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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 30 September - 03 October 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

30 September 2019, 13:00 – 19:30, room 1/C

01 October 2019, 08:30 – 19:30, room 1/C

02 October 2019, 08:30 – 19:30, room 1/C

03 October 2019, 08:30 – 16:00, room 1/C

Organisational, regulatory and methodological matters (ORGAM)

17 October 2019, 09:00-12:00, room 6-D, via teleconference

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

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

### Note on access to documents

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



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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 30 September – 03 October 2019. See (current) October 2019 minutes (to be published post November 2019 PRAC meeting).

### **1.2. Agenda of the meeting on 30 September-03 October 2019**

**Action:** For adoption

### **1.3. Minutes of the previous meeting on 02-05 September 2019**

**Action:** For adoption

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

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

None

### **2.2. Ongoing procedures**

None

### **2.3. Procedures for finalisation**

None

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

None

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

### **3.1. Newly triggered procedures**

None

## 3.2. Ongoing procedures

### 3.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/A-20/1483

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Applicant: Sanofi Belgium

PRAC Rapporteur: Brigitte Keller-Stanislawski; PRAC Co-rapporteur: Ulla Wändel Liminga

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

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

### 3.2.2. Fluorouracil and related substances: capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP); CAPECITABINE TEVA (CAP); ECANSYA (CAP); XELODA (CAP); NAP flucytosine (NAP); 5-fluorouracil (5-FU) (NAP); tegafur (NAP); tegafur, gimeracil, oteracil – TEYSUNO (CAP) - EMEA/H/A-31/1481

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Applicants: Accord Healthcare Limited (Capecitabine Accord), Krka, d.d., Novo mesto (Ecansya), Medac Gesellschaft für klinische Spezialpräparate mbH (Capecitabine medac), Nordic Group B.V. (Teysono), Roche Registration GmbH (Xeloda), Teva B.V. (Capecitabine Teva), various

PRAC Rapporteur: Jean-Michel Dogné; PRAC Co-rapporteur: Martin Huber

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 list of experts for the ad-hoc inter-Committee Scientific Advisory Group on Oncology (SAG-O)

### 3.2.3. Tofacitinib - XELJANZ (CAP) - EMEA/H/A-20/1485

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Applicant(s): Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan; PRAC Co-rapporteur: Amelia Cupelli

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

**Action:** For adoption of a list of experts for the ad-hoc expert group meeting

## 3.3. Procedures for finalisation

### 3.3.1. Estradiol<sup>1</sup> (NAP) - EMEA/H/A-31/1482

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Applicant(s): various

PRAC Rapporteur: Eva Jirsova; PRAC Co-rapporteur: Menno van der Elst

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<sup>1</sup> 0.01%, topical use only

Scope: Review of the benefit-risk balance following notification by European Commission 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>2</sup>

None

### 3.5. Others

None

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

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

#### 4.1.1. Bevacizumab – AVASTIN (CAP); MVASI (CAP); ZIRABEV (CAP)

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Applicant(s): Amgen Europe B.V. (Mvasi), Pfizer Europe MA EEIG (Zirabev), Roche Registration GmbH (Avastin)

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of Guillain-Barré syndrome (GBS)

**Action:** For adoption of PRAC recommendation

EPITT 19472 – New signal

Lead Member State(s): DK

#### 4.1.2. Nivolumab – OPDIVO (CAP)

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Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of haemophagocytic lymphohistiocytosis

**Action:** For adoption of PRAC recommendation

EPITT 19467 – New signal

Lead Member State(s): DE

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

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

### 4.1.3. Vismodegib – ERIVEDGE (CAP)

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Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Signal of pancreatitis

**Action:** For adoption of PRAC recommendation

EPITT 19470 – New signal

Lead Member State(s): SE

## 4.2. New signals detected from other sources

- 4.2.1. Hormone replacement therapy (HRT): chlorotrianisene (NAP); conjugated estrogens (NAP); conjugated estrogens, bazedoxifene - DUAVIVE (CAP); dienestrol (NAP); diethylstilbestrol (NAP); estradiol (NAP); estradiol, norethisterone (NAP); estriol (NAP); estrone (NAP); ethinylestradiol (NAP); methallenestril (NAP); moxestrol (NAP); promestriene (NAP); tibolone (NAP)
- 

Applicant(s): Pfizer Europe MA EEIG (Duavive), various

PRAC Rapporteur: To be appointed

Scope: New information on the known risk of breast cancer

**Action:** For adoption of PRAC recommendation

EPITT 19482 – New signal

Lead Member State(s): DE, FI, FR, IT, NL, RO, SE

### 4.2.2. Indapamide (NAP)

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Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of choroidal effusion

**Action:** For adoption of PRAC recommendation

EPITT 19468 – New signal

Lead Member State(s): DE

## 4.3. Signals follow-up and prioritisation

- 4.3.1. Direct-acting antivirals (DAAV): dasabuvir – EXVIERA (CAP) - EMEA/H/C/003837/SDA/020; elbasvir, grazoprevir – ZEPATIER (CAP) - EMEA/H/C/004126/SDA/012; glecaprevir, pibrentasvir – MAVIRET (CAP) - EMEA/H/C/004430/SDA/010; ledipasvir, sofosbuvir – HARVONI (CAP) - EMEA/H/C/003850/SDA/021; ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP) - EMEA/H/C/003839/SDA/022; sofosbuvir – SOVALDI (CAP) -

EMA/H/C/002798/SDA/027; sofosbuvir, velpatasvir – EPCLUSA (CAP) -  
EMA/H/C/004210/SDA/012; sofosbuvir, velpatasvir, voxilaprevir – VOSEVI (CAP) -  
EMA/H/C/004350/SDA/007

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Applicant(s): AbbVie Deutschland GmbH & Co. KG (Exviera, Maviret, Viekirax); Gilead Sciences Ireland UC (Eplusa, Harvoni, Sovaldi, Vosevi); Merck Sharp & Dohme B.V. (Zepatier)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of autoimmune hepatitis

**Action:** For adoption of PRAC recommendation

EPITT 19395 – Follow-Up to May 2019

#### 4.3.2. Durvalumab – IMFINZI (CAP) – EMA/H/C/004771/SDA/003

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Applicant(s): AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of myasthenia gravis

**Action:** For adoption of PRAC recommendation

EPITT 19451 – Follow-up to September 2019

#### 4.3.3. Lithium (NAP)

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Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of drug induced lichenoid reaction

**Action:** For adoption of PRAC recommendation

EPITT 19389 – Follow-up to May 2019

#### 4.3.4. Sebelipase alfa - KANUMA (CAP) - EMA/H/C/004004/SDA/007

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of nephrotic syndrome

**Action:** For adoption of PRAC recommendation

EPITT 19410 – Follow-up to May 2019



## 5. Risk management plans (RMPs)

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

#### 5.1.1. Adalimumab - EMEA/H/C/004879

---

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

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

#### 5.1.2. Azacitidine - EMEA/H/C/005147

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Scope: Treatment of myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML), acute myeloid leukaemia (AML) and AML with >30% marrow blasts according to the WHO<sup>4</sup> classification

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

#### 5.1.3. Azacitidine - EMEA/H/C/005075

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

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

#### 5.1.4. Brolocizumab - EMEA/H/C/004913

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Scope: Treatment of neovascular (wet) age-related macular degeneration (AMD)

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

#### 5.1.5. Budesonide, formoterol fumarate dihydrate - EMEA/H/C/004882

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Scope: Treatment of asthma and chronic obstructive pulmonary disease (COPD)

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

#### 5.1.6. Cholera vaccine, oral, live - EMEA/H/C/003876

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Scope: Active immunisation against disease caused by *Vibrio cholerae* serogroup O1 in adults and children aged 6 years and older

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

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<sup>4</sup> World Health Organization

### 5.1.7. Cinacalcet - EMEA/H/C/005236

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Scope: Treatment of secondary hyperparathyroidism and hypercalcaemia

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

### 5.1.8. Entrectinib - EMEA/H/C/004936

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Scope: Treatment of adult and paediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive locally advanced or metastatic solid tumours and treatment of patients with ROS1<sup>5</sup>-positive, advanced non-small cell lung cancer (NSCLC)

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

### 5.1.9. Givosiran - EMEA/H/C/004775, Orphan

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Applicant: Alnylam Netherlands B.V.

