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Inspections, Human Medicines Pharmacovigilance and Committees Division

## Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 28-31 October 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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

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

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

Organisational, regulatory and methodological matters (ORGAM)

14 November 2019, 09:00-12:00, room 2/B, via teleconference

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

### Disclaimers

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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 on 28-31 October 2019. See (current) November 2019 minutes (to be published post December 2019 PRAC meeting).

### 1.2. Agenda of the meeting on 28-31 October 2019

**Action:** For adoption

### 1.3. Minutes of the previous meeting on 30 September-03 October 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

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

### 3.1. Newly triggered procedures

None

## 3.2. Ongoing procedures

### 3.2.1. Cyproterone acetate (NAP) - EMEA/H/A-31/1488

---

Applicant(s): various

PRAC Rapporteur: Menno van der Elst; PRAC Co-rapporteur: Adam Przybylkowski

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 outstanding issues (LoOI)

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

---

Applicant(s): various

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

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

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

## 3.3. Procedures for finalisation

### 3.3.1. 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 recommendation to CHMP

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

---

Applicant: 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 recommendation to CHMP

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

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

#### 3.4.1. Estradiol<sup>3</sup> (NAP) - EMEA/H/A-31/1482

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Applicant(s): various

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

Scope: Request for re-examination under Article 32 of Directive 2001/83/EC for the review of the benefit-risk balance of medicinal products containing estradiol 0.01% for topical use following notification by the European Commission of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

**Action:** For discussion

### 3.5. Others

None

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

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

#### 4.1.1. Adalimumab – AMGEVITA (CAP), HALIMATOZ (CAP), HEFIYA (CAP), HULIO (CAP), HUMIRA (CAP), HYRIMOZ (CAP), IDACIO (CAP), IMRALDI (CAP), KROMEYA (CAP)

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Applicant(s): AbbVie Deutschland GmbH & Co. KG (Humira), Amgen Europe B.V. (Amgevita), Fresenius Kabi Deutschland GmbH (Idacio, Kromeya), Mylan S.A.S (Hulio), Samsung Bioepis NL B.V. (Imraldi), Sandoz GmbH (Halimatoz, Hefiya, Hyrimoz)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of autoimmune encephalitis

**Action:** For adoption of PRAC recommendation

EPITT 19483 – New signal

Lead Member State(s): SE

#### 4.1.2. Buprenorphine – BUVIDAL (CAP), SIXMO (CAP), NAP; buprenorphine, naloxone – SUBOXONE (CAP), ZUBSOLV (CAP), NAP; naloxone – NYXOID (CAP), NAP; Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluvoxamine (NAP); fluoxetine (NAP); paroxetine (NAP); sertraline (NAP); Serotonin norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN

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

<sup>3</sup> 0.01%, topical use only

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

(CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP), NAP; milnacipran (NAP); venlafaxine (NAP); Tricyclic antidepressants (TCAs): amitriptyline (NAP); clomipramine (NAP); doxepin (NAP); imipramine (NAP); nortriptyline (NAP); trimipramine (NAP); Monoamine oxidase inhibitors (MAOIs): isocarboxazid (NAP); phenelzine (NAP); selegiline (NAP); tranylcypromine (NAP); Other psychiatric medicines: amoxapine (NAP); buspirone (NAP); Ilthium (NAP); maprotiline (NAP); mirtazapine (NAP); trazodone (NAP); Serotonin receptor agonists: almotriptan (NAP); frovatriptan (NAP); naratriptan (NAP); rizatriptan (NAP); sumatriptan (NAP); zolmitriptan (NAP); Antiemetics: granisetron - SANCUSO (CAP), NAP; ondansetron (NAP); palonosetron – ALOXI (CAP), PALONOSETRON ACCORD (CAP), NAP; netupitant, palonosetron – AKYNZEO (CAP); tropisetron (NAP); Other serotonergic drugs: cyclobenzaprine (NAP); dextromethorphan (NAP); hypericum perforatum (NAP); linezolid (NAP); methylene blue (NAP); tryptophan (NAP)

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Applicant(s): Accord Healthcare S.L.U. (Palonosetron Accord), Camurus AB (Buvidal), Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Xeristar, Yentreve), Helsinn Birex Pharmaceuticals (Aloxi, Akynzeo), Indivior Europe Limited (Suboxone), Kyowa Kirin Holdings B.V. (Sancuso), L. Molteni & C. dei Fratelli Alitti (Sixmo), Mundipharma Corporation (Nyxoid), Mylan S.A.S (Duloxetine Mylan), Orexo AB (Zubsolv), Zentiva k.s. (Duloxetine Zentiva), various

PRAC Rapporteur: To be appointed

Scope: Signal of drug-drug interaction with serotonergic drugs leading to serotonin syndrome

**Action:** For adoption of PRAC recommendation

EPITT 19475 – New signal

Lead Member State(s): BE, CZ, DE, DK, EE, ES, FR, GR, HU, IE, LT, NL, PT, SE, SK, SI

#### 4.1.3. [Infliximab - FLIXABI \(CAP\), INFLECTRA \(CAP\), REMICADE \(CAP\), REMSIMA \(CAP\), ZESSLY \(CAP\)](#)

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Applicant(s): Celltrion Healthcare Hungary Kft. (Remsima), Janssen Biologics B.V. (Remicade), Pfizer Europe MA EEIG (Inflectra), Samsung Bioepis NL B.V. (Flixabi), Sandoz GmbH (Zessly)

PRAC Rapporteur: To be appointed

Scope: Signal of Kaposi's sarcoma

**Action:** For adoption of PRAC recommendation

EPITT 19480 – New signal

Lead Member State(s): FI, SE

#### 4.1.4. [Mycophenolic acid \(NAP\); mycophenolate mofetil - CELLCEPT \(CAP\), MYCLAUSEN \(CAP\), MYCOPHENOLATE MOFETIL TEVA \(CAP\), MYFENAX \(CAP\), NAP](#)

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Applicant(s): Passauer Pharma GmbH (Myclausen), Roche Registration GmbH (Cellcept), Teva B.V. (Mycophenolate Mofetil Teva, Myfenax)

PRAC Rapporteur: To be appointed

Scope: Signal of posterior reversible encephalopathy syndrome (PRES)

**Action:** For adoption of PRAC recommendation

EPITT 19473 – New signal

Lead Member State(s): DK

#### 4.1.5. Paroxetine (NAP)

---

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of microscopic colitis

**Action:** For adoption of PRAC recommendation

EPITT 19474 – New signal

Lead Member State(s): NL

#### 4.1.6. Pazopanib – VOTRIENT (CAP)

---

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of tumour lysis syndrome (TLS)

