



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines Pharmacovigilance and Committees Division

## Pharmacovigilance Risk Assessment Committee (PRAC)

### Draft agenda for the meeting on 09-12 July 2018

Chair: June Raine – Vice-Chair: Almath Spooner

09 July 2018, 13:00 – 19:30, room 3/A

10 July 2018, 08:30 – 19:30, room 3/A

11 July 2018, 08:30 – 19:30, room 3/A

12 July 2018, 08:30 – 16:00, room 3/A

Organisational, regulatory and methodological matters (ORGAM)

26 July 2018, 09:00-12:00, room 9/B, via teleconference

#### **Health and safety information**

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

#### **Disclaimers**

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

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

#### **Note on access to documents**

Some documents mentioned in the agenda cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to ongoing 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 09-12 July 2018. See July 2018 PRAC minutes (to be published post September 2018 PRAC meeting).

### **1.2. Agenda of the meeting on 09-12 July 2018**

**Action:** For adoption

### **1.3. Minutes of the previous meeting on 11-14 June 2018**

**Action:** For adoption

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

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

None

### **2.2. Ongoing procedures**

None

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

None

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

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

None

## 3.2. Ongoing procedures

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

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

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

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

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

## 3.3. Procedures for finalisation

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

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Martin Huber

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

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

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

None

## 3.5. Others

None

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

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

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

#### 4.1.1. Dasabuvir – EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP)

---

Applicant(s): AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of interstitial lung disease

**Action:** For adoption of PRAC recommendation

EPITT 19257 – New signal

Lead Member State(s): ES

#### 4.1.2. Montelukast (NAP)

---

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of dysphemia (speech disorders)

**Action:** For adoption of PRAC recommendation

EPITT 19275 – New signal

Lead Member State(s): FI

#### 4.1.3. Pembrolizumab – KEYTRUDA (CAP)

---

Applicant(s): Merck Sharp & Dohme B.V.

PRAC Rapporteur: Sabine Straus

Scope: Signal of systemic inflammatory response syndrome (SIRS)

**Action:** For adoption of PRAC recommendation

EPITT 19267 – New signal

Lead Member State(s): NL

#### 4.1.4. Perindopril (NAP)

---

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of Raynaud's phenomenon

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<sup>2</sup> Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required



**Action:** For adoption of PRAC recommendation

EPITT 19248 – New signal

Lead Member State(s): DK

## 4.2. New signals detected from other sources

### 4.2.1. Certolizumab pegol – CIMZIA (CAP); etanercept – ENBREL (CAP), LIFMIOR (CAP); golimumab – SIMPONI (CAP); infliximab – REMICADE (CAP)

---

Applicant(s): Janssen Biologics B.V. (Remicade, Simponi), Pfizer Limited (Enbrel, Lifmior), UCB Pharma S.A. (Cimzia)

PRAC Rapporteur: To be appointed

Scope: Signal of risk for lichenoid skin reactions for Tumour necrosis factor alfa (TNF $\alpha$ ) inhibitors

**Action:** For adoption of PRAC recommendation

EPITT 19128 – New signal

Lead Member State(s): SE, UK

### 4.2.2. Amitriptyline (NAP); dosulepin (NAP); oxybutynin - KENTERA (CAP), NAP; paroxetine (NAP); procyclidine (NAP); tolterodine( NAP)

---

Applicant(s): Nicobrand Limited (Kentera), various

PRAC Rapporteur: To be appointed

Scope: Signal of dementia

**Action:** For adoption of PRAC recommendation

EPITT 19263 – New signal

Lead Member State(s): AT, BE, DE, ES, GR, NL, SE

### 4.2.3. Olmesartan (NAP)

---

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of risk of autoimmune hepatitis

**Action:** For adoption of PRAC recommendation

EPITT 19258 – New signal

Lead Member State(s): DE, NL

### 4.2.4. Propranolol (NAP)

---

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of increased risk of Parkinson's disease

**Action:** For adoption of PRAC recommendation

EPITT 19223 – New signal

Lead Member State(s): ES

#### 4.2.5. Ranibizumab – LUCENTIS (CAP)

---

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of angioedema

**Action:** For adoption of PRAC recommendation

EPITT 19245 – New signal

Lead Member State(s): SE

#### 4.2.6. Thiamazole (NAP)

---

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of pancreatitis

**Action:** For adoption of PRAC recommendation

EPITT 19274 – New signal

Lead Member State(s): DE

#### 4.2.7. Vemurafenib – ZELBORAF (CAP)

---

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of cardiac failure

**Action:** For adoption of PRAC recommendation

EPITT 19268 – New signal

Lead Member State(s): SE

### 4.3. Signals follow-up and prioritisation

- 4.3.1. Fluoroquinolones:  
Ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)
- 

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

PRAC Rapporteur: Martin Huber

Scope: Signal of aortic aneurysm and dissection

**Action:** For adoption of PRAC recommendation

EPITT 18651 – Related to October 2016

Lead Member State: DE

- 4.3.2. Levothyroxine (NAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP)
- 

Applicant(s): AbbVie Deutschland GmbH, various

PRAC Rapporteur: Menno van der Elst

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

**Action:** For adoption of PRAC recommendation

EPITT 18896 – Follow-up to February 2018

- 4.3.3. Abacavir - ZIAGEN (CAP) - EMEA/H/C/000252/SDA/091, NAP; abacavir, dolutegravir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/SDA/008; abacavir, lamivudine - KIVEXA (CAP) - EMEA/H/C/000581/SDA/047, NAP; abacavir, lamivudine, zidovudine - TRIZIVIR (CAP) - EMEA/H/C/000338/SDA/092, NAP; atazanavir - REYATAZ (CAP) - EMEA/H/C/000494/SDA/087; atazanavir, cobicistat - EVOTAZ (CAP) - EMEA/H/C/003904/SDA/004; bicitegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP); darunavir - PREZISTA (CAP) - EMEA/H/C/000707/SDA/074; darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/SDA/006; darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/SDA/012; didanosine (NAP); dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/SDA/010; dolutegravir, rilpivirine - JULUCA (CAP); efavirenz - STOCRIN (CAP) - EMEA/H/C/000250/SDA/072.1, SUSTIVA (CAP) - EMEA/H/C/000249/SDA/083.1, NAP; efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/SDA/043.1; elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP); elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP); emtricitabine - EMTRIVA (CAP) - EMEA/H/C/000533/SDA/052.1; emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP); emtricitabine, rilpivirine, tenofovir disoproxil - EVIPLERA (CAP); emtricitabine, tenofovir alafenamide - DESCOVY (CAP); emtricitabine, tenofovir disoproxil - TRUVADA (CAP), NAP; enfuvirtide - FUZEON (CAP) - EMEA/H/C/000514/SDA/115; etravirine - INTELENCE (CAP) - EMEA/H/C/000900/SDA/051; fosamprenavir - TELZIR (CAP) - EMEA/H/C/000534/SDA/077; indinavir - CRIXIVAN (CAP) - EMEA/H/C/000128/SDA/040; lamivudine - EPIVIR (CAP) - EMEA/H/C/000107/SDA/054, NAP; lamivudine, tenofovir (NAP); lamivudine,

zidovudine - COMBIVIR (CAP) - EMEA/H/C/000190/SDA/040, NAP; lopinavir, ritonavir - KALETRA (CAP); maraviroc - CELSENTRI (CAP) - EMEA/H/C/000811/SDA/042; nevirapine - VIRAMUNE (CAP) - EMEA/H/C/000183/SDA/062; raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/SDA/058; rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/SDA/027; ritonavir - NORVIR (CAP), NAP; saquinavir - INVIRASE (CAP) - EMEA/H/C/000113/SDA/066; stavudine - ZERIT (CAP) - EMEA/H/C/000110/SDA/065; tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/SDA/275.1, NAP; tipranavir - APTIVUS (CAP) - EMEA/H/C/000631/SDA/070; zidovudine (NAP)

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Applicant(s): AbbVie Deutschland GmbH & Co. KG (Kaletra, Norvir), Boehringer Ingelheim International GmbH (Aptivus, Viramune), Bristol-Myers Squibb and Gilead Sciences Ltd. (Atripla), Bristol-Myers Squibb Pharma EEIG (Evotaz, Reyataz, Sustiva, Zerit), Gilead Sciences International Limited (Biktarvy, Viread), Gilead Sciences Ireland UC (Descovy, Emtriva, Eviplera, Genvoya, Odefsey, Stribild, Truvada), Janssen-Cilag International NV (Eduvant, Intelence, Prezista, Rezolsta, Symtuza), Merck Sharp & Dohme B.V. (Isentress, Stocrin), Merck Sharp & Dohme Limited (Crixivan), Roche Registration GmbH (Fuzeon, Invirase), Viiv Healthcare Limited (Celsentri, Combivir, Epivir, Juluca, Kivexa, Telzir, Tivicay, Triumeq, Trizivir, Ziagen), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of autoimmune hepatitis