Scope (accelerated assessment): Treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older

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

### 5.1.10. Imipenem, cilastatin, relebactam - EMEA/H/C/004808

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Scope: Treatment of bacterial infections due to gram-negative microorganisms

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

### 5.1.11. Pegfilgrastim - EMEA/H/C/005312

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Scope: Treatment of neutropenia

**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. Adalimumab - IDACIO (CAP) - EMEA/H/C/004475/WS1651/0003; KROMEYA (CAP) - EMEA/H/C/005158/WS1651/0003

---

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 4.0) for Idacio (adalimumab) and KromeYA (adalimumab) in order to align it with the reference product containing adalimumab. The risk minimisation measures of Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' are also updated. The MAH took the opportunity to introduce minor linguistic changes/corrections to the product information in German, French, Hungarian (Idacio only) and Slovenian

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<sup>5</sup> Proto-oncogene tyrosine-protein kinase

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

5.2.2. [Autologous CD34<sup>+</sup> enriched cell fraction that contains CD34<sup>+</sup> cells transduced with retroviral vector that encodes for the human ADA cDNA sequence - STRIMVELIS \(CAP\) - EMEA/H/C/003854/II/0022, Orphan](#)

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Applicant: Orchard Therapeutics (Netherlands) BV, ATMP<sup>6</sup>

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 2.0) in order to introduce changes to the design of the post-authorisation study STRIM-002: methodology study to investigate the utility of retroviral insertion site analysis in samples from subjects treated with Strimvelis gene therapy, from a prospective to a retrospective study. In addition, the RMP is brought in line with revision 2 of the guidance on the format of RMP in the EU (template) and the timelines for study STRIM-001: evaluation of referring healthcare professionals (HCPs)' and parents'/carers' understanding of specific risks associated with Strimvelis treatment, are updated

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

5.2.3. [Everolimus - AFINITOR \(CAP\) - EMEA/H/C/001038/WS1671/0063; VOTUBIA \(CAP\) - EMEA/H/C/002311/WS1671/0059](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 14.0) for Afinitor (everolimus) and Votubia (everolimus) in order to implement some safety concerns, to reflect the completion of several pharmacovigilance studies, namely: study CRAD001Y2201: a phase 2 study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in the treatment of postmenopausal women with oestrogen receptor positive (ER+) locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole (Afinitor, variation II/58 finalised in September 2018), CRAD001M2304: a three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures (Votubia, variation II/51 finalised in July 2018), CRAD001J2301: a randomized phase 3, double-blind, placebo-controlled multicentre trial of everolimus in combination with trastuzumab and paclitaxel, as first line therapy in women with human epidermal growth factor receptor 2 (HER2) positive locally advanced or metastatic breast cancer (Afinitor, variation II/51G finalised in March 2017), RAD00W2301: a randomized phase 3, double-blind, placebo-controlled multicentre trial of everolimus in combination with trastuzumab and vinorelbine, in pretreated women with human epidermal growth factor receptor 2 (HER2)/neu over-expressing locally advanced or metastatic breast cancer (Afinitor, variation II/51G finalised in March 2017); and to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template), as requested in the conclusions of the periodic safety update report single assessment (PSUSA) procedure PSUSA/00010268/201703 finalised in October 2017

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

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<sup>6</sup> Advanced therapy medicinal product

#### 5.2.4. Filgrastim - ACCOFIL (CAP) - EMEA/H/C/003956/II/0037

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP (version 4.0) in order to update the section of additional pharmacovigilance activities to remove the Severe Chronic Neutropenia International Registry (SCNIR) and the 'European Society for Blood and Marrow Transplantation' (EBMT) registries following the conclusion of the SCNIR and EBMT combined analysis report. The MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

#### 5.2.5. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/II/0115

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 12) in order to revise the lists of safety concerns and to bring it in line with revision 2 of GVP module V on 'Risk management systems'

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

#### 5.2.6. Irinotecan hydrochloride trihydrate - ONIVYDE (CAP) - EMEA/H/C/004125/II/0015, Orphan

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 2.7) in order to update the RMP in line with the conclusions of periodic safety update report single assessment (PSUSA) procedures PSUSA/00010534/201804 finalised in November 2018 and PSUSA procedure PSUSA/00010534/201810 finalised in May 2019. The RMP is also updated in line with revision 2 of GVP module V on 'Risk management systems'

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

#### 5.2.7. Measles, mumps, rubella and varicella vaccine (live) - PROQUAD (CAP) - EMEA/H/C/000622/II/0134

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Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 6.1) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

#### 5.2.8. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/II/0114

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 25.0) with data on extended interval dosing, including an update to key elements for inclusion of the physician information and management guidelines. In order to align with the changes in the RMP, the MAH submitted changes to sections 4.4 and 5.1 of the SmPC and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

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

#### 5.2.9. Pioglitazone - ACTOS (CAP) - EMEA/H/C/000285/WS1680/0082; GLUSTIN (CAP) - EMEA/H/C/000286/WS1680/0081; Pioglitazone, glimepiride - TANDEMACT (CAP) - EMEA/H/C/000680/WS1680/0060; Pioglitazone, metformin - COMPETACT (CAP) - EMEA/H/C/000655/WS1680/0074; GLUBRAVA (CAP) - EMEA/H/C/000893/WS1680/0060

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 27) in order to update and consolidate within a single RMP the RMPs for pioglitazone-containing product(s), pioglitazone/metformin-fixed dose combination (FDC) and pioglitazone/glimepiride-FDC. The list of safety concerns is revised in line with the conclusions of periodic safety update report single assessment (PSUSA) procedure PSUSA/00002417/201807 finalised in March 2019 with regards to the discontinuation of the additional risk minimisation measures (aRMMs)

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

#### 5.2.10. Posaconazole - NOXAFIL (CAP) - EMEA/H/C/000610/II/0057

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 15.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' with the consequent applicable re-evaluation of some safety concerns. In addition, the MAH took the opportunity to include data from the completed clinical trial in paediatric subjects PN097: a phase 1B study of the safety, tolerability, and pharmacokinetics of intravenous (IV) and powder for oral suspension formulations of posaconazole (POS) in immunocompromised paediatric subjects, and update the due date for submission changed from December 2019 to Q4 2020 for the final report of the ongoing post-marketing efficacy trial PN069: a phase 3 randomized study on the efficacy and safety of posaconazole versus voriconazole for the treatment of invasive aspergillosis in adults and adolescents

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

#### 5.2.11. Ribavirin - REBETOL (CAP) - EMEA/H/C/000246/II/0086

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 5.1) in order to revise safety concerns for ribavirin in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the MAH took the opportunity to revise the safety concerns of ribavirin in light of the current era of interferon (IFN) free regimen, as requested in a previous PSUSA procedure (EMA/H/C/PSUSA/00010007/201707) concluded in March 2018

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

#### 5.2.12. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/II/0073

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 17.0) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