**Action:** For adoption of PRAC recommendation

EPITT 19494 – New signal

Lead Member State(s): DK

## 4.2. New signals detected from other sources

#### 4.2.1. Ceftriaxone (NAP)

---

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of encephalopathy

**Action:** For adoption of PRAC recommendation

EPITT 19492 – New signal

Lead Member State(s): LV

### 4.3. Signals follow-up and prioritisation

#### 4.3.1. 5 alfa-reductase inhibitors (5ARIs): finasteride (NAP); dutasteride (NAP)

---

Applicant(s): various

PRAC Rapporteur: Annika Folin

Scope: Signal of type 2 diabetes mellitus (T2DM)

**Action:** For adoption of PRAC recommendation

EPITT 19424 – Follow-up to May 2019

#### 4.3.2. Azacitidine – AZACITIDINE CELGENE (CAP), VIDAZA (CAP)

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Applicant(s): Celgene Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

**Action:** For adoption of PRAC recommendation

EPITT 19422 – Follow-up to June 2019

#### 4.3.3. Ferric carboxymaltose (NAP); iron (NAP); iron dextran (NAP); iron (III) isomaltoside (NAP); iron sucrose (NAP); sodium ferric gluconate (NAP)

---

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of arteriospasm coronary

**Action:** For adoption of PRAC recommendation

EPITT 19408 – Follow-up to May 2019

#### 4.3.4. Ibuprofen – PEDEA (CAP); NAP; ketoprofen(NAP) and fixed-dose combinations: chlorphenamine, ibuprofen, phenylephrine (NAP); dimenhydrinate, ibuprofen, caffeine (NAP); ibuprofen, ascorbic acid (NAP); ibuprofen, caffeine (NAP); ibuprofen, codeine (NAP); ibuprofen, hydrocodone (NAP); ibuprofen, paracetamol (NAP); ibuprofen, phenylephrine (NAP); ibuprofen, pseudoephedrine (NAP); ketoprofen, omeprazole (NAP), ketoprofen, sucralfate (NAP)

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Applicant(s): Recordati Rare Diseases (Pedeia), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of serious exacerbation of infections

**Action:** For adoption of PRAC recommendation

EPITT 19415 – Follow-up to May 2019



#### 4.3.5. Imiquimod – ALDARA (CAP); ZYCLARA (CAP); NAP

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Applicant(s): Meda AB, various

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of pemphigus

**Action:** For adoption of PRAC recommendation

EPITT 19441 – Follow-up to July 2019

#### 4.3.6. Tigecycline – TYGACIL (CAP); NAP

---

Applicant(s): Pfizer Europe MA EEIG, various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Signal of bradycardia

**Action:** For adoption of PRAC recommendation

EPITT 19394 – Follow-up to May 2019

#### 4.3.7. Vascular endothelial growth factor (VEGF) inhibitors<sup>5</sup>: aflibercept – EYLEA (CAP), ranibizumab – LUCENTIS (CAP)

---

Applicant(s): Bayer AG (Eylea), Novartis Europharm Limited (Lucentis)

PRAC Rapporteur: Annika Folin

Scope: Signal of artery dissections and aneurysms

**Action:** For adoption of PRAC recommendation

EPITT 19330 – Follow-up to May 2019

## 5. Risk management plans (RMPs)

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

#### 5.1.1. Bempedoic acid - EMEA/H/C/004958

---

Scope: Treatment of primary hypercholesterolaemia or mixed dyslipidaemia

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

#### 5.1.2. Bempedoic acid, ezetimibe - EMEA/H/C/004959

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Scope: Treatment of primary hypercholesterolaemia or mixed dyslipidaemia

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

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<sup>5</sup> For intravitreal use

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

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

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

### 5.1.4. Darolutamide - EMEA/H/C/004790

---

Scope: Treatment of non-metastatic castration resistant prostate cancer (nmCRPC)

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

### 5.1.5. Insulin lispro - EMEA/H/C/005037

---

Scope: Treatment of diabetes mellitus in adults

**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. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0050/G

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 5.0) in order to amend the list of safety concerns to remove 'cataract (in the context of very low 'low-density lipoprotein cholesterol' (LDL-C))' as an important potential risk; 'long-term use (>5years)' and 'clinical impact of very low LDL-C for extended period of time' as missing information. As a consequence, the following additional pharmacovigilance activities (listed as category 3 studies in the RMP) are removed from the RMP: 1) study R727-CL-1609: a long term safety study of Praluent (alirocumab) in patients with heterozygous familial hypercholesterolemia or with non-familial hypercholesterolemia at high and very high cardiovascular risk and previously enrolled in the neurocognitive function trial (MEA 016); 2) study OBS14697: a drug utilisation study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low low-density lipoprotein (LDL)-C levels (MEA 019); 3) study ALIROC07997: a PASS using healthcare databases, in order to monitor the safety of Praluent (alirocumab) in patients affected with the human immunodeficiency virus (HIV) (MEA 017) based on a review of data since the marketing authorisation (MA) was granted including the first interim report for study OBS14697 (in fulfilment of MEA 019.4)

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

### 5.2.2. Bortezomib - VELCADE (CAP) - EMEA/H/C/000539/II/0093

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 30.1) in order to revise the list of safety

concerns as requested in the conclusions of periodic single assessment procedure PSUSA/00000424/201804 adopted in December 2018. As a consequence, Annex II is updated to reflect the removal of the additional risk minimisation activities. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is being brought in line with the latest quality review of documents (QRD) template (version 10.1)

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

### 5.2.3. [Brinzolamide, brimonidine - SIMBRINZA \(CAP\) - EMEA/H/C/003698/II/0019](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 3.0) in order to remove 'metabolic acidosis/renal impairment' as an important potential risk from the list 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

### 5.2.4. [Daptomycin - CUBICIN \(CAP\) - EMEA/H/C/000637/II/0074](#)

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Pernille Harg

Scope: Submission of an updated RMP (version 11.1) in order to delete all risks and additional risk minimisation measures in line with revision 2 of GVP module V on 'Risk management systems'. Annex II is updated accordingly. In addition, the MAH took the opportunity to align the product information with the quality review of documents (QRD) template (version 10.1) and update the list of local representatives

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

### 5.2.5. [Infliximab - FLIXABI \(CAP\) - EMEA/H/C/004020/II/0039](#)

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 9.0) to replace the current registries with one company-sponsored initiated registry, PERFUSE: one-year persistence to treatment of patients receiving Flixabi (infliximab): a French cohort study; together with three inflammatory bowel disease (IBD) registries, namely: long-term observation registry in German IBD patients (CEDUR), Czech registry of IBD patients on biological therapy (CREDIT) and Dutch network of hospitals IBD registry (DREAM)