**Action:** For adoption of PRAC recommendation

EPITT 18956 – Follow-up to March 2018

#### 4.3.4. Hormonal contraceptives:

Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol<sup>3</sup> (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, norgestrel acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene<sup>4</sup> (NAP); ethinylestradiol, gestodene<sup>5</sup> (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol<sup>6</sup> (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP)

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal related to a known association between hormonal contraceptives and a small increase in breast cancer following a recent publication

**Action:** For adoption of PRAC recommendation

EPITT 19143 – Follow-up to March 2018

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<sup>3</sup> Contraception indication

<sup>4</sup> All route of administrations except transdermal

<sup>5</sup> Transdermal application

<sup>6</sup> Combination pack

#### 4.3.5. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP), HIZENTRA (CAP), HYQVIA (CAP), KIOVIG (CAP), PRIVIGEN (CAP); NAP

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Applicant(s): Baxalta Innovations GmbH (HyQvia), Baxter AG (Kiovig), CSL Behring GmbH (Privigen, Hizentra), Instituto Grifols, S.A. (Flebogamma DIF), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of lupus-like syndrome and related terms

**Action:** For adoption of PRAC recommendation

EPITT 19098 – Follow-up to April 2018

#### 4.3.6. Hydrochlorothiazide (NAP); Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP)

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Applicant(s): Actavis Group PTC ehf (Actelsar HCT), Bayer Pharma AG (Kinzalkomb, PritorPlus), Boehringer Ingelheim International (MicardisPlus), Krka, d.d. (Ifirmacombi, Tolucombi), Noden Pharma DAC (Rasilez HCT), Novartis Europharm Limited (Copalia HCT, Dafiro HCT), Sanofi-aventis groupe (Irbesartan Hydrochlorothiazide Zentiva, Karvezide), Sanofi Clir SNC (CoAprovel), Teva B.V. (Irbesartan/Hydrochlorothiazide Teva), various

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of skin cancer

**Action:** For adoption of PRAC recommendation

EPITT 19138 – Follow-up to June 2018

## 5. Risk management plans (RMPs)

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

#### 5.1.1. Axalimogene filolisbac - EMEA/H/C/004473

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ATMP<sup>7</sup>

Scope: Treatment of cervical cancer

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

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

### 5.1.2. Buprenorphine - EMEA/H/C/004651

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Scope: Treatment of opioid dependence within a framework of medical, social and psychological treatment

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

### 5.1.3. Doxorubicin hydrochloride - EMEA/H/C/004110

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Scope: Treatment of breast and ovarian cancer

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

### 5.1.4. Galcanezumab - EMEA/H/C/004648

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Scope: Prophylaxis of migraine

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

### 5.1.5. Influenza vaccine surface antigen inactivated prepared in cell cultures - EMEA/H/C/004814

---

Scope: Prophylaxis of influenza in adults and children from 4 years of age

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

### 5.1.6. Mogamulizumab - EMEA/H/C/004232, Orphan

---

Applicant: Kyowa Kirin Limited

Scope: Treatment of cutaneous T-cell lymphoma

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

### 5.1.7. Pacritinib - EMEA/H/C/004793, Orphan

---

Applicant: CTI Life Sciences Limited

Scope: Treatment of disease-related splenomegaly and control of symptoms in patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF) who have thrombocytopenia (platelet counts  $\leq 100,000/\mu\text{L}$ )

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

### 5.1.8. Pegfilgrastim - EMEA/H/C/004802

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Scope: Treatment of neutropenia

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

### 5.1.9. [Ropeginterferon alfa-2b - EMEA/H/C/004128, Orphan](#)

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Applicant: AOP Orphan Pharmaceuticals AG

Scope: Treatment of polycythemia vera

**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. [Ambrisentan - VOLIBRIS \(CAP\) - EMEA/H/C/000839/II/0055](#)

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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the RMP (version 7.6) in order to remove the educational materials for healthcare professionals given the information provide in the product information and the experience gained in using ambrisentan, as requested by PRAC in the PSUR signal assessment procedure (PSUSA/00000129/201706) concluded in January 2018. Annex II of the product information is updated accordingly. In addition, the MAH took the opportunity to update Annex II to include minor changes including the correction of typographical errors

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

### 5.2.2. [Bosentan - STAYVEER \(CAP\) - EMEA/H/C/002644/II/0023](#)

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Applicant: Marklas Nederlands BV

PRAC Rapporteur: Caroline Laborde

Scope: Update of Annex II.D following the submission of the thirteenth and final study report for the DUO registry (listed as a category 3 study in the RMP): a non-interventional post-approval safety study and additional risk minimisation measure in the bosentan EU RMP. The RMP (version 9.1) is updated accordingly

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

### 5.2.3. [Bosentan - TRACLEER \(CAP\) - EMEA/H/C/000401/II/0086](#)

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Applicant: Actelion Registration Limited

PRAC Rapporteur: Caroline Laborde

Scope: Update of Annex II.D following the submission of the thirteenth and final study report for the DUO registry (listed as a category 3 study in the RMP): a non-interventional PASS and additional risk minimisation measure in the bosentan EU RMP. The RMP (version 9.1) is updated accordingly

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

### 5.2.4. [Bosutinib - BOSULIF \(CAP\) - EMEA/H/C/002373/II/0030](#)

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Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Update of the RMP (version 4.3) as requested by CHMP in variation II/25/G (REC 014) concluded in February 2018. In addition, the MAH took the opportunity to extend the due date of the final clinical study report for the specific obligation (SOB) for the single arm open-label multicentre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. Annex II is updated accordingly

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

#### 5.2.5. [Infliximab - INFLECTRA \(CAP\) - EMEA/H/C/002778/II/0060](#)

---

Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 8.0) to introduce the new RMP template, update some milestones of the pharmacovigilance plan and delete some safety concerns from the educational material to healthcare professionals

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

#### 5.2.6. [Infliximab - REMICADE \(CAP\) - EMEA/H/C/000240/II/0214](#)

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 17.0) and Annex II-D of the product information to remove the educational material for healthcare professionals. In addition, the MAH took the opportunity to update the package leaflet with some missing warnings and adverse drug reactions (ADR) already reflected in the SmPC, as requested by CHMP, and to introduce some minor QRD-related changes

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

#### 5.2.7. [Infliximab - REMSIMA \(CAP\) - EMEA/H/C/002576/II/0051](#)

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Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 8.0) to introduce the new RMP template, update some milestones of the pharmacovigilance plan and delete some safety concerns from the educational material to healthcare professionals

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

#### 5.2.8. [Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX \(CAP\) - EMEA/H/C/002226/II/0078](#)

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Applicant: Pfizer Limited



PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 8.0) to reflect changes requested in the conclusions of variations II/49 and II/73 adopted by CHMP in November 2016 and February 2018 respectively. The RMP is also revised to get aligned with the current EU RMP template, as per GVP module V revision 2 on 'Risk management systems' including proposals for the removal of some important potential risks: 'Guillain-Barré syndrome', 'purpura', 'vasculitis', 'acute disseminated encephalomyelitis', 'brachial neuritis', 'anaphylaxis', 'change in meningococcal epidemiology/serogroup replacement', 'lack of efficacy', 'administration via the intravascular', 'intra dermal or subcutaneous route', and 'administration to patients with thrombocytopenia or any coagulation disorder with a risk of haemorrhage'. In addition, the MAH proposed to remove the missing information on 'use in patients with chronic diseases' and 'use during pregnancy and lactation'

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

#### 5.2.9. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0092, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 21.0) in order to delete 'myelosuppression' as an important identified risk and to reclassify 'cardiac failure' from an important potential to an important identified risk. In addition, changes in the definition of the identified risks 'hepatotoxicity' and 'fluid retention' have been implemented

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

#### 5.2.10. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0133

Applicant: Roche Registration GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Update of the RMP (version 16) to discontinue the guided questionnaires (GQ) for neurological and psychiatric adverse events (NPAE), hepatobiliary disorders and hypothermia

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

#### 5.2.11. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0023

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of the RMP (version 9) in order to remove PASS D5160C00022 (listed as a category 3 study in the RMP): 'an open label, multinational, multicentre, real world treatment study of single agent osimertinib for patients with advanced/metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have received prior therapy with an EGFR tyrosine kinase inhibitor (EGFR-TKI) (ASTRIS)' from the pharmacovigilance plan

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

#### 5.2.12. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0099

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 5.1) in order to add study 20160176 (listed as category 3 in the RMP): a retrospective cohort study of female breast cancer patients aged 66 years and over selected from the US Surveillance, Epidemiology and End Results (SEER)-Medicare database to estimate the risk of acute myeloid leukaemia/myelodysplastic syndrome for breast cancer patients, as a new pharmacovigilance activity. In addition, the MAH submitted a draft protocol for study 20160176