#### 5.2.13. Umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMEA/H/C/002751/WS1586/0028; LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/003754/WS1586/0031

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of an updated RMP (version 8.0) following the completion of the annual renewal procedures (R/0022 and R/0025) in November 2018 concluding on the commitments to remove the important identified risks of 'hypersensitivity' and 'paradoxical bronchospasm' from the list of safety concerns and to update all relevant sections of the RMP in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH proposed to remove some additional risks ('narrow angle glaucoma', 'bladder outflow obstruction and urinary retention', 'safety in pregnancy and lactation', 'safety in long-term use' and 'safety in severe hepatic impairment')

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

#### 5.2.14. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/II/0040

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated RMP (version 13) in order to remove the healthcare professional survey from the list of additional pharmacovigilance activities and to remove several safety concerns from the list of important identified and potential risks and missing

information in line with revision 2 of GVP module V on 'Risk management systems' and in line with the conclusions of variation II/28 finalised in February 2019

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

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

### 5.3.1. Afatinib - GIOTRIF (CAP) - EMEA/H/C/002280/II/0031

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add gastrointestinal (GI) perforation as an additional side effect based on summaries of clinical trial and post-marketing safety data. The package leaflet is updated accordingly. In addition, the RMP (version 8.0) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template), taking also into consideration recommendations part of the conclusions of renewal procedure R/0026 adopted in March 2018. Furthermore, the MAH took the opportunity to correct some typographical errors in the German, Austrian and Spanish product information and to update the list of the local representatives for Austria in the package leaflet

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

### 5.3.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0075

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to reflect changes in the existing warning on immunogenicity and immunomodulation and to add new clinical information on infantile onset Pompe disease (IOPD) patients' immune tolerance induction based on data on use of immune tolerance induction in IOPD patients from two exploratory phase 4 studies, namely: study AGLU03707/MS12817: an exploratory study of the safety and efficacy of immune tolerance induction (ITI) in patients with Pompe disease who have previously received Myozyme (alglucosidase alfa); and companion study AGLU03807/MS12892: open-label, exploratory study of the safety and efficacy of prophylactic ITI in alglucosidase alfa-naïve cross reactive immunologic material (CRIM)(-) patients with IOPD, as well as the Duke Center of Excellence observational study (01562): open-label, retrospective cohort study of ITI regimens in combination with alglucosidase alfa in patients with CRIM(-) IOPD. The RMP (version 9.0) is updated accordingly

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

### 5.3.3. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/II/0063

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Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 4.9 of the SmPC in order to reflect the availability of a



reversal agent for apixaban following the recent approval of andexanet alfa in the EU. The package leaflet and labelling are updated accordingly. The RMP (version 20) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template). As a result, the list of safety concerns is updated and a number of safety concerns listed as missing information have been reclassified/removed from the RMP. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to update the information in the SmPC and package leaflet in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

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

#### 5.3.4. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0029

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 12.0) are updated accordingly

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

#### 5.3.5. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0070, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

EMA resources: PM: Irene Papadouli; RMS: Daniel Becker; EPL: Irene Papadouli

Scope: Extension of indication to add Adcetris (brentuximab vedotin) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for the treatment of adult patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 15.1) are updated accordingly

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

#### 5.3.6. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/II/0010

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of in vitro metabolism study report for study R188-A15. The RMP (version 1.6) is updated accordingly

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

#### 5.3.7. Carmustine - CARMUSTINE OBVIUS (CAP) - EMEA/H/C/004326/II/0002

Applicant: Obvius Investment B.V

PRAC Rapporteur: Jan Neuhauser

Scope: Extension of indication to add carmustine with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases. As a consequence, sections 4.1, 4.2 and 6.3 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly

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

#### 5.3.8. Cobicistat - TYBOST (CAP) - EMEA/H/C/002572/II/0051

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to modify the approved therapeutic indication to include new population, namely adolescents aged 12 years and older, weighing at least 35 kg for the treatment of human immunodeficiency virus 1 (HIV-1). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.1) are updated accordingly

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

#### 5.3.9. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0029, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to extend the existing therapeutic indication for Darzalex (daratumumab) in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 6.0 s1) are updated accordingly

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

#### 5.3.10. Darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/II/0033

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension of indication to extend the approved therapeutic indication of Rezolsta (darunavir/cobicistat) to include a new population, namely the adolescent population aged 12 years old and older with a body weight at least 40 kg. 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 6.0) are updated accordingly. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to update section 4.2 of the SmPC in line with recommendations for other human immunodeficiency virus (HIV) products with regards to administration Rezolsta (darunavir/cobicistat) in case

of vomiting

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

### 5.3.11. [Enzalutamide - XTANDI \(CAP\) - EMEA/H/C/002639/II/0047/G](#)

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) for Xtandi (enzalutamide) in combination with androgen deprivation therapy (ADT). As a consequence, sections 4.1, 4.7, 4.8, 5.1, 5.3 and 6.6 of the SmPC are updated. Furthermore the MAH took the opportunity to introduce minor corrections to section 4.7. The package leaflet and the RMP (version 13.0) are updated accordingly; 2) update of section 5.1 of the SmPC based on the 5-year overall survival (OS) results obtained from study MDV310003 (PREVAIL), a phase 3 study of enzalutamide in chemotherapy naïve patients with metastatic prostate cancer that progressed on ADT

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

### 5.3.12. [Exenatide - BYDUREON \(CAP\) - EMEA/H/C/002020/II/0064](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to remove the limitation of use in patients with moderate renal impairment (creatinine clearance [CrCl] 30 to 50 mL/min) based on pooled data from 8 EQW (exenatide once weekly)/EQWS (exenatide once weekly suspension) studies undertaken in patients with mild renal impairment/chronic kidney disease stage 2 or moderate renal impairment/chronic kidney disease stage 3, and on supportive data from study D5551C00003/BCB109 (EXSCEL): a randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus, including a subset of patients with moderate renal impairment. In addition, the MAH took the opportunity to introduce glomerular filtration rate (GFR) as the main indicator of renal function rather than CrCl. The package leaflet is updated accordingly and the MAH took the opportunity to implement some minor changes in the labelling. In addition, the RMP (version 34) is updated accordingly and include a proposal for removing acute renal failure (ARF) as an important identified risk based on revision 2 of GVP module V on 'Risk management systems'. Furthermore, the MAH introduced a pan-EU epidemiological study as an additional pharmacovigilance activity to monitor events of pancreatic cancer, as requested in the conclusions of variation II/54 finalised in April 2019

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

### 5.3.13. [Fidaxomicin - DIFICLIR \(CAP\) - EMEA/H/C/002087/X/0034/G](#)

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form associated with new strength (40 mg/mL granules for oral suspension); 2) extension of indication to include paediatric use of Difclir (fidaxomicin) in children from birth to less than 18 years of age. The RMP (version 11.0) is updated accordingly. The SmPC of Difclir (fidaxomicin) 200 mg film-coated tablet, labelling and package leaflet are updated accordingly. In addition, the MAH took the opportunity to update the package leaflet with the statement on 'sodium-free' in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, the MAH updated the details of the local representative in Czech Republic

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

#### 5.3.14. [Galcanezumab - EMGALITY \(CAP\) - EMEA/H/C/004648/X/0004](#)

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

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

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

#### 5.3.15. [Human fibrinogen, human thrombin - VERASEAL \(CAP\) - EMEA/H/C/004446/II/0006/G](#)

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Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Grouped variations consisting of: 1) addition of a new CE marked applicator tip as a replacement for the current application cannula which allows the application of the product both by dripping and spraying without gas assistance. The RMP (version 4.0) is updated accordingly; 2) modification of the syringe holder to a sterilised plastic cartridge, to allow the connection of the syringe holder to the new applicator tip; 3) changes to the blister packaging and removal of the outer pouch; 4) minor change in the manufacturing process