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

### 5.2.6. [Melatonin - SLENYTO \(CAP\) - EMEA/H/C/004425/II/0010](#)

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Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 1.3) to remove 'delay of sexual maturation and development' as an important potential risk based on the results of study NEUCH7911 showing a lack of effect on sexual maturation and growth after 2 years of continuous treatment, and temporary recommendation for use (RTU) data demonstrating a lack of effect on growth after continuous use of up to 3 years

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

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

#### 5.3.1. Adalimumab - HALIMATOZ (CAP) - EMEA/H/C/004866/X/0013

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Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg (20 mg/0.4 mL) for Halimatoz (adalimumab) solution for injection in pre-filled syringe. The RMP (version 2.0) is updated accordingly. The MAH took also the opportunity to consolidate the RMP with changes approved in two other procedures (WS1565 and IA/11 finalised in March 2019 and June 2019 respectively) and to align the product information with the latest quality review of documents (QRD) template (version 10.1)

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

#### 5.3.2. Adalimumab - HEFIYA (CAP) - EMEA/H/C/004865/X/0013

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Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg (20 mg/0.4 mL) for Hefiya (adalimumab) solution for injection in pre-filled syringe. The RMP (version 2.0) is updated accordingly. The MAH took also the opportunity to consolidate the RMP with changes approved in two other procedures (WS1565 and IA/11 finalised in March 2019 and June 2019 respectively) and to align the product information with the latest quality review of documents (QRD) template (version 10.1)

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

#### 5.3.3. Adalimumab - HYRIMOZ (CAP) - EMEA/H/C/004320/X/0013

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Applicant: Sandoz GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to add a new strength of 20 mg (20 mg/0.4 mL) for Hyrimoz (adalimumab) solution for injection in pre-filled syringe. The RMP (version 2.0) is updated accordingly. The MAH took also the opportunity to consolidate the RMP with changes approved in two other procedures (WS1565 and IA/11 finalised in March 2019 and June 2019 respectively) and to align the product information with the latest quality review of documents (QRD) template (version 10.1)

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

#### 5.3.4. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0110

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final report from study NEJ026 (listed as a category 1/obligation in Annex II): an open-label, randomized, phase 3 study conducted in Japan to compare erlotinib + bevacizumab combination therapy versus erlotinib monotherapy as first-line therapies for patients with non-small-cell lung carcinoma (NSCLC) with epidermal growth factor receptor (EGFR) gene mutations (exon 19 deletion or exon 21 L858R substitution). The RMP (version 30.0) is updated accordingly. In addition, the package leaflet is updated to reflect information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

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

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

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the treatment of Philadelphia chromosome positive CD19<sup>6</sup> positive B-cell precursor acute lymphoblastic leukaemia (ALL) in adult and paediatric patients with relapsed or refractory ALL and adult patients in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 10.0) are updated accordingly

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

#### 5.3.6. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0046

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to add the treatment of stage 2 or 3 chronic kidney disease (CKD) and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus (T2DM), based on new clinical efficacy and safety data from study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre phase 3 study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

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

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<sup>6</sup> Cluster of differentiation 19

### 5.3.7. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0051

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to add the treatment of stage 2 or 3 chronic kidney disease (CKD) and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus (T2DM), based on new clinical efficacy and safety data from study DNE3001 (CREDESCENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre phase 3 study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

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

### 5.3.8. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/II/0150

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on data from: 1) study 20070782: a phase 3, randomized, double-blind, placebo-controlled, non-inferiority study in subjects with chemotherapy-induced anaemia receiving multi-cycle chemotherapy for the treatment of advanced stage non-small cell lung cancer (NSCLC); 2) study EPO-ANE-3010: a randomized, open-label, multicentre, phase 3 study of epoetin alfa plus standard supportive care versus standard supportive care in anaemic patients with metastatic breast cancer receiving standard chemotherapy; 3) the company core data sheet (CCDS). In addition, section 4.6 of the SmPC is revised as requested in the outcome of the PSUR single assessment procedure (PSUSA/00000932/201710) finalised in June 2018. The package leaflet and the RMP (version 9.3) are updated accordingly. Furthermore, the MAH took the opportunity to introduce minor editorial changes, update the information on local representatives and align the product information (PI) with the QRD template (version 10.0)

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

### 5.3.9. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0058

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) of study 109MS310 (listed as category 3 study in the RMP): an open-label study to assess the effects of Tecfidera (dimethyl fumarate) on lymphocyte subsets in subjects with relapsing remitting multiple sclerosis (RRMS). The RMP (version 10.1) is updated accordingly, includes updates to reflect safety information available until the data lock point (DLP) of 24 January 2019 and in line with revision 2.01 of the guidance on the format of the risk management plan (RMP) accompanying GVP module V on 'Risk management systems'

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

5.3.10. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS1601/0022;  
Linagliptin, metformin hydrochloride - JENTADUETO (CAP) -  
EMEA/H/C/002279/WS1601/0051;  
Linagliptin - TRAJENTA (CAP) - EMEA/H/C/002110/WS1601/0038

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.1 of the SmPC for Trajenta (linagliptin), update of sections 4.2, 4.4 and 5.1 of the SmPC for Jentaduetto (linagliptin/metformin) and section 5.1 of the SmPC of Glyxambi (empagliflozin/linagliptin) based on the final results from study 1218.74 (CAROLINA) (listed as a category 3 study in the RMP of Jentaduetto (linagliptin/metformin) and Trajenta (linagliptin), in fulfilment of Trajenta MEA 008.1 and Jentaduetto MEA 001.1): a phase 3 randomised, parallel group, double blind study to evaluate cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus (T2DM) at high cardiovascular risk. The package leaflet for Trajenta (linagliptin) is updated accordingly. The RMPs (version 13.0 for Jentaduetto (linagliptin/metformin) and Trajenta (linagliptin) and version 5.0 for Glyxambi (empagliflozin/linagliptin)) are updated accordingly. In addition, the MAH took the opportunity to make corrections throughout the product information for Glyxambi (empagliflozin/linagliptin) and Jentaduetto (linagliptin/metformin) and to introduce corrections to the Bulgarian, French, Swedish translations for Glyxambi (empagliflozin/linagliptin)

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

5.3.11. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0018, Orphan

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Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final report from study SNT-EAP-001 (listed as a specific obligation (SOB11 (former SOB4) in Annex II): a follow-up study of patients in the expanded access programme (SNT-EPA-001) for Raxone (idebenone) in order to collect further long-term real-world efficacy and safety data. Annex II is updated accordingly. The RMP (version 1.9) is also updated accordingly

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

5.3.12. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/X/0169

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Extension application. The RMP is updated (version 9.3) 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

### 5.3.13. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/X/0130

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Extension application. The RMP is updated (version 9.3) 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