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

#### 5.2.13. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0144

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 16.0) to remove the additional risk minimisation measure of educational outreaches for the important identified risk of 'infusion related reactions' and 'acute infusion related reactions' (IRR)

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

#### 5.2.14. Zoledronic acid - ZOLEDRONIC ACID MYLAN (CAP) - EMEA/H/C/002482/WS1370/0015

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Applicant: Mylan S.A.S

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 7.0) to implement the latest RMP template and to include 'and other anatomical sites' in addition to 'osteonecrosis of the jaw' as an important identified risk, to be aligned with the conclusions of the PSUSA procedure for zoledronic acid (PSUSA/00003149/201608) concluded by PRAC/CHMP in April 2017

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

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

#### 5.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/X/0117/G

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped applications consisting of: 1) extension application to add two new strengths of 50 mg and 87.5 mg for solution for injection in a pre-filled syringe with needle guard for subcutaneous (SC) administration; 2) variation to include paediatric use of polyarticular juvenile idiopathic arthritis (2 years and above) for solution for injection (50 mg, 87.5 mg and 125 mg). The RMP (version 25.0) is updated accordingly. In addition, the

MAH took the opportunity to implement minor editorial changes in the product information

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

### 5.3.2. [Blinatumomab - BLINCYTO \(CAP\) - EMEA/H/C/003731/II/0011, Orphan](#)

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, and amend the safety information. The labelling and the RMP (version 4.0) are updated accordingly

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

### 5.3.3. [Canagliflozin - INVOKANA \(CAP\) - EMEA/H/C/002649/II/0034](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC in order to include the safety and efficacy information on cardiovascular events following the final results from the CANVAS programme consisting of study DIA3008 (CANVAS study): a phase 3 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM); and study DIA4004 (CANVAS-R study): a phase 4 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM. The package leaflet and the RMP (version 7.2) are updated accordingly

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

### 5.3.4. [Canagliflozin, metformin - VOKANAMET \(CAP\) - EMEA/H/C/002656/II/0034](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC in order to include the safety and efficacy information on cardiovascular events following the final results from CANVAS programme consisting of study DIA3008 (CANVAS study): a phase 3 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM); and study DIA4004 (CANVAS-R study): a phase 4 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM. The package leaflet and the RMP (version 7.2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest QRD template (version 10)

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

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

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include the combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.1) are updated accordingly. In addition, the MAH took the opportunity to update the contact details of the Lithuanian and Slovenian local representatives in the package leaflet

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

### 5.3.6. Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/II/0033, Orphan

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to reflect the results from the paediatric study DACOGENAML2004: a phase 1-2 safety and efficacy study of Dacogen (decitabine) in sequential administration with cytarabine in children with relapsed or refractory acute myeloid leukaemia' as per the requirement of Article 46 of Regulation (EC) No1901/2006. The RMP (version 3.1), in line with the revision 2 of the RMP template, is updated accordingly. In addition, the MAH took the opportunity to update section 4.4 of the SmPC to align the safety warning related to sodium excipient with the Annex to the revised European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The package leaflet is updated accordingly. Moreover, the contact details of the local representative in Slovenia are updated in the package leaflet

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

### 5.3.7. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/X/0004/G

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 200 mg solution for injection in pre-filled syringe with safety system (PFS-S) and pre-filled pen (PFP); 2) extensions of indication to add as indications: 'add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, who are inadequately controlled with medium-to-high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment, including those with or without an eosinophilic phenotype', 'maintenance therapy to improve lung function' and 'maintenance therapy to reduce oral steroid use and improve lung function in steroid-dependent asthma patients' based on pivotal studies, namely: study DRI12544: a randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma; study LIBERTY ASTHMA QUEST: a randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma; and study VENTURE: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe

steroid dependent asthma. As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH proposed to merge the SmPCs for the 200 mg and 300 mg strengths

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

#### 5.3.8. [Eltrombopag - REVOLADE \(CAP\) - EMEA/H/C/001110/II/0049](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia. 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 50.0) are updated accordingly

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

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

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) submission of the final report from study ELX-PH-08 (listed as a category 3 study in the RMP). This is an in vitro evaluation study aimed to investigate the effects on treating primary cultures of cryopreserved human hepatocytes with eluxadoline on the expression of cytochrome P450 (CYP) enzymes; 2) submission of the final report from study 3030-102-002 (listed as a category 3 study in the RMP). This is a randomised, open label study aimed to evaluate the effect of eluxadoline as a potential time dependent inhibitor of CYP3A4<sup>8</sup> with the substrate midazolam. The RMP (version 2.0) is updated to refine the important identified risk of 'sphincter of Oddi (SO) spasm' to 'SO spasm (sphincter of Oddi dysfunction, SOD)' and to include pancreatitis as an important identified risk as agreed in the conclusions of PSUSA/00010528/201703 finalised at PRAC/CHMP in October 2017

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

#### 5.3.10. [Emicizumab - HEMLIBRA \(CAP\) - EMEA/H/C/004406/II/0002](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include routine prophylaxis of bleeding episodes in patients with haemophilia A without factor VIII (FVIII) inhibitors. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information of the following pivotal trials: 1) study BH30071 (HAVEN 3): an ongoing, multicentre, open-label, randomized phase 3 clinical study evaluating the efficacy, safety and pharmacokinetic (PK) of emicizumab prophylaxis at doses of 1.5 mg/kg/week (QW) and 3 mg/kg/every 2 weeks

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<sup>8</sup> Cytochrome P 450 3A4

(Q2W) versus no prophylaxis in adults and adolescent patients (age of 12 or above) with haemophilia A without inhibitors against FVIII; 2) study BO39182 (HAVEN 4): an ongoing multicentre, open-label, non-randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab given as the dose of 6 mg/kg/every 4 weeks (Q4W) in adults and adolescent patients (age of 12 or above) with haemophilia A with or without FVIII inhibitors; 3) study BH29992 (HAVEN 2): a multicentre, open-label, non-randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab at the QW dose in paediatric patients (<12 years old or 12-17 years old and <40kg) with haemophilia A with FVIII inhibitors. The package leaflet and the RMP (version.2.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor corrections and clarity to sections 4.4, 4.5 and 4.6 of the SmPC

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

### 5.3.11. [Enzalutamide - XTANDI \(CAP\) - EMEA/H/C/002639/II/0039/G](#)

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include patients with non-metastatic castration-resistant prostate cancer (CRPC). As a consequence, sections 4.1 and 5.1 of the SmPC are updated based on the supportive clinical study results of study MDV3100-14 (PROSPER): a phase 3 randomized controlled study, designed to investigate the safety and efficacy of enzalutamide in patients with non-metastatic castration-resistant prostate cancer; study MDV3100-09 (STRIVE): a multicentre phase 2 study to investigate the safety and efficacy of enzalutamide versus bicalutamide in men with non-metastatic or metastatic castration-resistant prostate cancer; and based on supportive non-clinical data from 7 new reports. The package leaflet and the RMP (version 12.1) are updated accordingly; 2) update of sections 4.4, 4.7, 4.8 and 5.2 of the SmPC in order to amend the warning on possible association with seizure, the effects on driving or operating machines, the identified adverse reactions and to amend the 'race' subsection regarding pharmacokinetic properties based on the results from the completed study PROSPER (a phase 3 randomized controlled study, designed to investigate the safety and efficacy of enzalutamide in patients with non-metastatic castration-resistant prostate cancer) and study Asian PREVAIL (a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral enzalutamide in chemotherapy-naive subjects with progressive metastatic prostate cancer who have failed androgen deprivation therapy); as well as the updated integrated clinical safety database. The package leaflet is updated accordingly

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

### 5.3.12. [Epoetin alfa - ABSEAMED \(CAP\) - EMEA/H/C/000727/WS1406/0070; BINOCRIT \(CAP\) - EMEA/H/C/000725/WS1406/0070; EPOETIN ALFA HEXAL \(CAP\) - EMEA/H/C/000726/WS1406/0069](#)

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Applicant: Sandoz GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include the treatment of symptomatic anaemia (haemoglobin concentration of  $\leq 10$  g/dl) in adults with low- or intermediate-1-risk primary

myelodysplastic syndromes (MDS) who have low serum erythropoietin (< 200 mU/ml). As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated with safety and efficacy information. The package leaflet and the RMP (version 17.0) are updated accordingly. In addition, the MAH took the opportunity to align information with the reference medicinal product and with the EC guideline on excipients to improve the quality and readability of the translations in the product information and to update Annex A in line with the relevant EMA guideline