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

#### 5.3.16. [Human papillomavirus vaccine \[types 6, 11, 16, 18, 31, 33, 45, 52, 58\] \(recombinant, adsorbed\) - GARDASIL 9 \(CAP\) - EMEA/H/C/003852/II/0033](#)

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Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.2, 4.6, 4.8 and 5.1 of the SmPC in order to update the safety and immunogenicity information based on final results from study V503-P004 (listed as a category 3 study in the RMP): an open-label phase 3 clinical trial to study the immunogenicity and tolerability of Gardasil 9 in adult women (27 to 45 year-olds) compared to young adult women (16 to 26 year-olds) (in fulfilment of MEA007). The package leaflet and the RMP (version 4.1) are updated accordingly. In addition, the MAH took the

opportunity to update section 4.4 of the SmPC in line with the 'Guideline on quality aspects included in the product information for vaccines for human use (EMA/CHMP/BWP/133540/2017)' and to include editorial changes in section 5.1 of the SmPC

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

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

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to the treatment of diabetes mellitus in adolescents and children from the age of 6 years based on the 6-month on-treatment data of study EFC13597: a 6-month, multicentre, randomized, open-label, 2-arm, parallel-group study comparing the efficacy and safety of a new formulation of insulin glargine and Lantus (insulin glargine) injected once daily in children and adolescents age 6-17 years with type 1 diabetes mellitus (T1DM) with a 6-month safety extension period study. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 6.0) are updated accordingly

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

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

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment in combination with metformin of adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or basal insulin, based on phase 3 study EFC13794: a 26-week randomised, open-label, active controlled, parallel-group study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with type 2 diabetes inadequately controlled on glucagon-like peptide-1 (GLP-1) receptor agonist and metformin (alone or with pioglitazone and/or sodium-glucose co-transporter-2 (SGLT2) inhibitors), followed by a fixed ratio combination single-arm 26-week extension period. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in Denmark, the Netherlands and the UK in the package leaflet and to implement minor editorial changes in Annexes

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

#### 5.3.19. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/II/0130

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final clinical study report (CSR) from study HUBIN\_L\_05335

(listed as a category 3 study in the RMP): a phase 3 study covering the evaluation of Insuman Implantable 400 IU/mL (insulin human) in patients with type 1 diabetes treated with the Medtronic MiniMed Implantable Pump System using Insuplant 400 IU/mL (in fulfilment of post-authorisation measure (PAM) MEA040). The RMP (version 4.0) is updated accordingly and includes the amended protocol (version 2) of the ongoing study HUBIN\_C\_06380: an European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman Implantable 400 IU/mL (insulin human) in Medtronic MiniMed implantable pump as endorsed by PRAC in procedure MEA 047.5 in May 2018

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

### 5.3.20. [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/II/0064](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

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

**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/X/0081/G](#)

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength (45/200 mg film-coated tablets) and a new pharmaceutical form (oral granules) associated with new strengths (33.75/150 mg and 45/200 mg). The new presentations are indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in patients aged 3 to <12 years; 2) inclusion of paediatric use in patients aged 3 to < 12 years who weigh greater than or equal to 35 kg to the existing presentations of 90/400 mg film-coated tablets. The RMP (version 8.3) is updated accordingly. In addition, the MAH took the opportunity to implement minor linguistic corrections throughout the product information

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

### 5.3.22. Nalotimagene carmaleucel - ZALMOXIS (CAP) - EMEA/H/C/002801/II/0016, Orphan

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Applicant: MolMed S.p.A, ATMP<sup>7</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Proposal to terminate study TK008 (listed as a category 2 study, specific condition to the conditional marketing authorisation): a phase 3, randomised trial of haploidentical hematopoietic cell transplantation (HCT) with or without an add back strategy of human herpes simplex virus thymidine kinase type 1 gene (HSV-Tk) donor lymphocytes in patients with high risk acute leukaemia, and replace it with study TK013: a two-step study consisting in an initial feasibility study, followed by a single-arm trial with matched-pair controls from the European Society for Blood and Marrow Transplantation (EBMT) registry. The RMP (version 8.1) is updated accordingly

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

### 5.3.23. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0033

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Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to support the use of Lynparza (olaparib) tablets (100 mg and 150 mg) for the maintenance treatment of germline BRCA<sup>8</sup> mutation (gBRCAm) metastatic pancreatic cancer based on the results from pivotal study POLO: a phase 3 randomised, double blind, placebo controlled, multicentre study of maintenance olaparib monotherapy in patients with gBRCA mutated metastatic pancreatic cancer whose disease has not progressed on first line platinum based chemotherapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 18) are updated accordingly. In addition, the MAH took the opportunity to update section 4.8 for Lynparza (olaparib) hard capsules 50 mg to revise the list of adverse drug reactions (ADR) based on the pooled safety data analysis. Furthermore, the MAH took the opportunity to update the product information on sodium content in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Finally, the MAH introduced some minor editorial changes throughout the product information

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

### 5.3.24. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0142

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC following completion of paediatric studies NV25719 and NV20234 and downstream population pharmacokinetic (PK) and PK/pharmacodynamic (PD) analysis in order to include a dose recommendation for the treatment of paediatric immunocompromised (IC) patients. Study NV25719 was a prospective, open-label, randomized study which investigated PK and PD of two weight adjusted oseltamivir doses for the treatment of influenza-infected immunocompromised (IC)

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<sup>7</sup> Advanced therapy medicinal product

<sup>8</sup> BRCA1/2 gene



children less than 13 years of age. Study NV20234 was a prospective, double-blind, randomized trial which investigated safety and viral resistance to oseltamivir treatment in influenza-infected IC adults, adolescents and children. The package leaflet, labelling and the RMP (version 19.0) are updated accordingly

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

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

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

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

#### 5.3.26. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0080

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC on the safety information for immune-related endocrinopathies following a safety review for Addison's disease/primary adrenal insufficiency. The RMP (version 26.1) is updated accordingly. The MAH also took the opportunity to include changes in Annex II in line with the latest quality review of documents (QRD) template (version 10.1) and to update the list of local representatives of Portugal in the package leaflet

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

#### 5.3.27. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0033

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Cyramza (ramucirumab) in combination with erlotinib for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 9) are updated accordingly

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

#### 5.3.28. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0162

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Extension of indication to include the treatment of paediatric patients (aged  $\geq 2$  to  $<18$  years old) with active polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) for the 100 mg and 500 mg concentrate for solution based on efficacy and safety data from study WA25615: a phase 2A, international, multicentre, open-label, uncontrolled study to evaluate the safety and pharmacokinetics of  $4 \times 375$  mg/m<sup>2</sup> intravenous rituximab in paediatric patients with severe granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis (PePRS). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC is updated. The package leaflet and the RMP (version 20.0) are updated accordingly. In addition, the product information is brought in line with the latest quality review document (QRD) template (version 10) and the opportunity is taken to combine the SmPC and package leaflet for the 100 mg and 500 mg concentrate for solution presentations. Furthermore, the MAH took the opportunity to implement minor editorial changes in the SmPC

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

### 5.3.29. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/X/0059/G

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength (200 mg film-coated tablets) and a new pharmaceutical form (oral granules) associated with new strengths (150 mg and 200 mg). The new presentations are indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in patients aged 3 to  $<12$  years; 2) inclusion of paediatric use in patients aged 3 to  $<12$  years who weigh greater than or equal to 35 kg to the existing presentations of 400 mg film-coated tablets. The RMP (version 8.3) is updated accordingly. In addition, the MAH took the opportunity to implement minor linguistic corrections throughout the product information