### 5.3.14. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0107, Orphan

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Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include Revlimid (lenalidomide) in combination with rituximab for the treatment of adult patients with previously treated follicular lymphoma or marginal zone lymphoma. 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 36.2) are updated accordingly

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

### 5.3.15. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0049

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Updated of section 4.8 of the SmPC with safety data from study 109: a phase 3, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis (CF), homozygous for the deletion of phenylalanine in position 508 of the cystic fibrosis transmembrane conductance regulator (F508del-CFTR) mutation; and study 011 Part B (study 011B): a phase 3, open-label study to evaluate the pharmacokinetics, safety, and tolerability of lumacaftor in combination with ivacaftor in subjects 6 through 11 years of age with CF, homozygous for the F508del-CFTR mutation (receiving lumacaftor 200 mg in fixed-dose combination with ivacaftor 250 mg orally q12h for 24 weeks). The RMP (version 7.0) is updated accordingly

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

### 5.3.16. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0060

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Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.1, 4.2, 4.3, 4.4, 4.8 and 4.9 of the SmPC in order to update the safety information on benign or malignant neoplasia based on a EU registry study: the Ipsen global safety database and literature review. The package leaflet and the RMP (version 11) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

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



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

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Eva Segovia

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

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

### 5.3.18. [Netupitant, palonosetron - AKYNZEO \(CAP\) - EMEA/H/C/003728/X/0018](#)

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Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension application to introduce a new pharmaceutical form 'powder for concentrate for solution for infusion' and a new strength for the fixed combination of fosnetupitant (pro-drug of netupitant)/palonosetron of 235 mg/0.25 mg, to be administered intravenously (new route of administration). The RMP (version 2.4) is updated accordingly

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

### 5.3.19. [Nintedanib - OFEV \(CAP\) - EMEA/H/C/003821/II/0026, Orphan](#)

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

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

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

### 5.3.20. [Pegfilgrastim - UDENYCA \(CAP\) - EMEA/H/C/004413/II/0003](#)

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Applicant: ERA Consulting GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.6 of the SmPC to amend the safety information based on feasibility data regarding the pregnancy and lactation registry (listed as a category 3 study in the RMP). The package leaflet and the RMP (version 1.5) are updated accordingly

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

#### 5.3.21. Pemetrexed - PEMETREXED FRESENIUS KABI (CAP) - EMEA/H/C/003895/X/0009

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application to introduce a new pharmaceutical form (concentrate for solution for infusion) associated with new strength 25 mg/mL. The RMP (version 2.0) is updated accordingly

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

#### 5.3.22. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0002

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include the treatment of patients with atypical haemolytic uremic syndrome (aHUS). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 1.6) are updated accordingly. In addition, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated to include in the educational materials the risk of thrombotic microangiopathy (TMA) with the new indication

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

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

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

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

#### 5.3.24. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0024

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Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Submission of the final report of study CLDE225X2116 (listed as a category 3 study in the RMP): an interventional phase 1b/2, open-label, multicentre, dose-finding study to assess the safety and efficacy of the oral combination of LDE225 (sonidegib) and INC424 (ruxolitinib) in subjects with myelofibrosis. The RMP (version 7.1) is updated accordingly

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

#### 5.3.25. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/II/0047/G

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of 1) extension of indication to include in co administration with acetylsalicylic acid (ASA) the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) without a history of myocardial infarction who have undergone percutaneous coronary intervention (PCI) based on the final results of study D513BC00001 (THEMIS): a phase 3 multinational, randomised, double-blind, placebo controlled study to evaluate the effect of ticagrelor twice daily on the incidence of cardiovascular death, myocardial infarction or stroke in patients with T2DM. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated; 2) update of section 4.8 of the SmPC with new safety information on traumatic haemorrhages based on the final results from study D513BC00001 (THEMIS) and data from the ticagrelor clinical development programme and post-marketing data. The Package Leaflet and the RMP (version 12) are updated accordingly

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

#### 5.3.26. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/II/0030/G

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of submission of: 1) results of study NN7008-3809 (Guardian 4): safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in paediatric previously untreated patients (PUPs) with haemophilia A and; 2) results of study NN7008-4239 (Guardian 9): a multicentre, open-label trial evaluating the pharmacokinetics (PK) of NovoEight (turoctocog alfa) in relation to body mass index (BMI) in subjects with haemophilia A. In addition, the product information is brought in line with revision 3 of the 'Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products' (EMA/CHMP/BPWP/1619/1999 rev. 3) and in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Sections 2, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet are updated accordingly. The RMP (version 6) is also updated accordingly. Furthermore, the MAH took the opportunity to introduce some administrative updates in the product information

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

#### 5.3.27. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/II/0054

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to add information and a precaution regarding concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors based on final results from study GO29475 (MEA-011) (listed as a category 3 study in the RMP): a two-part, phase 1, open-label, multicentre, two-period, one-sequence study to investigate the effect of itraconazole and rifampicin on the pharmacokinetic (PK) of vemurafenib at steady state. The package leaflet and the RMP (version 12.0) are updated accordingly. In addition, the package leaflet is updated to reflect information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

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

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

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Applicant: Correvio

PRAC Rapporteur: Menno van der Elst

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

**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. Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/201903

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.2. Alogliptin – VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone - INCRESYNC (CAP) - PSUSA/00010061/201904

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Applicant(s): Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.3. Aprepitant - EMEND (CAP) - PSUSA/00000229/201903

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.4. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/201904

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Applicant: Kite Pharma EU B.V., ATMP<sup>7</sup>

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.5. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/201904

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

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

6.1.6. [Canagliflozin – INVOKANA \(CAP\); canagliflozin, metformin - VOKANAMET \(CAP\) - PSUSA/00010077/201903](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

6.1.7. [Cariprazine - REAGILA \(CAP\) - PSUSA/00010623/201904](#)

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

6.1.8. [Chenodeoxycholic acid<sup>8</sup> - CHENODEOXYCHOLIC ACID LEADIANT \(CAP\) - PSUSA/00010590/201904](#)

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Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

6.1.9. [Defibrotide - DEFITELIO \(CAP\) - PSUSA/00010086/201904](#)

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Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

6.1.10. [Dimethyl fumarate<sup>9</sup> - TECFIDERA \(CAP\) - PSUSA/00010143/201903](#)

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

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<sup>8</sup> Indicated for the treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults – centrally authorised product(s) only

<sup>9</sup> Indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS)

6.1.11. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin) (acellular, component), hepatitis b (rDNA<sup>10</sup>), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) – HEXAXIM (Art 58<sup>11</sup>); HEXACIMA (CAP); HEXYON (CAP) - PSUSA/00010091/201904

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Applicants: Sanofi Pasteur (Hexaxim, Hexacima), Sanofi Pasteur Europe (Hexyon)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