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

### 5.3.13. Erlotinib - TARCEVA (CAP) - EMEA/H/C/000618/II/0058

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.2, and 5.1 of the SmPC based on phase 3 clinical study MO22162 (CURRENTS) comparing a higher dose of Tarceva (300 mg) over the recommended daily dose (150 mg) in current smokers with locally advanced or metastatic non-small cell lung cancer (NSCLC) in the second-line setting after failure of chemotherapy. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in sections 4.4, 4.5, 4.6, 4.7, 4.8 and 5.2 of the SmPC

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

### 5.3.14. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/X/0044/G

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped application consisting of: 1) extension application to introduce a new strength of hard capsules (0.25 mg) to the currently approved presentations; 2) extension of indication to add a new indication for the treatment of paediatric patients of 10 years of age and above with relapsing multiple sclerosis (RMS). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3, 6 and 8 of the SmPC are updated. The package leaflet, labelling and the RMP (version 13.0) are updated accordingly. In addition, Annex II is updated to be brought in line with the latest QRD template (version 10)

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

### 5.3.15. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0002/G

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 1, 2, 3, 5.1, 6.4, 6.5, 6.6, of the SmPC based on the results from study CNTO1959PSO3006: an open-label, randomized study to assess the design features of an investigational prefilled syringe-facilitated injection device (PFS-FID) and the ability of subjects with rheumatoid arthritis or psoriasis to self-administer placebo with the PFS-FID. In addition, the MAH included a new presentation, constituting a pre-filled syringe assembled with a patient facilitated, manually operated pre-filled pen, referred to as

'SelfDose'. The package leaflet, labelling and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

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

#### 5.3.16. [Human coagulation factor X - COAGADEX \(CAP\) - EMEA/H/C/003855/II/0007, Orphan](#)

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Applicant: Bio Products Laboratory Limited

PRAC Rapporteur: Julie Williams

Scope: Update of section sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include safety and efficacy data in children aged less than 12 years of age based on final results from study Ten02: a phase 3 open-label multicentre study to confirm the safety, pharmacokinetics and efficacy of Bio Products Laboratory (BPL)'s high purity factor X in the prophylaxis of bleeding in factor X deficient children under the age of 12 years, provided in accordance with the agreed paediatric investigational plan (PIP). The package leaflet and the RMP (version 7.0) are updated accordingly

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

#### 5.3.17. [Infliximab - REMICADE \(CAP\) - EMEA/H/C/000240/II/0209](#)

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC to amend the current warning on colon cancer and dysplasia based on the final report of the OPUS registry (P04808): a prospective, observational, non-interventional, post-marketing safety surveillance programme in subjects with ulcerative colitis (UC). The provision of the study report fulfils MEA 121. In addition, the MAH took the opportunity to add a warning on screening tests for tuberculosis to align it with current medical practice, to add a reminder on the patient alert card in the package leaflet. Furthermore, the MAH introduced some editorial changes in line with the latest QRD template. The RMP (version 14.1) is updated accordingly

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

#### 5.3.18. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS1278/0042; Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS1278/0053](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

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



### 5.3.19. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS1372/0053;](#) [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS1372/0057](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include first-line treatment of adult patients with metastatic non-small cell lung carcinoma (NSCLC). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information from pivotal study CA209227: an open-label, randomised phase 3 trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in subjects with chemotherapy-naïve stage IV or recurrent NSCLC. The package leaflet and RMP (version 14.0 for Opdivo and version 21.0 for Yervoy) are updated accordingly. In addition, the MAH has taken the opportunity to introduce minor editorial and formatting revisions in the product information

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

### 5.3.20. [Lenvatinib - KISPLYX \(CAP\) - EMEA/H/C/004224/WS1396/0011;](#) [LENVIMA \(CAP\) - EMEA/H/C/003727/WS1396/0015](#)

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Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.5 of the SmPC to include that there is no significant drug-drug interaction (DDI) risk with midazolam based on the results of study E7080-A001-109: a phase 1 study to determine DDI of lenvatinib and midazolam, a cytochrome P450 3A4 (CYP3A4) substrate, in subjects with advanced solid tumours. The RMP (version 10.4) is updated accordingly

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

### 5.3.21. [Mepolizumab - NUCALA \(CAP\) - EMEA/H/C/003860/II/0013/G](#)

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

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

### 5.3.22. [Nusinersen - SPINRAZA \(CAP\) - EMEA/H/C/004312/II/0004, Orphan](#)

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: Ulla Wändel Liminga

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

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

### 5.3.23. [Ocrelizumab - OCREVUS \(CAP\) - EMEA/H/C/004043/II/0002](#)

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to include information on vaccination based on interim results from study BN29739 (listed as a category 3 study in the RMP): a phase 3b, multicentre, randomised, parallel-group, open-label study to evaluate the effects of ocrelizumab on immune response in patients with relapsing forms of multiple sclerosis (MS). The package leaflet and the RMP (version 2.0) are updated accordingly

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

### 5.3.24. [Pembrolizumab - KEYTRUDA \(CAP\) - EMEA/H/C/003820/II/0047](#)

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include (as monotherapy) adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection, based on study KEYNOTE-054: a randomized, double-blind, phase 3 study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), undertaken to evaluate adjuvant therapy with pembrolizumab compared to placebo in patients with resected high-risk melanoma (stages IIIA [ $> 1$  mm lymph node metastasis], IIIB and IIIC). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 17.1) are updated accordingly

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

### 5.3.25. [Rituximab - RIXATHON \(CAP\) - EMEA/H/C/003903/WS1335/0010; RIXIMYO \(CAP\) - EMEA/H/C/004729/WS1335/0010](#)

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Applicant: Sandoz GmbH

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final clinical study reports (CSR) for: 1) study GP13-302: a randomized, double-blind, parallel-group safety study with the aim to specifically address a potential safety risk of a switch from treatment with originator rituximab containing product to treatment with GP2013 (biosimilar rituximab containing products); 2) study GP13-201: a 52-week multicentre, randomized, double-blind, parallel-arm, comparative study in patients with active rheumatoid arthritis (RA) refractory or intolerant to standard disease modifying anti-rheumatic drugs (DMARDs) and one or up to three anti-tumour necrosis factor (TNF) therapies. The RMP (version 3.0) is updated accordingly

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

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

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Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

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

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

#### 5.3.27. Rolapitant - VARUBY (CAP) - EMEA/H/C/004196/II/0007/G

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Applicant: Tesaro UK Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) update of SmPC section 4.5 regarding interaction with organic cation transporter 1 (OCT1) substrates to reflect results from non-clinical study 17TESAP2R1: an in vitro evaluation of the substrate and inhibitor potential of rolapitant for efflux and update of transporters; 2) update of SmPC section 4.5 regarding interaction with UDP-glucuronosyltransferase (UGT) substrates following the submission of the results from non-clinical studies, namely: study 170594: evaluation of potential UGT inhibition by rolapitant in cryopreserved human hepatocytes and study TSRP/REP/07CRD75486/2017: evaluation of potential rolapitant metabolism by recombinantly expressed human UGT enzymes; 3) update of SmPC section 4.5 following the submission of the results for study 1000-01-001: an open-label, single-dose study to assess the effects of rolapitant (oral) on the pharmacokinetics of caffeine (CYP1A2) in healthy subjects. The RMP (version 1.2) is updated accordingly

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

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

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

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

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

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

---

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

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

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

### 5.3.30. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0012

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Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension application to introduce a new pharmaceutical form (prolonged-release tablet) associated with a new strength (11 mg), and presented in pack sizes of 28, 30, 90 and 91 tablets. The extension of indication includes a change in pharmacokinetics. The RMP (version 4.0) is updated accordingly

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

### 5.3.31. Trastuzumab - HERZUMA (CAP) - EMEA/H/C/002575/II/0006

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Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Addition of a new presentation (420 mg/vial) drug product for single-dose, partial use. The strength (concentration after reconstitution) is identical to the previously authorised 150mg/vial presentation. The RMP (version 3.1) is updated accordingly

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

### 5.3.32. Vismodegib - ERIVEDGE (CAP) - EMEA/H/C/002602/II/0039/G

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of SmPC section 4.4 and 4.8 in order to amend the special warnings and precautions for use on the effects of post-natal development as well as to include a new adverse event (precocious puberty) observed in children in post marketing; 2) submission of the final study report for study ML28296 (post approval commitment MEA 18): a prospective observational study of treatment patterns and effectiveness and safety outcomes in advanced basal cell carcinoma and basal cell carcinoma nevus syndrome patients. The RMP (version 13.0) is updated accordingly. In addition, the MAH took the opportunity to include some editorial changes in the product information

**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. Adalimumab<sup>9</sup> - AMGEVITA (CAP), CYLTEZO (CAP), IMRALDI (CAP), SOLYMBIC (CAP) - PSUSA/00010589/201712