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

### 5.3.30. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/X/0049/G, Orphan

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped application consisting of: extension application to introduce a new strength (61 mg soft capsules, pack-size of 30 and 90 capsules) including an extension of indication to include treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation (ATTR-CM); update of section 4.6 of the SmPC of 20 mg soft capsules to reflect some wording pertaining to the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme. The RMP (version 9.0) is updated accordingly, including proposed new dosage/indication, review of the additional data collected from the ATTR-CM clinical programme and post marketing reporting, a reclassification of the safety concerns and the removal of healthcare professional (HCP) educational leaflet. Annex II is updated in accordance. In addition, the MAH proposed to update the information in Braille of Annex III-

A on 'labelling' to differentiate between the dosage forms

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

### 5.3.31. Telotristat ethyl - XERMELO (CAP) - EMEA/H/C/003937/II/0015, Orphan

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 5.1 of the SmPC based on final results from study LX1606.1-302.CS (TELEPATH) (listed as a category 3 study in the RMP): a multicentre, phase 3, long-term extension study to further evaluate the safety and tolerability of telotristat etiprate in patients with carcinoid syndrome (CS). The RMP (version 4.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

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

### 5.3.32. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0020

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: Update of sections 4.8 and 5.1 of the SmPC based on safety information from interim results at week 48 of study GS-US-320-4018 (listed as a category 3 study in the RMP): a phase 3, randomized, double blind study conducted to evaluate the efficacy and safety of switching from tenofovir disoproxil fumarate (TDF) 300 mg once a day (QD) to tenofovir alafenamide (TAF) 25 mg QD in subjects with chronic hepatitis B (CHB) who are virologically suppressed. The package leaflet and the RMP (version 4.1) are updated accordingly

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

### 5.3.33. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0086/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.8 of the SmPC to change the frequency for anaphylaxis (fatal) and Stevens-Johnson syndrome to 'rare'. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to sections 4.2, 4.8 and 5.1 of the SmPC, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the package leaflet; 2) submission of an updated RMP (version 25.2) in order to remove the reference to the neutropenia guided questionnaire in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to introduce minor changes to the RMP, including the removal of study WA22479 (British Society of Rheumatology Biologics Register (BSRBR)) (in fulfilment of post-authorisation measure (PAM) MEA-045), inclusion of study ZUMA-8 (KTE-X19-108): a phase 1/2 multicentre study evaluating KTE-X19 in patients with relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL), as requested in the conclusions of variation II/0076 finalised in September 2018

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

#### 5.3.34. [Ustekinumab - STELARA \(CAP\) - EMEA/H/C/000958/II/0073](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to include a new population for Stelara (ustekinumab) solution for injection in children aged 6 to 12 years with moderate to severe psoriasis based on the results of study CNTO1275PSO3013: a phase 3 open-label study to assess the efficacy, safety, and pharmacokinetics of subcutaneously administered ustekinumab in the treatment of moderate to severe chronic plaque psoriasis in paediatric subjects greater than or equal to 6 to less than 12 years of age. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Section 4.8 of the SmPC for Stelara (ustekinumab) concentrate for solution for infusion is updated accordingly. The package leaflet and the RMP (version 15.0) are updated accordingly. The MAH also updated the RMP to add 'follow-up of pregnancy registry'. The MAH took the opportunity to introduce minor editorial changes to section 4.5 for both formulations and 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

#### 5.3.35. [Venetoclax - VENCLYXTO \(CAP\) - EMEA/H/C/004106/II/0023/G](#)

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include Venclyxto (venetoclax) in combination with an anti-CD20 antibody (obinutuzumab) for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) based on the results of pivotal study CLL14/BO25323: a prospective, open-label, multicentre randomized phase 3 trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax (GDC-0199/ABT-199) versus obinutuzumab and chlorambucil in previously untreated patients with CLL and coexisting medical conditions. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.1) are updated accordingly. Furthermore, section 5.3 of the SmPC is updated based on the 6 month-carcinogenicity mouse study report, supported by the 4 week dose ranging study in mice and embryo-foetal development (EFD) data. The MAH took the opportunity to introduce minor editorial changes throughout the product information (PI)

**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. Apremilast - OTEZLA (CAP) - PSUSA/00010338/201903

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Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.2. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/201903

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.3. Belimumab - BENLYSTA (CAP) - PSUSA/00009075/201903

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.4. Bosutinib - BOSULIF (CAP) - PSUSA/00010073/201903

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.5. Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/201903

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.6. Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/201902

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Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.7. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/201903

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.8. Cholic acid<sup>9</sup> - KOLBAM (CAP) - PSUSA/00010182/201903

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Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.9. Ciclosporin<sup>10</sup> - IKERVIS (CAP); VERKAZIA (CAP) - PSUSA/00010362/201903

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Applicant(s): Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.10. Cinacalcet - MIMPARA (CAP) - PSUSA/00000756/201902

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.11. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/201903

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Applicant: Boehringer Ingelheim International GmbH

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<sup>9</sup> Indicated in the treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or  $\alpha$ -) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7 $\alpha$ -hydroxylase (CYP7A1) deficiency

<sup>10</sup> Topical use only

PRAC Rapporteur: Anette Kirstine Stark  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.12. [Damoctocog alfa pegol - JIVI \(CAP\) - PSUSA/00010732/201902](#)

Applicant: Bayer AG  
PRAC Rapporteur: Menno van der Elst  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.13. [Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA \(CAP\) - PSUSA/00010646/201903](#)

Applicant: Janssen-Cilag International N.V.  
PRAC Rapporteur: Ana Sofia Diniz Martins  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.14. [Darvadstrocel - ALOFISEL \(CAP\) - PSUSA/00010676/201903](#)

Applicant: Takeda Pharma A/S  
PRAC Rapporteur: Brigitte Keller-Stanislawski  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.15. [Degarelix - FIRMAGON \(CAP\) - PSUSA/00000944/201902](#)

Applicant: Ferring Pharmaceuticals A/S  
PRAC Rapporteur: Ghania Chamouni  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.16. [Doravirine - PIFELTRO \(CAP\) - PSUSA/00010729/201902](#)

Applicant: Merck Sharp & Dohme B.V.  
PRAC Rapporteur: Ana Sofia Diniz Martins  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP



6.1.17. [Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO \(CAP\) - PSUSA/00010731/201902](#)

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

6.1.18. [Eftrenonacog alfa - ALPROLIX \(CAP\) - PSUSA/00010499/201903](#)

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

6.1.19. [Eluxadoline - TRUBERZI \(CAP\) - PSUSA/00010528/201903](#)

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Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

6.1.20. [Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY \(CAP\) - PSUSA/00010514/201902](#)

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

6.1.21. [Ferric citrate coordination complex - FEXERIC \(CAP\) - PSUSA/00010418/201903](#)

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Applicant: Akebia Europe Limited c/o Matheson

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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

6.1.22. [Fingolimod - GILENYA \(CAP\) - PSUSA/00001393/201902](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

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

**6.1.23. Fluticasone furoate, umecclidinium, vilanterol - ELEBRATO ELLIPTA (CAP); TRELEGY ELLIPTA (CAP) - PSUSA/00010653/201903**

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Applicant(s): GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

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

**6.1.24. Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/201903**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

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

**6.1.25. Glycopyrronium<sup>11</sup> - SIALANAR (CAP) - PSUSA/00010529/201903**

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Applicant: Proveca Pharma Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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

