MEA 005.5](#)

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 005.4 [annual reports from rheumatoid arthritis registries from the US National Databank of Rheumatic Diseases (RA0005), German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (RA0020), Register for Antirheumatic Therapies in Sweden (ARTIS) (RA0021), British Society for Rheumatology Biologicals Register (BSRBR) (RA0022)] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

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

#### 7.5.7. [Filgrastim - FILGRASTIM HEXAL \(CAP\) - EMEA/H/C/000918/MEA 006.3](#)

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Applicant: Hexal AG

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 006.2 [Sixth annual interim safety report for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase IV study; safety data are collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients are followed-up for a total of five years (one year in the SCN study and four years within the registry) [final clinical study report (CSR) due date: 31/12/2019]] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

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

#### 7.5.8. Filgrastim - NIVESTIM (CAP) - EMEA/H/C/001142/MEA 015.2

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Applicant: Hospira UK Limited

PRAC Rapporteur: Kirsti Villikka

Scope: First annual report for study ZOB-NIV-1513: a multinational, multicentre, prospective, non-interventional PASS in healthy donors (HDs) exposed to Nivestim (biosimilar filgrastim) for haematopoietic stem cell (HSC) mobilisation (NEST) [final clinical study report due date: March 2023]

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

#### 7.5.9. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 006.3

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Applicant: Sandoz GmbH

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA-006.2 [Sixth annual interim safety report for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase IV study; safety data are collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients are followed-up for a total of five years (one year in the SCN study and four years within the registry) [final clinical study report (CSR) due date: 31/12/2019]] 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. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/ANX 003.1

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Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Annual report for study VX14 809 108: An observational study to evaluate the utilisation patterns and long-term effects of lumacaftor/ivacaftor therapy in patients with cystic fibrosis (CF) [final report due date: December 2021] (from initial opinion/MA)

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

#### 7.5.11. Meningococcal group B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 017.4

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Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Fourth interim report for study V72\_36OB: a post-licensure observational safety study after Bexsero (meningococcal B vaccine 4CMenB) vaccination in routine UK care [final report due date: 31/12/2019]

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

#### 7.5.12. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - EMEA/H/C/002705/MEA 002.6

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Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Third interim report for study VFMCRP-MEAF-PA21-01-EU (Velphoro Evaluation of Real-life saFety, effectiveness and adherence 'VERIFY' study): a non-interventional study to investigate the short and long-term real-life safety, effectiveness, and adherence of Velphoro in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis (PD)

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

#### 7.5.13. Pegvisomant - SOMAVERT (CAP) - EMEA/H/C/000409/MEA 061.1

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Applicant: Pfizer Limited

PRAC Rapporteur: Caroline Laborde

Scope: MAH's response to MEA 061 [Interim report from study A6291010 (ACROSTUDY): a multicentre, post marketing surveillance study of pegvisomant therapy in patients with acromegaly [due date: final report due date: 2019]] as per the request for supplementary information (RSI) adopted in September 2017

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

### 7.6. Others

#### 7.6.1. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.11

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Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 012.10 [Statistical analysis plan (SAP) for PASS B1781044: a cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe], as per the request for supplementary information (RSI) adopted in September 2017

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

#### 7.6.2. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/MEA 005

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Protocol for a PASS RGH-188-303: a randomized, open-label, ophthalmologist-masked study in approximately 1,000 schizophrenic patients to compare lens opacity changes during long-term treatment with cariprazine versus risperidone (from initial opinion/MA)

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



### 7.6.3. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/MEA 166.1

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Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Interim analysis report for study B1801023: an open-label extension study to assess the long-term safety and clinical benefit of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1-3338-WW (B1801014)

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

### 7.6.4. Etanercept - LIFMIOR (CAP) - EMEA/H/C/004167/MEA 002

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Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Interim analysis report for study B1801023: an open-label extension study to assess the long-term safety and clinical benefit of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1-3338-WW (B1801014)

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

### 7.6.5. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/MEA 014.3

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Pilot study report for study NN8022-4241 (MEA014): a drug utilisation study (DUS) in Europe including retrospective chart review. The study consists of two parts: the pilot study and the full study. The objective of the pilot study is to evaluate the feasibility of conducting the full study in order to evaluate whether Saxenda is used according to approved indication and posology and whether Victoza (liraglutide) is used for weight management

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

## 7.7. New Scientific Advice

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

## 7.8. Ongoing Scientific Advice

None

## 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 - ORPHACOL (CAP) - EMEA/H/C/001250/S/0022 (without RMP)

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Applicant: Laboratoires CTRS