---

Applicants: Amgen Europe B.V. (Amgevita, Solymbic), Boehringer Ingelheim International GmbH (Cyltezo), Samsung Bioepis UK Limited (SBUK) (Imraldi)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.2. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201712

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Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.3. Alectinib - ALECENSA (CAP) - PSUSA/00010581/201801

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.4. Amifampridine - FIRDAPSE (CAP) - PSUSA/00000141/201712

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Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.5. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201801

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

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<sup>9</sup> Biosimilar products only

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.6. Asparginase alfa - SPECTRILA (CAP) - PSUSA/00010455/201801**

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Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.7. Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW (CAP) - PSUSA/00010617/201801**

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.8. Birch bark extract<sup>10</sup> - EPISALVAN (CAP) - PSUSA/00010446/201801**

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Applicant: Amryt AG

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.9. Brodalumab - KYNTHEUM (CAP) - PSUSA/00010616/201801**

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Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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

#### **6.1.10. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/201801**

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Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

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<sup>10</sup> Centrally authorised product(s) only

#### 6.1.11. Clofarabine - EVOLTRA (CAP) - PSUSA/00000805/201712

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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

#### 6.1.12. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - PSUSA/00010028/201712

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Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.13. Darunavir - PREZISTA (CAP) - PSUSA/00000934/201712

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.14. Dimethyl fumarate<sup>11</sup> - SKILARENCE (CAP) - PSUSA/00010647/201712

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Applicant: Almirall S.A

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.15. Edotreotide - SOMAKIT TOC (CAP) - PSUSA/00010552/201712

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Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.16. Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/201801

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

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<sup>11</sup> Indicated in the treatment of psoriasis

Scope: Evaluation of a PSUSA procedure

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

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#### 6.1.17. Epoetin zeta - RETACRIT (CAP), SILAPO (CAP) - PSUSA/00001241/201712

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Applicant: Hospira UK Limited (Retacrit), Stada Arzneimittel AG (Silapo)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

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#### 6.1.18. Eptacog alpha - NOVOSEVEN (CAP) - PSUSA/00001245/201712

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

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#### 6.1.19. Human fibrinogen, human thrombin - EVICEL (CAP), RAPLIXA<sup>12</sup>, TACHOSIL (CAP), VERASEAL (CAP) - PSUSA/00010297/201712

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Applicants: Omrix Biopharmaceuticals N. V. (Evicel), Mallinckrodt Pharmaceuticals Ireland Limited (Raplixa), Takeda Austria GmbH (TachoSil), Instituto Grifols, S.A. (VeraSeal)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

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#### 6.1.20. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201712

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Applicant: MSD Vaccins

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

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#### 6.1.21. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201801

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Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**Action:** For preliminary discussion

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<sup>12</sup> European Commission (EC) decision on the marketing authorisation (MA) withdrawal of Raplixa dated 27 March 2018



#### 6.1.22. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/201712

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Applicant: Pfizer Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.23. Lenalidomide - REVLIMID (CAP) - PSUSA/00001838/201712

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Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.24. Lesinurad - ZURAMPIC (CAP) - PSUSA/00010470/201712

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Applicant: Grunenthal GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.25. Liraglutide - SAXENDA (CAP), VICTOZA (CAP) - PSUSA/00001892/201712

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.26. Lutetium (<sup>177</sup>Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/201712

---

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.27. Matrix-applied characterised autologous cultured chondrocytes - MACI<sup>13</sup> - PSUSA/00010116/201712

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Applicant: Vericel Denmark ApS, ATMP<sup>14</sup>

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<sup>13</sup> European Commission (EC) decision on the marketing authorisation (MA) withdrawal of Maci dated 1 July 2018

<sup>14</sup> Advanced therapy medicinal product

PRAC Rapporteur: Julie Williams  
Scope: Evaluation of a PSUSA procedure  
**Action:** For discussion

#### 6.1.28. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201801

Applicant: Bristol-Myers Squibb Pharma EEIG  
PRAC Rapporteur: Brigitte Keller-Stanislawski  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.29. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201712

Applicant: Baxalta Innovations GmbH  
PRAC Rapporteur: Brigitte Keller-Stanislawski  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.30. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/201712

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

#### 6.1.31. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201712

Applicant: AstraZeneca AB  
PRAC Rapporteur: Amelia Cupelli  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.32. Opicapone - ONGENTYS (CAP) - PSUSA/00010516/201712

Applicant: Bial - Portela & C<sup>a</sup>, S.A.  
PRAC Rapporteur: Dolores Montero Corominas  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.33. Pegaspargase<sup>15</sup> - ONCASPAR (CAP) - PSUSA/00010457/201801

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.34. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201712

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Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.35. Reteplase - RAPILYSIN (CAP) - PSUSA/00002623/201711

---

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.36. Roflumilast - DAXAS (CAP) - PSUSA/00002658/201801

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.37. Sarilumab - KEVZARA (CAP) - PSUSA/00010609/201712

---

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.38. Saxagliptin, dapagliflozin - QTERN (CAP) - PSUSA/00010520/201801

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

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

Scope: Evaluation of a PSUSA procedure

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

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#### 6.1.39. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201712

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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

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#### 6.1.40. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201712

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Applicant: Actelion Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

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#### 6.1.41. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/201712

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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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#### 6.1.42. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - PSUSA/00010619/201801

---

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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#### 6.1.43. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201712

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Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

6.1.44. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/201801

---

Applicant: CO.DON AG, ATMP<sup>16</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

6.1.45. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201801

---

Applicant: Vanda Pharmaceuticals Ltd.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

6.1.46. Ticagrelor - BRILIQUE (CAP) - PSUSA/00002948/201712

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

6.1.47. Umeclidinium bromide, vilanterol - ANORO (CAP), LAVENTAIR (CAP) - PSUSA/00010264/201712

---

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

6.1.48. Ustekinumab - STELARA (CAP) - PSUSA/00003085/201712

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

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

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

### 6.2.1. Human hepatitis B immunoglobulin - ZUTECTRA (CAP); NAP - PSUSA/00001631/201711

---

Applicants: Biotest Pharma GmbH (Zutectra), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

### 6.2.2. Lutetium (<sup>177</sup>Lu) chloride - ENDOLUCINBETA (CAP), LUMARK (CAP); NAP - PSUSA/00010391/201712

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Applicants: ITG Isotope Technologies Garching GmbH (EndolucinBeta), I.D.B. Holland B.V. (LuMark), various

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

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

### 6.2.3. Riluzole - RILUTEK (CAP), RILUZOLE ZENTIVA (CAP); NAP - PSUSA/00002645/201712

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Applicants: Aventis Pharma S.A. (Rilutek), Zentiva, k.s. (Riluzole Zentiva), various

PRAC Rapporteur: Julie Williams

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. Abciximab (NAP) - PSUSA/00000014/201711

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Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

### 6.3.2. Alfuzosin (NAP) - PSUSA/00000084/201711

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

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6.3.3. [Amino acid combinations, glucose, triglyceride combinations<sup>17</sup>, with or without electrolytes, mineral compounds<sup>18 19</sup> \(NAP\) - PSUSA/00010190/201712](#)

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

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6.3.4. [Amlodipine, indapamide \(NAP\); amlodipine, indapamide, perindopril \(NAP\) - PSUSA/00010358/201711](#)

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

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6.3.5. [Antithrombin III \(NAP\) - PSUSA/00003159/201712](#)

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Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

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6.3.6. [Bambuterol \(NAP\) - PSUSA/00000295/201712](#)

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

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6.3.7. [Bromperidol \(NAP\) - PSUSA/00000439/201711](#)

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Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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<sup>17</sup> E.g. olive oil, soya bean oil, fish oil

<sup>18</sup> Intravenous (I.V.) application only

<sup>19</sup> Nationally authorised product Numeta only

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

6.3.8. [Caffeine, drotaverine hydrochloride, metamizol sodium \(NAP\) - PSUSA/00001996/201711](#)

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Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

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

6.3.9. [Cetirizine \(NAP\) - PSUSA/00000628/201711](#)

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Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

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

6.3.10. [Ciprofloxacin hydrochloride, hydrocortisone \(NAP\) - PSUSA/00000774/201711](#)

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Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

6.3.11. [Clevidipine \(NAP\) - PSUSA/00010288/201711](#)

---

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

6.3.12. [Diacerein \(NAP\) - PSUSA/00001026/201712](#)

---

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

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



6.3.13. [Diphtheria, tetanus, pertussis \(acellular, component\), poliomyelitis \(inactivated\), haemophilus type b conjugate vaccine \(adsorbed\) \(NAP\) - PSUSA/00001124/201711](#)

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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

6.3.14. [Dutasteride \(NAP\); dutasteride, tamsulosine \(NAP\) - PSUSA/00010506/201711](#)