**6.1.26. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/201903**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

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

**6.1.27. Human coagulation factor X - COAGADEx (CAP) - PSUSA/00010481/201903**

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Applicant: BPL Bioproducts Laboratory GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

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<sup>11</sup> Centrally authorised product(s) only, indicated for the treatment of severe sialorrhea (chronic pathological drooling)

6.1.28. [Influenza vaccine \(surface antigen, inactivated, prepared in cell cultures\) - FLUCELVAX TETRA \(CAP\) - PSUSA/00010737/201903](#)

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Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

6.1.29. [Ipilimumab - YERVOY \(CAP\) - PSUSA/00009200/201903](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

6.1.30. [Isavuconazole - CRESEMBA \(CAP\) - PSUSA/00010426/201903](#)

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Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

6.1.31. [Ixekizumab - TALTZ \(CAP\) - PSUSA/00010493/201903](#)

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

6.1.32. [Lapatinib - TYVERB \(CAP\) - PSUSA/00001829/201903](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

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

6.1.33. [Lusutrombopag - MULTPLEO \(CAP\) - PSUSA/00010755/201903](#)

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Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.34. Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/201902**

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.35. Mifamurtide - MEPACT (CAP) - PSUSA/00002059/201903**

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Applicant: Takeda France SAS

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.36. Naldemedine - RIZMOIC (CAP) - PSUSA/00010753/201903**

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Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.37. Niraparib - ZEJULA (CAP) - PSUSA/00010655/201903**

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Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.38. Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/201903**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.39. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201903**

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

**6.1.40. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58<sup>12</sup>) - EMEA/H/W/002300/PSUV/0042**

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUR procedure

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

**6.1.41. Ribociclib - KISQALI (CAP) - PSUSA/00010633/201903**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

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

**6.1.42. Rolapitant - VARUBY (CAP) - PSUSA/00010592/201902**

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Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

**6.1.43. Sodium zirconium cyclosilicate - LOKELMA (CAP) - PSUSA/00010675/201903**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

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

**6.1.44. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/201903**

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Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

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<sup>12</sup> Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

#### 6.1.45. Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/201903

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.46. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/201903

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

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. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/201902

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Applicant(s): Clinigen Healthcare B.V. (Savene), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

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

#### 6.2.2. Orlistat - ALLI (CAP); XENICAL (CAP); NAP - PSUSA/00002220/201902

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Applicant(s): GlaxoSmithKline Dungarvan Ltd (alli), Cheplapharm Arzneimittel GmbH (Xenical), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

#### 6.2.3. Trientine - CUPRIOR (CAP); NAP - PSUSA/00010637/201903

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Applicant(s): GMP-Orphan SA (Cuprior), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

#### 6.2.4. Vardenafil - LEVITRA (CAP); VIVANZA (CAP); NAP - PSUSA/00003098/201903

Applicant(s): Bayer AG (Levitra, Vivanza), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

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

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

#### 6.3.1. Acetylsalicylic acid (NAP) - PSUSA/00000039/201902

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.2. Amitriptyline hydrochloride, chlordiazepoxide (NAP) - PSUSA/00000171/201902

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.3. Amlodipine, atorvastatin (NAP) - PSUSA/00000177/201901

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.4. Cabergoline (NAP) - PSUSA/00000477/201903

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.5. Cilostazol (NAP) - PSUSA/00010209/201902

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.6. Dorzolamide (NAP) - PSUSA/00003168/201902

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Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.7. Dorzolamide, timolol (NAP) - PSUSA/00001166/201902

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.8. Ethanol, orthophenylphenol (NAP) - PSUSA/00010416/201902

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Applicant(s): various

PRAC Lead: Jana Lukačičinová

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.9. Gabapentin (NAP) - PSUSA/00001499/201902

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.10. Glipizide (NAP) - PSUSA/00001535/201901

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Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

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



#### 6.3.11. Human coagulation factor VIII<sup>13</sup> (NAP) - PSUSA/00009174/201902

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Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.12. Hydroxyethyl starch (NAP) - PSUSA/00001694/201903

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.13. Interferon gamma (NAP) - PSUSA/00001760/201901

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.14. Levothyroxine (NAP) - PSUSA/00001860/201901

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Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.15. Lisdexamfetamine (NAP) - PSUSA/00010289/201902

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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

#### 6.3.16. Mesterolone (NAP) - PSUSA/00010551/201901

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Applicant(s): various

PRAC Lead: Julia Pallos

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<sup>13</sup> Inhibitor bypassing fraction

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.17. Octenidine dihydrochloride, 1-propanol, 2-propanol (NAP) - PSUSA/00010417/201901

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Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.18. Trandolapril (NAP) - PSUSA/00003004/201902

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

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

None

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

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>14</sup>

#### 7.1.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/PSP/S/0079.1

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Applicant: Kite Pharma EU B.V., ATMP<sup>15</sup>

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to PSP/S/0079 [protocol for a long-term, non-interventional study in patients taking Yescarta (axicabtagene ciloleucel) for the treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma to evaluate the safety of patients, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinaemia and pregnancy outcomes in female patients of childbearing potential] as per the request for supplementary information (RSI) adopted in May 2019 and following discussion in September 2019

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

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<sup>14</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>15</sup> Advanced therapy medicinal product

### 7.1.2. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSP/S/0071.1

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: MAH's response to PSP/S/0071 [protocol for study 20180130: an observational PASS to describe the long-term safety profile of first-relapse B-precursor acute lymphoblastic leukaemia (ALL) paediatric patients who have been treated with blinatumomab or chemotherapy prior to undergoing haematopoietic stem cell transplant] as per the request for supplementary information (RSI) adopted in May 2019

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

### 7.1.3. Iron<sup>16, 17</sup> (NAP) - EMEA/H/N/PSA/J/0042

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Applicant(s): Mesama Consulting (on behalf of a consortium) (Cosmofer, Ferinject, Monofer, Venofer)

PRAC Rapporteur: Ghania Chamouni

Scope: Amendment to a previously agreed protocol in September 2017 (PSP/J/0053.1) for a joint PASS evaluating the risk of severe hypersensitivity reactions with intravenous (IV) iron use

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

### 7.1.4. Tisagenlecleucel - KYMRIA<sup>18</sup> (CAP) - EMEA/H/C/PSP/S/0066.2

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Applicant: Novartis Europharm Ltd, ATMP<sup>18</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0066.1 [protocol for non-interventional study CCTL019B2401 with secondary use of data from two registries conducted by the 'European Society for Blood and Marrow Transplantation' (EBMT) and 'Centre for International Blood and Marrow Transplant Research' (CIBMTR) to evaluate the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel (chimeric antigen receptor (CAR)-T cell therapy) in a real-world setting] as per the request for supplementary information (RSI) adopted in April 2019 and following discussion in September 2019

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

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>19</sup>

### 7.2.1. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/MEA 001.1

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Applicant: Amgen Europe B.V.