6.1.12. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/201903

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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

6.1.13. Empagliflozin – JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) - PSUSA/00010388/201904

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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

6.1.14. Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/201904

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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

6.1.15. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/201904

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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

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<sup>10</sup> Ribosomal deoxyribonucleic acid

<sup>11</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)

#### 6.1.16. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/201904

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.17. Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/201903

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.18. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/201904

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.19. Fenofibrate, pravastatin - PRAVAFENIX (CAP) - PSUSA/00001363/201904

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.20. Florbetapir (<sup>18</sup>F) - AMYVID (CAP) - PSUSA/00010032/201904

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.21. Fosaprepitant - IVEMEND (CAP) - PSUSA/00001471/201903

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure



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

6.1.22. [Glycopyrronium bromide, formoterol fumarate dihydrate - BEVESPI AEROSPHERE \(CAP\) - PSUSA/00010739/201904 \(with RMP\)](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

6.1.23. [Herpes zoster vaccine \(recombinant, adjuvanted\) - SHINGRIX \(CAP\) - PSUSA/00010678/201904](#)

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

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

6.1.24. [Histamine<sup>12</sup> - CEPLENE \(CAP\) - PSUSA/00001610/201904](#)

---

Applicant: Noventia Pharma Srl

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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

6.1.25. [Insulin glargine - ABASAGLAR \(CAP\); LANTUS \(CAP\); SEMGLEE \(CAP\); TOUJEO \(CAP\) - PSUSA/00001751/201904](#)

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Applicant(s): Eli Lilly Nederland B.V. (Abasaglar), Mylan S.A.S (Semglee), Sanofi-Aventis Deutschland GmbH (Lantus, Toujeo)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

6.1.26. [Insulin glulisine - APIDRA \(CAP\) - PSUSA/00001752/201904](#)

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Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

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

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<sup>12</sup> Indicated for the treatment of acute myeloid leukaemia (AML)

6.1.27. [Irinotecan<sup>13</sup> - ONIVYDE \(CAP\) - PSUSA/00010534/201904](#)

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

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

6.1.28. [Mannitol<sup>14</sup> - BRONCHITOL \(CAP\) - PSUSA/00009226/201904](#)

---

Applicant: Pharmaxis Europe Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

6.1.29. [Meningococcal group A, C, W-135, Y conjugate vaccine \(conjugated to tetanus toxoid carrier protein\) - NIMENRIX \(CAP\) - PSUSA/00010044/201904](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

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

6.1.30. [Methylnaltrexone bromide - RELISTOR \(CAP\) - PSUSA/00002023/201903](#)

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Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

6.1.31. [Mogamulizumab - POTELIGEO \(CAP\) - PSUSA/00010741/201903](#)

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

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

6.1.32. [Oestrogens conjugated, bazedoxifene - DUAVIVE \(CAP\) - PSUSA/00010321/201904](#)

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Applicant: Pfizer Europe MA EEIG

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<sup>13</sup> Liposomal formulation(s) only

<sup>14</sup> Indicated for the treatment of cystic fibrosis

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

#### 6.1.33. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/201904

Applicant: Shire Pharmaceuticals Ireland Limited  
PRAC Rapporteur: Rhea Fitzgerald  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.34. Patiromer - VELTASSA (CAP) - PSUSA/00010618/201904

Applicant: Vifor Fresenius Medical Care Renal Pharma France  
PRAC Rapporteur: Kirsti Villikka  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.35. Propranolol<sup>15</sup> - HEMANGIOL (CAP) - PSUSA/00010250/201904

Applicant: Pierre Fabre Dermatologie  
PRAC Rapporteur: Eva Segovia  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.36. Ramucirumab - CYRAMZA (CAP) - PSUSA/00010323/201904

Applicant: Eli Lilly Nederland B.V.  
PRAC Rapporteur: Brigitte Keller-Stanislowski  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.37. Regadenoson - RAPISCAN (CAP) - PSUSA/00002616/201904

Applicant: GE Healthcare AS  
PRAC Rapporteur: Eva Segovia  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

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<sup>15</sup> Centrally authorised product(s) only

#### 6.1.38. Siltuximab - SYLVANT (CAP) - PSUSA/00010254/201904

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Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.39. Tocilizumab - ROACTEMRA (CAP) - PSUSA/00002980/201904

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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

#### 6.1.40. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/201904

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

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. Dexmedetomidine - DEXDOR (CAP); NAP - PSUSA/00000998/201903

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Applicant(s): Orion Corporation, various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

#### 6.2.2. Enoxaparin<sup>16</sup> - INHIXA (CAP); NAP - PSUSA/00010553/201904

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Applicant(s): Techdow Europe AB (Inhixa), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

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<sup>16</sup> Biosimilar(s) only

### 6.2.3. Tenofovir disoproxil - TENOFOVIR DISOPROXIL MYLAN (CAP); TENOFOVIR DISOPROXIL ZENTIVA (CAP); VIREAD (CAP); NAP - PSUSA/00002892/201903

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Applicant(s): Mylan S.A.S (Tenofovir disoproxil Mylan), Zentiva k.s. (Tenofovir disoproxil Zentiva), Gilead Sciences Ireland UC (Viread), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

### 6.2.4. Travoprost - IZBA (CAP); TRAVATAN (CAP); NAP - PSUSA/00003011/201902

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Applicant(s): Novartis Europharm Limited (Izba, Travatan), various

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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

### 6.2.5. Zonisamide - ZONEGRAN (CAP); NAP - PSUSA/00003152/201903

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Applicant(s): Eisai GmbH (Zonegran), various

PRAC Rapporteur: Ronan Grimes

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. Ambrosia artemisiifolia<sup>17 18 19 20</sup> (NAP) - PSUSA/00010693/201904

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Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

### 6.3.2. Alprazolam (NAP) - PSUSA/00000109/201903

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Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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<sup>17</sup> 302

<sup>18</sup> Allergen for therapy

<sup>19</sup> For sublingual use only

<sup>20</sup> Medicinal product(s) authorised via decentralised procedure only

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

#### 6.3.3. Amifostine (NAP) - PSUSA/00000142/201903

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Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.4. Dermatophagoides pteronyssinus, Dermatophagoides farina<sup>21 22 23</sup> (NAP) - PSUSA/00010582/201903

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Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.5. Enoxaparin<sup>24</sup> (NAP) - PSUSA/00010560/201904

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Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.6. Erythromycin (NAP) - PSUSA/00001257/201903

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Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.7. Ezetimibe, simvastatin (NAP) - PSUSA/00001347/201903

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

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<sup>21</sup> Allergen for therapy

<sup>22</sup> For oromucosal use only

<sup>23</sup> Medicinal product(s) authorised via mutually recognition procedure and decentralised procedure only