---

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

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

6.3.15. [Econazole \(NAP\); econazole nitrate, triamcinolone acetonide \(NAP\); econazole nitrate, zinc oxide \(NAP\) - PSUSA/00001195/201711](#)

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Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

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

6.3.16. [Fludeoxyglucose \(<sup>18</sup>F\) \(NAP\) - PSUSA/00001437/201711](#)

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Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

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

6.3.17. [Furosemide, spironolactone \(NAP\) - PSUSA/00001493/201712](#)

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Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

6.3.18. [Glatiramer \(NAP\) - PSUSA/00001529/201711](#)

---

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

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#### 6.3.19. Hydroxycarbamide<sup>20</sup> (NAP) - PSUSA/00009182/201712

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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

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#### 6.3.20. Iron<sup>21</sup> (NAP) - PSUSA/00010236/201801

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Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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

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#### 6.3.21. Lamotrigine (NAP) - PSUSA/00001825/201711

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Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

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#### 6.3.22. Levocabastine (NAP) - PSUSA/00001849/201711

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Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

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#### 6.3.23. Methylprednisolone (NAP) - PSUSA/00002026/201711

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Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

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<sup>20</sup> Non-centrally authorised products only

<sup>21</sup> Parenteral preparations only

#### 6.3.24. Mizolastine (NAP) - PSUSA/00002078/201711

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Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.25. Paroxetine (NAP) - PSUSA/00002319/201712

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Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.26. Phenylephrine, tropicamide (NAP) - PSUSA/00010430/201711

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Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.27. Propofol (NAP) - PSUSA/00002555/201711

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Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.28. Rosuvastatin (NAP) - PSUSA/00002664/201711

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.29. Rupaadine (NAP) - PSUSA/00002673/201712

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Applicant(s): various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

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

#### **6.3.30. Tafluprost, timolol (NAP) - PSUSA/00010324/201712**

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### **6.3.31. Tapentadol (NAP) - PSUSA/00002849/201711**

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

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

#### **6.4.1. Oxybutynin - KENTERA (CAP) - EMEA/H/C/000532/LEG 022**

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Applicant: Nicobrand Limited

PRAC Rapporteur: Laurence de Fays

Scope: Critical assessment as requested in the conclusions of PSUSA/00002253/201707 adopted by PRAC in March 2018

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

#### **6.4.2. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 037.2**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 037.1 [Review of cases of lymphopenia as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017] as per the conclusions adopted by PRAC/CHMP in February 2018

**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>22</sup>

#### 7.1.1. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/PSP/S/0057.1

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Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to PSP/S/0057 [protocol for a cerebrotendinous xanthomatosis registry: a long term non-interventional follow-up of safety and effectiveness of Chenodeoxycholic acid Leadiant (chenodeoxycholic acid)] as per the request for supplementary information (RSI) adopted in February 2018

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

#### 7.1.2. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/PSP/S/0065

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Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a registry of patients with high-risk neuroblastoma being treated with Qarziba (dinutuximab beta) to assess: 1) pain severity and use of analgesics during treatment; 2) incidence of neurotoxicity, visual impairment, capillary leak syndrome, cardiovascular events and hypersensitivity reactions; 3) long term safety

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

#### 7.1.3. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064

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Applicant: Medice Arzneimittel Pütter GmbH & Co. KG (Medikinet Retard)

PRAC Rapporteur: Martin Huber

Scope: Protocol for a multicentre, observational, prospective PASS to evaluate the safety concerns of long-term cardiovascular and psychiatric risks within the adult attention deficit/hyperactivity disorder (ADHD) population taking Medikinet Retard (methylphenidate hydrochloride) according to normal standard clinical practice

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

#### 7.1.4. Valproate (NAP) - EMEA/H/N/PSA/J/0015.3

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

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to PSA/J/0015.2 [protocol for a joint drug utilisation study (DUS) using EU databases to study the effectiveness of the imposed risk minimisation measures

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<sup>22</sup> In accordance with Article 107n of Directive 2001/83/EC

following the conclusion of the referral procedure under Article 31 of Directive 2001/83/EC completed in 2014 (EMA/H/A-31/1387) and to further characterise the prescribing patterns for valproate] as per the request for supplementary information (RSI) adopted in February 2018

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

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>23</sup>

### 7.2.1. Canagliflozin - INVOKANA (CAP) - EMA/H/C/002649/MEA 008.4

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 008.3 [protocol for a retrospective, observational new user cohort study, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with medicines containing sodium-glucose co-transporter-2 (SGLT2) inhibitors or other antihyperglycemic agents], as per the request for supplementary information (RSI) adopted in March 2018

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

### 7.2.2. Canagliflozin - INVOKANA (CAP) - EMA/H/C/002649/MEA 012.3

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 012.2 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as per the request for supplementary information (RSI) adopted in February 2018

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

### 7.2.3. Canagliflozin - INVOKANA (CAP) - EMA/H/C/002649/MEA 013.2

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 013.1 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information

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<sup>23</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

(RSI) adopted in February 2018

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

#### 7.2.4. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 007.4

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.3 [protocol for a retrospective, observational new user cohort study, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with medicines containing sodium-glucose co-transporter-2 (SGLT2) inhibitors or other antihyperglycemic agents], as per the request for supplementary information (RSI) adopted in March 2018

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

#### 7.2.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 011.3

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 011.3 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as per the request for supplementary information (RSI) adopted in February 2018

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

#### 7.2.6. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 012.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 012.1 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in February 2018

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

#### 7.2.7. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 003.1

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 003 [protocol for PASS MS700568-0004 on pregnancy aimed at assessing the occurrence of major congenital abnormalities (MCA), estimating proportions of pregnancy outcomes, proportions of alterations in foetal growth and pre-term births in pregnant women exposed to oral cladribine and in pregnancies fathered by male partner exposed to oral cladribine, and comparison of study outcomes with pregnant women with multiple sclerosis (MS) not exposed to any disease modifying drugs (DMDs) [final study report due date: Q1/2028] as per the request for supplementary information (RSI) adopted in February 2018

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

#### 7.2.8. [Cobimetinib - COTELLIC \(CAP\) - EMEA/H/C/003960/MEA 003.2](#)

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 003.1 [protocol for study ML39302 (COVENIS) (listed as a category 3 study in the RMP): a non-interventional study to investigate the effectiveness, safety and utilisation of cobimetinib and vemurafenib in patients with and without brain metastases with BRAF V600 mutant melanoma under real world conditions (final clinical study report (CSR) due date: December 2022)] as per the request for supplementary information (RSI) adopted in February 2018

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

#### 7.2.9. [Daclatasvir - DAKLINZA \(CAP\) - EMEA/H/C/003768/MEA 019.2](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 019.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

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

#### 7.2.10. [Dasabuvir - EXVIERA \(CAP\) - EMEA/H/C/003837/MEA 007.2](#)

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 007 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of



Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

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

#### 7.2.11. Denosumab - XGEVA (CAP) - EMA/H/C/002173/MEA 026

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 20170728: a retrospective cohort study to measure the incidence of new primary malignancies among patients with bone metastases from breast, prostate, or lung cancer treated with Xgeva (denosumab) or intravenous zoledronic acid

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

#### 7.2.12. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMA/H/C/004126/MEA 004.2

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 004 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

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

#### 7.2.13. Emicizumab - HEMLIBRA (CAP) - EMA/H/C/004406/MEA 001

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for a PASS based on the European Haemophilia Safety Surveillance (EUHASS) registry to characterise the safety profile of patients with haemophilia A exposed to emicizumab under real-world conditions, including an estimate of event rates of the following important risks: thromboembolic events, thrombotic microangiopathy, systemic hypersensitivity, anaphylaxis and anaphylactoid events [final clinical study report: (CSR) expected in June 2024] (from initial opinion/MA)

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

#### 7.2.14. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMA/H/C/000594/MEA 045.5

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 045.4 [PASS protocol for study GS-EU-276-4027, a drug utilisation study (DUS) to characterize: 1) prescribers' level of knowledge about the key risks of Truvada for a pre-exposure prophylaxis (PrEP) indication and assess the effectiveness of risk minimisation measures; 2) prescribing practices in routine clinical practice of Truvada for PrEP by describing the demographics of human immunodeficiency virus 1 (HIV-1) uninfected individuals who were prescribed Truvada for PrEP, and the prescribed dosing schedule for Truvada for PrEP as reported by the prescriber] as per the request for supplementary information (RSI) adopted in March 2018

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

#### 7.2.15. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/MEA 006.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 006 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

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

#### 7.2.16. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 002

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for a study listed as a category 3 in the RMP: a national prospective study to assess long-term toxicity from the use of biological agents to treat patients with rheumatological disorders in routine clinical practice using the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR): an established nationwide register [final clinical study report expected in 2027] (from initial opinion/MA)