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.2. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0009 (without RMP)

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Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0050 (without RMP)

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Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.4. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0016 (without RMP)

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.5. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0027 (without RMP)

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Applicant: Orphan Europe SARL

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

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

## 8.2. Conditional renewals of the marketing authorisation

### 8.2.1. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0027 (with RMP)

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Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

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

## 8.3. Renewals of the marketing authorisation

### 8.3.1. 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

### 8.3.2. Avanafil - SPEDRA (CAP) - EMEA/H/C/002581/R/0029 (without RMP)

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.3. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/R/0030 (without RMP)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.4. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/R/0086 (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

### 8.3.5. Esomeprazole - NEXIUM CONTROL (CAP) - EMEA/H/C/002618/R/0021 (without RMP)

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Applicant: Pfizer Consumer Healthcare Limited

PRAC Rapporteur: Simona Kudeliene

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.6. 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

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#### 8.3.7. Human coagulation factor VIII, human von willebrand factor - VONCENTO (CAP) - EMEA/H/C/002493/R/0032 (without RMP)

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Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.8. Imatinib - IMATINIB MEDAC (CAP) - EMEA/H/C/002692/R/0008 (with RMP)

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Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.9. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/R/0056 (without RMP)

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Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.10. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/R/0047 (without RMP)

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Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.11. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/R/0039 (with RMP)

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Applicant: Sicom Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.12. [Lomitapide - LOJUXTA \(CAP\) - EMEA/H/C/002578/R/0029 \(with RMP\)](#)

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Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.13. [Memantine - MEMANTINE RATIOPHARM \(CAP\) - EMEA/H/C/002671/R/0011 \(without RMP\)](#)

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Applicant: Ratiopharm GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.14. [Modified vaccinia Ankara virus - IMVANEX \(CAP\) - EMEA/H/C/002596/R/0032 \(without RMP\)](#)

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Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.15. [Pandemic influenza vaccine \(H5N1\) \(live attenuated, nasal\) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA \(CAP\) - EMEA/H/C/003963/R/0011 \(without RMP\)](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Daniela Philadelphly

Scope: 5-year renewal of the marketing authorisation

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

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#### 8.3.16. [Pomalidomide - IMNOVID \(CAP\) - EMEA/H/C/002682/R/0028 \(without RMP\)](#)

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Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.17. 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

## 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. Oseltamivir – TAMIFLU (CAP) - EMEA/H/C/000402/II/128

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Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: PRAC consultation on a variation to update of section 4.6 of the SmPC in order to reflect the final study results from a non-interventional safety study BV29684, which assessed the safety of oseltamivir exposure in pregnant women (listed as a category 3 study in the RMP (MEA099)). The RMP (version 15.0) is updated accordingly

**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. Dienogest, estradiol valerate (NAP) - NL/H/1230/001/II/034

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Applicant: Bayer BV (Oclaira)

PRAC Lead: Menno van der Elst

Scope: PRAC consultation on a variation on the final results of cohort study INAS-SCORE an 'international active surveillance study, safety of contraceptives: role of estrogens' conducted in the US and Europe and the proposed amendments to the product information and the risk of venous thromboembolism (VTE), on request of the Netherlands

**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

None

### 12.4. Cooperation within the EU regulatory network

#### 12.4.1. Brexit: preparedness of the regulatory network and capacity increase

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**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

None

## 12.9. Pharmacovigilance audits and inspections

### 12.9.1. Pharmacovigilance systems and their quality systems

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None

### 12.9.2. Pharmacovigilance inspections

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None

### 12.9.3. Pharmacovigilance audits

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None

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

### 12.10.1. Periodic safety update reports

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None

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

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PRAC lead: Menno van der Elst, Maia Uusküla

**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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None

### 12.11.2. Signal management – Guidance for signal detection of terms related to listed terms

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**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

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

### 12.14.1. Risk management systems

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None

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

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None

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

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

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None

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

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None

## 12.16. Community procedures

### 12.16.1. Referral procedures for safety reasons

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None

## 12.17. Renewals, conditional renewals, annual reassessments

None

## 12.18. Risk communication and transparency

### 12.18.1. Public participation in pharmacovigilance

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None

### 12.18.2. Safety communication

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None

## 12.19. Continuous pharmacovigilance

### 12.19.1. Incident management

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None

## 12.20. Others

### 12.20.1. Public hearing – Outcome report

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**Action:** For discussion

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

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**Action:** For discussion

## 13. Any other business

## 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=WCOB01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WCOB01ac05800240d0)

### **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/)