<sup>24</sup> Except biosimilar(s)

6.3.8. Germanium (<sup>68</sup>Ge) chloride, gallium (<sup>68</sup>Ga) chloride (NAP) - PSUSA/00010364/201903

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Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

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

6.3.9. Influenza vaccine (split virion, inactivated)<sup>25</sup> (NAP) - PSUSA/00010298/201903

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Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

6.3.10. Influenza vaccine (split virion, inactivated, prepared in cell cultures) (NAP) - PSUSA/00010299/201903

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Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

6.3.11. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/201903

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Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

6.3.12. Influenza vaccine (surface antigen, inactivated, adjuvanted) (NAP) - PSUSA/00010300/201903

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Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

6.3.13. Nicorandil (NAP) - PSUSA/00002152/201902

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Applicant(s): various

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<sup>25</sup> Non centrally authorised product(s) only

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.14. Rocuronium (NAP) - PSUSA/00002656/201902

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Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

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

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

#### 6.4.1. Dibotermin alfa - INDUCTOS (CAP) - EMEA/H/C/000408/LEG 074.1

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Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 074 [detailed evaluation of the effectiveness of the current educational materials as requested in the conclusions of PSUSA/00001034/201709 adopted in April 2018] as per the request for supplementary information (RSI) adopted in January 2019

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

#### 6.4.2. Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/LEG 040

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Discussion on the association between bullous pemphigoid and saxagliptin/metformin and saxagliptin as a single active substance as requested in the conclusions of PSUSA/00002686/201811 for saxagliptin/metformin adopted in June 2019

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

#### 6.4.3. Saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/LEG 018

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Discussion on the association between bullous pemphigoid and saxagliptin/metformin and saxagliptin as a single active substance as requested in the conclusions of PSUSA/00002686/201811 for saxagliptin/metformin adopted in June 2019

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



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

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>26</sup>

#### 7.1.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/PSP/S/0079.2

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Applicant: Kite Pharma EU B.V., ATMP<sup>27</sup>

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to PSP/S/0079.1 [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 October 2019

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

#### 7.1.2. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/PSA/S/0043

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Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Substantial amendment to a protocol previously endorsed in September 2017 for a prospective, multi-country, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole using the existing European Registry on Cushing's Syndrome (ERCUSYN) in order to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

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

#### 7.1.3. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0044

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Applicant: Bayer Pharma AG (Jaydess, Luadei)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Substantial amendment to a protocol previously endorsed in February 2018 for study EURAS-LCS12: a European active surveillance study of LCS-12 (levonorgestrel intrauterine contraceptive system releasing 12 µg levonorgestrel/24h in vitro), an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to investigate whether LCS-12 is associated with an increased risk of unintended pregnancy compared to Mirena (levonorgestrel-releasing intrauterine system) and to copper IUDs

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

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<sup>26</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>27</sup> Advanced therapy medicinal product

#### 7.1.4. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/PSA/S/0041.1

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0041 [amendment to a protocol previously endorsed in June 2018 (PSP/S/0059) for a non-interventional PASS in male patients with haemophilia B receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate safety of N9-GP during long-term routine use] as per the request for supplementary information (RSI) adopted in September 2019

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

#### 7.1.5. Oral retinoids: acitretin (NAP), alitretinoin (NAP), isotretinoin (NAP) - EMEA/H/N/PSP/J/0069.2

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

PRAC Rapporteur: Ana Sofia Diniz Martins

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

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

#### 7.1.6. Tisagenlecleucel - KYMRIA (CAP) - EMEA/H/C/PSP/S/0066.3

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Applicant: Novartis Europharm Ltd, ATMP<sup>28</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0066.2 [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 October 2019

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

#### 7.1.7. Umeclidinium bromide – INCRUSE ELLIPTA (CAP), ROLUFTA ELLIPTA (CAP); umeclidinium bromide, vilanterol – ANORO ELLIPTA (CAP), LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/PSA/S/0032.3

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Applicant: Glaxo Group Limited

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<sup>28</sup> Advanced therapy medicinal product

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to PSA/S/0032.1 [substantial amendment to a protocol previously endorsed by PRAC in March 2015 (EMA/H/C/PSP/J/003.1) for study 201038: a post-authorisation safety (PAS) observational cohort study to quantify the incidence of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients using inhaled umeclidinium bromide/vilanterol (UMEC/VI) combination, inhaled UMEC, or tiotropium] as per the request for supplementary information (RSI) adopted in March 2019

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

#### 7.1.8. Valproate (NAP) - EMA/H/N/PSP/J/0074.1

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

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to PSP/J/0074 [protocol for an observational study to evaluate and identify the best practices for switching of valproate in clinical practice, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in February 2019

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

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

#### 7.2.1. Dimethyl fumarate - TECFIDERA (CAP) - EMA/H/C/002601/MEA 008.3

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 008.3 [updated protocol for study 109MS402: Biogen multiple sclerosis (MS) pregnancy exposure registry to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product] as per the request for supplementary information (RSI) adopted in June 2019

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

#### 7.2.2. Epoetin zeta - RETACRIT (CAP) - EMA/H/C/000872/MEA 033

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed in September 2015 (MEA 031.1) for study PMS-830-09-0082 (PASCO II): a post-authorisation safety cohort observation of Retacrit (epoetin zeta) administered subcutaneously for the treatment of renal anaemia

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<sup>29</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

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

### 7.2.3. Epoetin zeta - SILAPO (CAP) - EMEA/H/C/000760/MEA 033

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Applicant: Stada Arzneimittel AG

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed in September 2015 (Retacrit, MEA 031.1) for study PMS-830-09-0082 (PASCO II): a post-authorisation safety cohort observation of Silapo (epoetin zeta) administered subcutaneously for the treatment of renal anaemia

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

### 7.2.4. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/MEA 009.1

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Applicant: Shire Services BVBA

PRAC Rapporteur: Annika Folin

Scope: Amendment to protocol for study SHP617-400 (EU AIR) (0918-400): a non-interventional (PASS) registry study: A European multicentre, multi-country, post-authorisation observational study (registry) of patients with chronic adrenal insufficiency

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

### 7.2.5. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.2

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001.1 [protocol for a long-term observational study to evaluate and further characterize the events of thrombocytopenia, glomerulonephritis and retinal toxicity/eye disease related to vitamin A deficiency when Tegsedi (inotersen) is prescribed in normal clinical practice, consisting of a protocol for a cohort of inotersen-exposed patients (TEG4001) and a protocol for an external comparator cohort (TEG4003)] as per the request for supplementary information (RSI) adopted in June 2019

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

### 7.2.6. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 002.2

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002.1 [protocol for study TEG4002: a retrospective chart review for evaluating adherence to and effectiveness of the proposed platelet monitoring schedule, proposed cut-off points, dose adaptation, and initiation of corticosteroids on thrombocyte recovery] as per the request for supplementary information (RSI) adopted in June 2019