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

#### 7.2.17. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 005

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for a study listed as a category 3 in the RMP: a prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of rheumatoid arthritis (RA) and to compare this to a cohort of RA patients who are treated with non-

biologic disease-modifying antirheumatic drugs (DMARDs) using the German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT<sup>24</sup>) [final clinical study report planned expected in 2027] (from initial opinion/MA)

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

#### 7.2.18. [Infliximab - FLIXABI \(CAP\) - EMEA/H/C/004020/MEA 006](#)

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Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for a study listed as a category 3 in the RMP conducted in the Spanish register of adverse events of biological therapies in rheumatic diseases (BIOBADASER<sup>25</sup>) in order to identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, to estimate the frequency of their occurrence; to identify unexpected adverse events; to identify relevant adverse events that occur following the suspension of the treatment, to estimate the relative risk of occurrence of adverse events with biological therapies in patients with rheumatoid arthritis (RA) compared to those not exposed to these treatments; to identify risk factors for suffering adverse reactions with these treatments; to evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment [final clinical study report planned expected in 2027] (from initial opinion/MA)

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

#### 7.2.19. [Ledipasvir, sofosbuvir - HARVONI \(CAP\) - EMEA/H/C/003850/MEA 017.2](#)

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Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 017.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

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

#### 7.2.20. [Meningococcal group B vaccine \(recombinant, adsorbed\) - TRUMENBA \(CAP\) - EMEA/H/C/004051/MEA 003](#)

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Applicant: Pfizer Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Protocol for study B1971060: a phase 4, open-label, single-arm trial, to describe the

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<sup>24</sup> Rheumatoide Arthritis: Beobachtung der Biologika-Therapie

<sup>25</sup> Registro español de acontecimientos adversos de terapias biológicas en enfermedades reumáticas

safety, tolerability and immunogenicity of Trumenba (bivalent rLP2086 vaccine) when administered in immunocompromised subjects  $\geq$  10 years of age

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

#### 7.2.21. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.5

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Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Amended protocol to a previously agreed protocol (D3820R00009) for study D2288R00084: a naloxegol post-market observational safety study in patients taking opioids for non-cancer pain

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

#### 7.2.22. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 003

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Applicant: Tesaro UK Limited

PRAC Rapporteur: Patrick Batty

Scope: 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

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

#### 7.2.23. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 007.2

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 007.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

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

#### 7.2.24. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 059

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Protocol for study 20170701: an observational study to assess the effectiveness of the Neulasta (pegfilgrastim) patient alert card (PAC) and to measure medication errors

related to the use of the on-body injector (OBI) to assess respondent awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC and to estimate the proportion of OBI administrations associated with medication error [final study report expected in March 2022] (from variation II/093/G)

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

#### 7.2.25. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 004.2

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Amendment to the initially approved PASS protocol in September 2017 for study C38072-AS-50026, a non-interventional phase 4 study active pregnancy surveillance: effect of reslizumab exposure on pregnancy outcomes [final clinical study report (CSR) expected in December 2028]

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

#### 7.2.26. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/MEA 093.7

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Updated protocol for study BE29950 [PASS registry protocol for a long-term surveillance study of Mabthera (rituximab)-treated patients with granulomatosis, with polyangiitis (GPA) or microscopic polyangiitis (MPA) (RIVAS)] following the assessment of the revised statistical analysis plan (SAP) concluded at the November 2017 PRAC/CHMP

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

#### 7.2.27. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/MEA 024.2

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 024.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

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

#### 7.2.28. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/MEA 008.2

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 008.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

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

### 7.2.29. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMA/H/C/004350/MEA 002.1

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 002 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

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

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

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

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Applicant: Janssen Pharmaceutical Companies of Johnson & Johnson

PRAC Rapporteur: Caroline Laborde

Scope: Results for a PASS assessing the effectiveness of the risk minimisation measures of domperidone to characterise prescribers' knowledge, understanding and extent of awareness regarding new safety information for domperidone following the change in SmPC and the distribution of a direct healthcare professional communication (DHPC), as imposed in the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2013, as per the request for supplementary information (RSI) adopted by PRAC in March 2018

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

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<sup>26</sup> In accordance with Article 107p-q of Directive 2001/83/EC

## 7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>27</sup>

### 7.4.1. Miglustat - ZAVESCA (CAP) - EMEA/H/C/000435/II/0062/G, Orphan

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Applicant: Actelion Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report of the ninth Niemann-Pick disease type C (NPC) registry report including an RMP update within the context of variation II/56 finalised at CHMP in July 2017; 2) submission of an updated RMP (version 14) in order to remove the important identified risks: 'reduced platelet counts and weight loss' as requested in the conclusions of the PSUSA procedure for miglustat (EMEA/H/C/PSUSA/00002062/201710) adopted by PRAC in May 2018

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

### 7.4.2. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0070/G

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report from the LUMINOUS study (CRFB002A2406): an observational, multicentre study to assess the long term safety and effectiveness of ranibizumab in routine clinical practice, in fulfilment of the post-authorisation measures MEA 036, MEA 048 and MEA 054; The RMP is updated accordingly; 2) submission of an updated RMP (version 17.0) to include changes not consequential to LUMINOUS study. In addition, the MAH is proposing the removal of the use of educational materials and targeted follow-up checklists listed in Annex II-D of the product information

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

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

### 7.5.1. Aclidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/ANX 001.5

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: MAH's response to ANX 001.4 [First interim report for imposed study D6560R00004: an observational study evaluating the risk of cardiovascular endpoints of acclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. The report addresses the all-cause mortality component of the PASS programme] as per the request for supplementary information (RSI) adopted in February 2018

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

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<sup>27</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

### 7.5.2. [Aclidinium - EKLIRA GENUAIR \(CAP\) - EMEA/H/C/002211/ANX 001.5](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: MAH's response to ANX 001.4 [First interim report for imposed study D6560R00004: an observational study evaluating the risk of cardiovascular endpoints of acclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. The report addresses the all-cause mortality component of the PASS programme] as per the request for supplementary information (RSI) adopted in February 2018

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

### 7.5.3. [Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR \(CAP\) - EMEA/H/C/003969/ANX 003.2](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: MAH's response to ANX 003.1 [First interim report for imposed study D6560R00004: an observational study evaluating the risk of cardiovascular endpoints of acclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. The report addresses the all-cause mortality component of the PASS programme] as per the request for supplementary information (RSI) adopted in February 2018

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

### 7.5.4. [Aclidinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR \(CAP\) - EMEA/H/C/003745/ANX 003.2](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: MAH's response to ANX-003.1 [First interim report for imposed study D6560R00004: an observational study evaluating the risk of cardiovascular endpoints of acclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. The report addresses the all-cause mortality component of the PASS programme] as per the request for supplementary information (RSI) adopted in February 2018

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

### 7.5.5. [Ataluren - TRANSLARNA \(CAP\) - EMEA/H/C/002720/MEA 002.3](#)

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Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Three year interim report for study PTC124-GD-025o-DMD (listed as a category 3 study in the RMP): a post-approval registry observational study exploring the long-term of



ataluren safety and effectiveness in usual care setting [final clinical study report (CSR) expected in: April 2023]

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

#### 7.5.6. [Bedaquiline - SIRTURO \(CAP\) - EMEA/H/C/002614/MEA 010.3](#)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth interim results (semi-annual report) for study TMC207TBC4002 (listed as a category 3 study in the RMP): a multi-country prospective multidrug-resistant tuberculosis (MDRTB) disease registry to monitor bedaquiline safety, utilisation, and emergence of resistance [final study report expected in Q2 2020]

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

#### 7.5.7. [Elosulfase alfa - VIMIZIM \(CAP\) - EMEA/H/C/002779/ANX 005.3](#)

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Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Fourth annual study report (reporting period: 14 February 2017 to 13 February 2018) for the multicentre, multinational, observational Morquio A registry study (MARS): a voluntary observational registry study to characterise and describe the mucopolysaccharidosis IV type A (MPS IVA) population and to evaluate the long-term effectiveness and safety of Vimizim (elosulfase alfa) (final clinical study report (CSR): March 2025), including the MAH's responses to ANX 005.2 to the request for supplementary information (RSI) adopted in July 2017

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

#### 7.5.8. [Dasabuvir - EXVIERA \(CAP\) - EMEA/H/C/003837/MEA 001.3](#)

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Interim results for study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting

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

#### 7.5.9. [Florbetapir \(<sup>18</sup>F\) - AMYVID \(CAP\) - EMEA/H/C/002422/MEA 001.5](#)

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Martin Huber

Scope: Second interim report for study I6E-MC-AVBE: a non-interventional PASS evaluating the effectiveness of Amyvid (florbetapir (<sup>18</sup>F)) reader training programme