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<sup>16</sup> Intravenous applications only

<sup>17</sup> Iron(III)-hydroxide dextran complex, iron sucrose complex/iron(III)-hydroxide sucrose complex, ferric carboxymaltose complex, iron(III) isomaltoside complex, sodium ferric gluconate complex

<sup>18</sup> Advanced therapy medicinal product

<sup>19</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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 001 [protocol for study 20160264 (ABP 501) - British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR): an observational study to evaluate long term safety of Amgevita (adalimumab) in patients with rheumatoid arthritis [final report due date: Q3 2027]] as per the request for supplementary information (RSI) adopted in April 2019

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

#### 7.2.2. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/MEA 003.1

Applicant: Kite Pharma EU B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 003 [protocol for study KT-EU-471-0116: a prescriber survey to assess the prescribers' understanding of serious neurologic adverse reactions and cytokine release syndrome (CRS)] as per the request for supplementary information (RSI) adopted in June 2019

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

#### 7.2.3. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 003.2

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Amendment to a previously agreed protocol in November 2018 for study D3250R00026 'the benralizumab pregnancy exposure study': a post-marketing surveillance study on vaccines and medications in pregnancy surveillance system (VAMPSS)

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

#### 7.2.4. Brigatinib - ALUNBRIG (CAP) - EMEA/H/C/004248/MEA 002.1

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 002 [protocol for study Brigatinib-5007: a cohort study to describe the occurrence of early-onset pulmonary events in patients with anaplastic lymphoma kinase-positive (ALS+) advance non-small cell lung cancer (NSCLC) treated with brigatinib] as per the request for supplementary information (RSI) adopted in June 2019

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

#### 7.2.5. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 006

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Protocol for study H9X-MC-B013: a non-interventional retrospective study to estimate the incidence rates of events of interest among type 2 diabetes mellitus (T2DM)

patients treated with dulaglutide compared to other glucagon-like peptide 1 (GLP-1) receptor agonists in order to better characterise the safety profile of dulaglutide in terms of acute pancreatitis, pancreatic and thyroid malignancies

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

#### 7.2.6. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/MEA 010

Applicant: Aziende Chimiche Riunite Angelini Francesco S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 151(A)PO19107 (lurasidone PASS programme): an evaluation of the safety profile of lurasidone: a PASS using United States administrative claims databases

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

#### 7.2.7. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/MEA 011

Applicant: Aziende Chimiche Riunite Angelini Francesco S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 151(A)PO19056: a drug utilisation study (DUS) to evaluate the characteristics of lurasidone-treated patients in real world clinical practice in the United Kingdom

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

#### 7.2.8. Mexiletine - NAMUSCLA (CAP) - EMEA/H/C/004584/MEA 001.1

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: MAH's response to MEA 001 [protocol for a registry study to determine the long-term safety and tolerability of Namuscla (mexiletine) for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorder] as per the request for supplementary information (RSI) adopted in May 2019

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

#### 7.2.9. Radium-223 - XOFIGO (CAP) - EMEA/H/C/002653/MEA 014.1

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's response to MEA 014 [protocol for a drug utilisation study (DUS) of Xofigo (radium-223) under routine clinical practice in Europe to investigate the risk of off-label use, as requested in the conclusions of the referral procedure on Xofigo (radium-223) under Article 20 of Regulation (EC) No 726/2004 (EMA/H/A-20/1459) finalised in 2018] as per the request for supplementary information (RSI) adopted in May 2019

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

#### 7.2.10. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.5

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 044.4 [Amendment to a previously agreed protocol in February 2017 (MEA 044.2) for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)] as per the request for supplementary information (RSI) adopted in June 2019

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

### 7.3. Results of PASS imposed in the marketing authorisation(s)<sup>20</sup>

#### 7.3.1. Valproate (NAP) - EMEA/H/N/PSR/J/0021

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSR/J/0021 [results for a joint drug utilisation study (DUS) of valproate and related substances, in Europe, using databases to describe the prescribing practices before and after the dissemination of risk minimisations measures (RMMs) (i.e. educational materials and direct healthcare professional communication (DHPC) between December 2014 and June 2015) and to assess the effectiveness of these measures, as imposed in the outcome of the referral procedure on valproate and related substances (EMA/H/A-31/1387) concluded in 2014] as per the request for supplementary information (RSI) adopted in May 2019

**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>21</sup>

#### 7.4.1. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS1663/0046/G; Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS1663/0055/G

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped variations consisting of: 1) submission of final report from study P15-421, (listed as a category 3 study in the RMP): a prospective, observational cohort study utilising the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine aminotransferase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/r), ombitasvir and dasabuvir (3-direct acting antiviral (DAAV) regimen) or

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<sup>20</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>21</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

paritaprevir/r and ombitasvir (2-DAAV regimen) with or without ribavirin for hepatitis C infection (HCV); 2) change in the final due date for the prospective safety study report in order to evaluate the recurrence of hepatocellular carcinoma associated with Exviera (dasabuvir) and Viekirax (ombitasvir/paritaprevir/ritonavir) from Q2 2021 to Q2 2023. Annex II of the product information is updated accordingly. The RMP (version 5.0) is also updated accordingly

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

#### 7.4.2. [Deferasirox - EXJADE \(CAP\) - EMEA/H/C/000670/II/0068](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

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

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

#### 7.4.3. [Etanercept - ENBREL \(CAP\) - EMEA/H/C/000262/WS1614/0227;](#) [Etanercept - LIFMIOR \(CAP\) - EMEA/H/C/004167/WS1614/0021](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study B1801035 (081X1-4654) (listed as a category 3 study in the RMP): a non-interventional, multicentre, prospective, observational, cohort study conducted to evaluate the long-term safety and effectiveness of etanercept prescribed by dermatologists to paediatric patients for the treatment of plaque psoriasis (Paediatric Registry of Psoriasis and Enbrel - The PURPOSE Study)

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

#### 7.4.4. [Idebenone - RAXONE \(CAP\) - EMEA/H/C/003834/II/0016, Orphan](#)

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Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final report from study SNT-CRS-002 (listed as a specific obligation (SOB10, former SOB2) in Annex II): a historical case record survey (CRS) of visual acuity data from patients with Leber's hereditary optic neuropathy (LHON) aiming at generating a natural history group to serve as a comparator group of idebenone-naïve patients for open-label study SNT-IV-005: an external natural history controlled, open-label intervention study to assess the efficacy and safety of long-term treatment with Raxone (idebenone) in LHON which will assess long-term efficacy and safety in patients with LHON treated with Raxone (idebenone). Annex II is updated accordingly. The RMP (version 1.8) is updated accordingly

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

#### **7.4.5. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/II/0037**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report for study register EUPAS5766 in EuroSIDA cohort (listed as a category 3 study in the RMP): a drug utilisation study (DUS), observational cohort study to assess rilpivirine (RPV) utilisation. The RMP (version 9.0) is updated accordingly

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

#### **7.4.6. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0043**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report for study INC424AIC01T (listed as a category 3 study in the RMP): a non-interventional, observational PASS in order to provide real-world safety data on patients with myelofibrosis (MF) who were exposed and non-exposed to ruxolitinib and provide insights into disease management and the safety profile of ruxolitinib. The RMP (version 11) is updated accordingly

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

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

#### **7.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 042**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Interim report for an observational registry of abatacept in patients with juvenile idiopathic arthritis (JIA) in order to describe the long-term safety of abatacept treatment for JIA in routine clinical practice by quantifying the incidence rates of serious infections, autoimmune disorders, and malignancies (from R/055)

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

#### **7.5.2. Everolimus - VOTUBIA (CAP) - EMEA/H/C/002311/MEA 014.4**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Fifth interim analysis for a sub-study of PASS CRAD001MIC03 (TOSCA): an international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex (TSC)



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

### 7.5.3. [Filgrastim - FILGRASTIM HEXAL \(CAP\) - EMEA/H/C/000918/MEA 007.5](#)

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Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: Eighth annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal (filgrastim) and Zarzio (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) expected date: December 2019]

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

### 7.5.4. [Filgrastim - ZARZIO \(CAP\) - EMEA/H/C/000917/MEA 007.5](#)

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Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Eighth annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal (filgrastim) and Zarzio (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) expected date: December 2019]