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

### 7.2.7. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 003.3

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Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 003.2 [protocol and statistical analysis plan for a non-interventional non-imposed PASS: a pooled analysis of the incidence of acute myelogenous leukaemia, myelodysplastic syndrome, and other secondary primary malignancies in patients treated with niraparib] as per the request for supplementary information (RSI) adopted in May 2019

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

### 7.2.8. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study P19-633: a post-marketing registry-based prospective cohort study of long-term safety of risankizumab in real world setting in Denmark and Sweden [final study report due in December 2031]

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

### 7.2.9. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 002

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study P16-751 on pregnancy exposures and outcomes in psoriasis patients treated with risankizumab: a cohort study utilising large healthcare databases with mother-baby linkage in the United States [final study report due in Q3 2026]

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

### 7.2.10. Sotagliflozin - ZYNQUISTA (CAP) - EMEA/H/C/004889/MEA 004

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Protocol for a PASS to evaluate the risk of malignancies (bladder, renal, breast, Leydig cell, pancreatic, thyroid, and prostate cancers) in adult patients with type 1 diabetes mellitus (T1DM) using sotagliflozin [final clinical study report (CSR) expected in April 2030] (from initial opinion/MA)

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

### 7.2.11. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 028.2

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 028.1 [protocol for study PGL18-001: a retrospective drug utilisation study (DUS) through a chart review across four major EU countries [final study report expected by Q2 2020], as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMA/H/A-20/1460)] 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>30</sup>

None

### 7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>31</sup>

#### 7.4.1. Canagliflozin - INVOKANA (CAP) - EMA/H/C/002649/II/0045/G

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of the submission of the final reports for three non-interventional studies (listed as category 3 studies in the RMP): 1) study RRA-21410: an epidemiology study to characterise the risk of lower limb amputations (LLA) in subjects in the overall type 2 diabetes mellitus (T2DM) population and in a subpopulation with established cardiovascular disease (CVD); 2) study NAP4001: a meta-analysis from studies DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)), DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM), and DNE3001 (CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy) to characterize the risk of LLA in subjects at high risk for cardiovascular (CV) events and/or progression of kidney disease; 3) meta-analysis from CANVAS, CANVAS-R and CREDENCE to evaluate the incidence of bladder cancer in the canagliflozin group compared to the placebo group

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

#### 7.4.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMA/H/C/002656/II/0050/G

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of the submission of the final reports for three non-interventional studies (listed as category 3 studies in the RMP): 1) study RRA-21410: an epidemiology study to characterise the risk of lower limb amputations (LLA) in subjects in the overall type 2 diabetes mellitus (T2DM) population and in a subpopulation with

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<sup>30</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>31</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

established cardiovascular disease (CVD); 2) study NAP4001: a meta-analysis from studies DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)), DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM), and DNE3001 (CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy) to characterize the risk of LLA in subjects at high risk for cardiovascular (CV) events and/or progression of kidney disease; 3) meta-analysis from CANVAS, CANVAS-R and CREDENCE to evaluate the incidence of bladder cancer in the canagliflozin group compared to the placebo group

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

#### 7.4.3. Colistimethate sodium - COLOBREATHE (CAP) - EMEA/H/C/001225/II/0044/G

Applicant: Teva B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of the submission of the final report for study CLB-MD-05 (listed as a category 3 study in the RMP): an observational safety study of Colobreathe (colistimethate sodium dry powder for inhalation) compared with other inhaled anti-pseudomonal antibiotics in cystic fibrosis patients using cystic fibrosis registries. The RMP (version 9.0) is updated accordingly, together with the results from study CLB-MD-08: (listed as a category 3 study in the RMP): a non-interventional PASS cross-sectional survey study to evaluate the effectiveness of Colobreathe (colistimethate sodium) risk minimisation educational programme among healthcare professionals and patients, as per the outcome of variation II/39 adopted in February 2019

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

#### 7.4.4. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1654/0228; LIFMIOR (CAP) - EMEA/H/C/004167/WS1654/0022

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study B1801311 (British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR)) (listed as a category 3 study in the RMP): a prospective cohort study that compared patients treated with biologic interventions (etanercept, adalimumab and ustekinumab) and patients with similar disease characteristics but exposed only to conventional non-biologic systemic therapies

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

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

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

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

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

#### 7.4.6. Nalmefene - SELINCRO (CAP) - EMEA/H/C/002583/II/0025

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Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Submission for the final study reports for: 1) study 15649A on the use of Selincro (nalmefene) using European databases: a cohort design study using longitudinal electronic medical records or claims databases; 2) study 14910A: a non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro (nalmefene) and frequency of selected adverse reactions in routine clinical practice

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

#### 7.4.7. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0030, Orphan

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Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final report for study 16657, EXPERT (EXPosurE Registry RiociguaT in patients with pulmonary hypertension) (listed as a category 3 study in the RMP) to collect information about the long term use of Adempas (riociguat) in real clinical practice. The RMP (version 7.1) is updated accordingly

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

#### 7.4.8. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/II/0025

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Submission of the final survey reports (listed as a category 3 study in the RMP) for patients and healthcare professionals (HCPs) to assess the effectiveness of the education materials. As part of the submission, the MAH proposes a revised patient card

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



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

### 7.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.11

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 024.10 [Annual report on adverse events and/or lack of efficacy, immunological data, follow-up growth disturbances in children and data on urinary hexose tetrasaccharide (Hex4) from the Pompe registry: a global, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children] as per the request for supplementary information (RSI) as adopted in April 2019

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

### 7.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.11

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 025.10 [annual report on data on patients with renal or hepatic insufficiency from the Pompe registry: a global, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children] as per the request for supplementary information (RSI) adopted in April 2019

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

### 7.5.3. Autologous CD34<sup>+</sup> enriched cell fraction that contains CD34<sup>+</sup> cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/ANX 004.2

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Applicant: Orchard Therapeutics (Netherlands) BV, ATMP<sup>32</sup>

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to ANX 004.1 [biennial progress report for study GSK2696273 entitled 'adenosine deaminase severe combined immunodeficiency (ADA-SCID) registry for patients treated with Strimvelis gene therapy: long-term prospective, non-interventional follow-up of safety and effectiveness' (PSP/004) [final clinical study report (CSR) after the 50<sup>th</sup> patient has 15 year follow-up visit - Q4 2037] as per the request for supplementary information (RSI) adopted in June 2019

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

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<sup>32</sup> Advanced therapy medicinal product

#### 7.5.4. [Dapagliflozin - EDISTRIDE \(CAP\) - EMEA/H/C/004161/MEA 006.2](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTI) and evaluating severe complications of UTI [final clinical study report (CSR) due in 2020]