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

### 7.5.5. [Fingolimod - GILENYA \(CAP\) - EMEA/H/C/002202/MEA 012.8](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Eighth annual interim pooled report for studies D2403 (a long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started on fingolimod once daily or treated with another approved disease-modifying therapy), D2404 (multinational Gilenya pregnancy exposure registry in multiple sclerosis (MS)), D2406 (a long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS newly initiated on fingolimod once daily or treated with another approved disease-modifying therapy) and study D2409 (a long-term, open-label, multicentre study assessing long-term cardiovascular risks in patients treated with fingolimod). This procedure also includes an annual report for the pregnancy intensive monitoring (PRIM) study

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

### 7.5.6. [Human papillomavirus vaccine \[types 6, 11, 16, 18\] \(recombinant, adsorbed\) - GARDASIL \(CAP\) - EMEA/H/C/000703/MEA 086](#)

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Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Yearly interim results for study P070 (listed as category 3 study in the RMP): a post-

licensure safety study in males to monitor safety signals through a systematic evaluation in a research database

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

#### 7.5.7. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 060.1

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Six-monthly summary report of medication error events reported with the on body injector in the EU market, as requested in the conclusions of variation II/093/G finalised in February 2018

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

#### 7.5.8. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/MEA 003.9

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Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Ninth annual interim report for the Kuvan Adult Maternal Paediatric European registry (KAMPER) registry, study EMR700773-001: a non-imposed, non-interventional exploring the long-term safety of Kuvan (sapropterin) use in patients with hyperphenylalaninaemia (HPA) as well as information on Kuvan use during pregnancy in women with HPA and data regarding childhood growth and neurocognitive outcomes

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

### 7.6. Others

#### 7.6.1. Lusutrombopag - MULPLEO (CAP) - EMEA/H/C/004720/MEA 002

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Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Feasibility assessment for a protocol for study VV-REG-090246: a PASS exploring the hepatic safety of lusutrombopag Shionogi in patients with Child-Pugh class C liver disease (from initial opinion/MA) [final study report expected in December 2025]

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

#### 7.6.2. Pantoprazole - CONTROLOC CONTROL (CAP) - EMEA/H/C/001097/LEG 018

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Applicant: Takeda GmbH

PRAC Rapporteur: Rugile Pilviniene

Scope: Feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population, as requested in the conclusions of variation WS/1422 finalised in January 2019

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

#### **7.6.3. Pantoprazole - PANTOLOC CONTROL (CAP) - EMEA/H/C/001100/LEG 017**

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Applicant: Takeda GmbH

PRAC Rapporteur: Rugile Pilviniene

Scope: Feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population, as requested in the conclusions of variation WS/1422 finalised in January 2019

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

#### **7.6.4. Pantoprazole - PANTOZOL CONTROL (CAP) - EMEA/H/C/001013/LEG 018**

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Applicant: Takeda GmbH

PRAC Rapporteur: Rugile Pilviniene

Scope: Feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population, as requested in the conclusions of variation WS/1422 finalised in January 2019

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

#### **7.6.5. Pantoprazole - SOMAC CONTROL (CAP) - EMEA/H/C/001098/LEG 023**

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Applicant: Takeda GmbH

PRAC Rapporteur: Rugile Pilviniene

Scope: Feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population, as requested in the conclusions of variation WS/1422 finalised in January 2019

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

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

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

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

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

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

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

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

### 8.1. Annual reassessments of the marketing authorisation

#### 8.1.1. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0010 (without RMP)

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Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.2. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/S/0016 (without RMP)

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Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.3. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0048 (without RMP)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

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. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/R/0009 (without RMP)

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

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

#### 8.2.2. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0026 (without RMP)

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Applicant: Chiesi Farmaceutici S.p.A., ATPM<sup>22</sup>

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

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

#### 8.2.3. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0018 (without RMP)

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Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

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

#### 8.2.4. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0041 (without RMP)

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Conditional renewal of the marketing authorisation

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

### 8.3. Renewals of the marketing authorisation

#### 8.3.1. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/R/0020 (without RMP)

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.2. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/R/0022 (without RMP)

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

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

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<sup>22</sup> Advanced therapy medicinal product

### 8.3.3. Fosnetupitant, netupitant, palonosetron - AKYNZEO (CAP) - EMEA/H/C/003728/R/0024 (without RMP)

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Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.4. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/002789/R/0022 (with RMP)

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.5. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/R/0024 (without RMP)

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.6. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/R/0031 (without RMP)

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

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

None

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

None

### 10.3. Other requests

None

### 10.4. Scientific Advice

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

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

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

#### 11.1.1. Etonogestrel (NAP) - NL/H/0150/001/II/050

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Applicant(s): N.V. Organon (Implanon NXT)

PRAC Lead: Menno van der Elst

Scope: PRAC consultation on a type II variation procedure referred to the CMDh under Article 13(1) of EC/1234/2008 relating to an update of the SmPC on the implant insertion and removal instructions and risk minimisation measures on intravascular insertion and neurovascular injury, on request of the Netherlands

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

### 11.2. Other requests

None

## 12. Organisational, regulatory and methodological matters

### 12.1. Mandate and organisation of the PRAC

None

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

None

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

12.3.1. Scientific Advice Working Party (SAWP) – consultation procedure: update and practical aspects

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**Action:** For discussion

### 12.4. Cooperation within the EU regulatory network

12.4.1. Communication harmonisation within the network - naming convention

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**Action:** For discussion

12.4.2. European Network Training Centre (EU NTC) - Pharmacovigilance - Training curriculum (TC) – Update on training activities

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**Action:** For discussion

### 12.5. Cooperation with International Regulators

12.5.1. International Conference on Harmonisation (ICH) E2B(R3) guideline on electronic transmission of individual case safety reports - data elements and message specification - stakeholder readiness for mandatory use

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**Action:** For adoption

12.5.2. International Conference on Harmonisation (ICH) E2D guideline on post-approval safety data management: definitions and standards for expedited reporting - revision

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**Action:** For discussion



12.5.3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-E19 on 'optimisation of safety data collection' – draft guideline

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**Action:** For adoption

**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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PRAC lead: Menno van der Elst

**Action:** For discussion

## 12.12. Adverse drug reactions reporting and additional monitoring

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

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None

### 12.12.2. Additional monitoring

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None

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

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**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

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

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None

#### 12.14.3. Good pharmacovigilance practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' – revision 3

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PRAC lead: Sabine Straus

**Action:** For discussion

### **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. Biosimilar medicines and identification – update

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**Action:** For discussion

### 12.20.2. Capacity-building activities in human and veterinary pharmacovigilance - EMA survey for its staff and the EU network on 02-11 October 2019

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**Action:** For discussion

### 12.20.3. Drug-induced hepatotoxicity – review

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PRAC lead: Amelia Cupelli, Liana Gross-Martirosyan, Martin Huber, Menno van der Elst, Stefan Weiler, Zane Neikena

**Action:** For discussion

### 12.20.4. EMA pre-submission activities - European Ombudsman enquiry outcome

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**Action:** For discussion

### 12.20.5. Good Pharmacovigilance Practice (GVP) Guideline on product or population specific considerations III: pregnancy and breastfeeding – draft guideline

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PRAC lead: Ulla Wändel Liminga

**Action:** For adoption

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

### **Signals assessment and prioritisation**

(Item 4 of the PRAC agenda)

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

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

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

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

(Item 5 of the PRAC agenda)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects.

RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

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

(Item 6 of the PRAC agenda)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

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

(Item 7 of the PRAC agenda)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC agenda)

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

More detailed information on the above terms can be found on the EMA website: [www.ema.europa.eu/](http://www.ema.europa.eu/)