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

#### 7.5.5. [Dapagliflozin - EDISTRIDE \(CAP\) - EMEA/H/C/004161/MEA 007.2](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.6. [Dapagliflozin - EDISTRIDE \(CAP\) - EMEA/H/C/004161/MEA 008.2](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.7. [Dapagliflozin - EDISTRIDE \(CAP\) - EMEA/H/C/004161/MEA 009.2](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

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

#### 7.5.8. [Dapagliflozin - FORXIGA \(CAP\) - EMEA/H/C/002322/MEA 001.7](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a

pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTI) and evaluating severe complications of UTI [final clinical study report (CSR) due in 2020]

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

#### 7.5.9. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 002.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.10. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 003.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.11. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 004.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

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

#### 7.5.12. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 005.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTI) and evaluating severe complications of UTI [final clinical study report (CSR) due in 2020]

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

#### 7.5.13. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 006.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.14. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 007.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.15. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 008.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

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

#### 7.5.16. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 008.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTI) and evaluating severe complications of UTI [final clinical study report (CSR) due in 2020]

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

#### 7.5.17. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 009.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a

pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.18. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 010.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.19. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 011.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

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

#### 7.5.20. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001.3

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

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

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

#### 7.5.21. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/MEA 009

Applicant: Shire Services BVBA

PRAC Rapporteur: Annika Folin

Scope: Interim report for study SHP617-400 (EU AIR): a non-interventional (PASS) registry study: A European multicentre, multi-country, post-authorisation observational study (registry) of patients with chronic adrenal insufficiency

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

#### 7.5.22. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/MEA 003

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Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Second interim results for study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTI) and evaluating severe complications of UTI [final clinical study report (CSR) due in 2020]

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

#### 7.5.23. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/MEA 004

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Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Second interim results for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.24. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/MEA 005

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Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Second interim results for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2020]

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

#### 7.5.25. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/MEA 006

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Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Second interim results for study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

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

#### 7.5.26. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.6

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 044.3 [first interval safety report for study

CNT01275PSO4056: 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

## 7.6. Others

### 7.6.1. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/MEA 075

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Interim study results for study C1CL670F2202: a randomized, open-label, multicentre, two arm, phase 2 study allowing to evaluate the safety of deferasirox granules in paediatric patients with iron overload [final clinical study report (CSR) due in June 2021] (from X/54)

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

### 7.6.2. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/MEA 022.1

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Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 022 relating to the statistical analysis plan (SAP) [SAP and protocol for study E7389-M044-504: an observational post-authorisation, single-arm, prospective, multicentre cohort study to investigate the frequency of and time to resolution of eribulin-induced or aggravated peripheral neuropathy (PN) in patients with locally advanced or metastatic breast cancer in a real-life setting (from variation II/33)] as per the request for supplementary information (RSI) adopted in April 2019

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

### 7.6.3. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.5

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Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 005.4 [feasibility assessment conducted in US and non-US healthcare databases for study C38072-AS-50027 (listed as category 3 study in the RMP): a long-term non-interventional cohort study comparing the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using secondary administrative healthcare data [final clinical study report (CSR) expected January 2020]] as per the request for supplementary information (RSI) adopted in February 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)

None

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

## 8.1. Annual reassessments of the marketing authorisation

### 8.1.1. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0018 (without RMP)

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

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

### 8.1.2. 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., ATMP<sup>33</sup>

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual reassessment of the marketing authorisation

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

### 8.1.3. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0078 (without RMP)

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Annual reassessment of the marketing authorisation

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

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<sup>33</sup> Advanced therapy medicinal product(s)



#### 8.1.4. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0036 (without RMP)

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Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.5. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0041 (without RMP)

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Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.6. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/S/0007 (without RMP)

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Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Annual reassessment of the marketing authorisation

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

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

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

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

## 8.2. Conditional renewals of the marketing authorisation

#### 8.2.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0035 (without RMP)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

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

#### 8.2.2. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/R/0032 (with RMP)

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Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

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

### 8.3. Renewals of the marketing authorisation

#### 8.3.1. [Ciclosporin - IKERVIS \(CAP\) - EMEA/H/C/002066/R/0017 \(without RMP\)](#)

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Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.2. [Denosumab - PROLIA \(CAP\) - EMEA/H/C/001120/R/0082 \(without RMP\)](#)

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.3. [Empagliflozin, metformin - SYNJARDY \(CAP\) - EMEA/H/C/003770/R/0044 \(with RMP\)](#)

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.4. [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

#### 8.3.5. [Human papillomavirus vaccine \[types 6, 11, 16, 18, 31, 33, 45, 52, 58\] \(recombinant, adsorbed\) - GARDASIL 9 \(CAP\) - EMEA/H/C/003852/R/0035 \(without RMP\)](#)

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Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.6. [Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA \(CAP\) - EMEA/H/C/003687/R/0033 \(without RMP\)](#)

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Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.7. [Oritavancin - ORBACTIV \(CAP\) - EMEA/H/C/003785/R/0027 \(without RMP\)](#)

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.8. [Tolvaptan - JINARC \(CAP\) - EMEA/H/C/002788/R/0027 \(without RMP\)](#)

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

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**

None

### **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

None

### 12.4. Cooperation within the EU regulatory network

12.4.1. Heads of Medicines Agencies (HMA)-EMA joint big data taskforce – draft recommendations

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**Action:** For discussion

### 12.5. Cooperation with International Regulators

None

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

None

### 12.7. PRAC work plan

None

### 12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q3 2019 and predictions

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**Action:** For discussion

### 12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

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None

12.9.2. Pharmacovigilance inspections

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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. Periodic safety update reports single assessment (PSUSA) – updates to the assessment report template – call for volunteers

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**Action:** For discussion

### 12.10.4. Union reference date (EURD) list –maintenance process optimisation

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PRAC lead: Menno van der Elst

**Action:** For adoption

### 12.10.5. PSURs repository

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None

### 12.10.6. 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

### 12.11.2. Signal Management Review Technical (SMART) methods activities - update

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**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

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

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None

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

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

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None

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

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None

## 12.16. Community procedures

### 12.16.1. Referral procedures for safety reasons

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None

## 12.17. Renewals, conditional renewals, annual reassessments

None

## 12.18. Risk communication and transparency

### 12.18.1. Public participation in pharmacovigilance

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None

### 12.18.2. Safety communication

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None

## 12.19. Continuous pharmacovigilance

### 12.19.1. Incident management

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None

## 12.20. Others

None

### 12.20.1. Type II variations – PRAC and CHMP involvement

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PRAC lead: Ghania Chamouni, Laurence de Fays, Martin Huber, Eva Segovia, 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/)