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

#### 7.5.10. [Micafungin - MYCAMINE \(CAP\) - EMEA/H/C/000734/MEA 013.6](#)

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Annual report for study ISN 9463-CL-1401 (period from 01 November 2016 until 31 October 2017): an observational database-assisted comparative multicentre cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma, and short and long-term safety of micafungin and other parenteral antifungal agents (MYCOS)

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

#### 7.5.11. [Mixture of polynuclear iron\(III\)-oxyhydroxide, sucrose and starches - VELPHORO \(CAP\) - EMEA/H/C/002705/MEA 002.7](#)

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Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Fourth interim report (semi-annual) for study VFMCRP-MEAF-PA21-01-EU (Velphoro Evaluation of Real-life saFety, effectIveness and adherence 'VERIFIE' study): a non-interventional study to investigate the short and long-term real-life safety, effectiveness, and adherence of Velphoro (mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches) in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis (PD)

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

#### 7.5.12. [Ombitasvir, paritaprevir, ritonavir - VIEKIRAX \(CAP\) - EMEA/H/C/003839/MEA 001.3](#)

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Interim results for study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting)

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

### 7.5.13. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.3

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: Interim results for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterize the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4/2022]

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

### 7.5.14. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.3

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: First interim report for study CLCZ696B2015 (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final report expected in Q2/2020]

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

### 7.5.15. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: Interim results for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterize the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4/2022]

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

### 7.5.16. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: First interim report for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final report expected in Q2/2020]

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

### 7.5.17. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.11

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Eighth annual interim report for study CNT01275PS04007 (pregnancy research initiative) (C0743T): exposure to ustekinumab during pregnancy in patients with psoriasis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers. In addition, the submission includes a summary document on pregnancy outcomes from study CNT01275PS04037: pregnancy exposure registry OTIS (Organisation of Teratology Information Specialists) study conducted in North America on autoimmune diseases in pregnancy; study C0168Z03: a multicentre, prospective, observational PSOLAR (Psoriasis Longitudinal Assessment and Registry) study tracking the long-term safety experience and clinical status of patients with psoriasis who are eligible to receive (or are actively receiving) systemic therapies for psoriasis; and study CNT01275PS04007: a prospective, observational, exposure-based cohort Nordic Pregnancy Registry study analysing maternal and birth outcome data obtained from the Swedish Medical Birth Register (SMBR), Danish Medical Birth Register (DMBR) and Finnish Medical Birth Register (FMBR)

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

## 7.6. Others

### 7.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.9

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Bi-annual status report for study 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 type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (seventh IDMC report dated March 2018)

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

### 7.6.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.9

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Bi-annual status report for study 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 type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (seventh IDMC report dated March 2018)

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

### 7.6.3. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 001.4

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Proposal to terminate study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting

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

### 7.6.4. Desloratadine - AERIUS (CAP) - EMEA/H/C/000313/MEA 065.3

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Status update and study milestones for a Nordic register-based study exploring the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter

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

### 7.6.5. Desloratadine - AZOMYR (CAP) - EMEA/H/C/000310/MEA 065.3

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Status update and study milestones for a Nordic register-based study exploring the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter

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

### 7.6.6. Desloratadine - NEOCLARITYN (CAP) - EMEA/H/C/000314/MEA 065.3

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Status update and study milestones for a Nordic register-based study exploring the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter

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

### 7.6.7. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/MEA 005

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for study WA40404 (listed as category 3 study in the RMP): a phase 3b multicentre, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis later in their disease course

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

### 7.6.8. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 001.4

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Proposal to terminate study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting

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

## 7.7. New Scientific Advice

None

## 7.8. Ongoing Scientific Advice

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

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

None

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

### 8.1. Annual reassessments of the marketing authorisation

#### 8.1.1. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0053 (without RMP)

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Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.2. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0006 (without RMP)

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Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.3. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/S/0006 (without RMP)

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Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

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

#### 8.1.4. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0075 (without RMP)

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Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

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

### 8.2. Conditional renewals of the marketing authorisation

#### 8.2.1. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/R/0058 (without RMP)

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

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

#### **8.2.2. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/R/0012 (without RMP)**

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

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

#### **8.2.3. Olaratumab - LARTRUVO (CAP) - EMEA/H/C/004216/R/0010 (without RMP)**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

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

#### **8.2.4. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/R/0013 (without RMP)**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Patrick Batty

Scope: Conditional renewal of the marketing authorisation

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

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

#### **8.3.1. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/R/0044 (without RMP)**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

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

#### **8.3.2. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/R/0053 (without RMP)**

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

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



### 8.3.3. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/R/0040 (with RMP)

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Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.4. Filgrastim - GRASTOFIL (CAP) - EMEA/H/C/002150/R/0020 (without RMP)

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Applicant: Apotex Europe BV

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.5. Florbetaben (<sup>18</sup>F) - NEURACEQ (CAP) - EMEA/H/C/002553/R/0025 (with RMP)

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Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.6. Levetiracetam - LEVETIRACETAM HOSPIRA (CAP) - EMEA/H/C/002783/R/0018 (without RMP)

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Applicant: Hospira UK Limited

PRAC Rapporteur: Laurence de Fays

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.7. Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/R/0023 (with RMP)

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Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.8. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/R/0050 (with RMP)

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Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.9. Stiripentol - DIACOMIT (CAP) - EMEA/H/C/000664/R/0021 (without RMP)

Applicant: BIOCODEX

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.10. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/R/0039 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.11. Travoprost - IZBA (CAP) - EMEA/H/C/002738/R/0011 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.12. Vortioxetine - BRINTELLIX (CAP) - EMEA/H/C/002717/R/0019 (with RMP)

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

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

#### 9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders connected with human centrally authorised products

Scope: Pharmacovigilance inspection programme 2018-2021 (first revision for 2018)

**Action:** For adoption

## 9.2. Ongoing or concluded pharmacovigilance inspections

Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the agenda.

## 9.3. Others

None

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

## 10.1. Safety related variations of the marketing authorisation

### 10.1.1. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0073

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Julie Williams

Scope: PRAC consultation on a variation to update sections 4.6 and 5.3 of the SmPC as requested in the conclusions of the PSUSA procedure (PSUSA/00010373/201703) adopted by PRAC at its November 2017 meeting in order to include revised safety information about pregnancy and risk of malformative or foetal toxicity. The package leaflet is updated accordingly

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

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

None

## 10.3. Other requests

None

## 10.4. Scientific Advice – PRAC consultation

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

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

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

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

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Applicant(s): Bayer BV (Qlaira)

PRAC Lead: Menno van der Elst

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

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

### 11.2. Other requests

#### 11.2.1. Flecainide (NAP) - NO/H/PSUFU/00001396/201706

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Applicant(s): Meda Pharma GmbH & Co. KG, Laboratorios Liconsa S.A., Aurobindo Pharma (Malta) Limited

PRAC Lead: Karen Pernille Harg

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on antiarrhythmic efficacy of flecainide in combination with beta blockade in patients carrying the Gly389 variant in the beta1 adrenoceptor gene, including a consultation of the CHMP Pharmacogenomics Working Party (PgWP) as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on flecainide (PSUSA/00001396/201706) concluded in March 2018

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

#### 11.2.2. Fluoxetine (NAP) - FR/H/PSUFU/00001442/201709

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Applicant(s): Eli Lilly

PRAC Lead: Ghania Chamouni

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure conducted within the EU network on: 1) MAH's detailed reviews on the risk of autism spectrum disorders (ASD) and on the risk of other neurodevelopmental disorders after in-utero exposure to selective serotonin reuptake inhibitors (SSRI) in general and to fluoxetine in particular, as well as a detailed review on cardiac valve disorders, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on fluoxetine (PSUSA/00001442/201709) concluded in May 2018

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

## **12. Organisational, regulatory and methodological matters**

### **12.1. Mandate and organisation of the PRAC**

#### 12.1.1. PRAC Chairperson - election

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**Action:** For adoption

#### 12.1.2. PRAC working group - Best practice guide – recommendations on efficiency of plenary meetings - implementation

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PRAC lead: Martin Huber, Ulla Wändel Liminga, Menno van der Elst, Tatiana Magálová, Ghania Chamouni, Albert van der Zeijden, Jan Neuhauser

**Action:** For discussion

### **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. Reflection paper on the use of extrapolation in the development of medicines for paediatrics

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**Action:** For adoption

### **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

### 12.7.1. PRAC work plan 2018 – status update

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PRAC lead: June Raine, Almath Spooner

**Action:** For discussion

## 12.8. Planning and reporting

### 12.8.1. European Commission (EC) report on performance of pharmacovigilance tasks - second three-yearly report

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**Action:** For discussion

### 12.8.2. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q2 2018 and predictions

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**Action:** For discussion

### 12.8.3. Marketing authorisation applications (MAA) expected for 2018 – planning update dated Q2 2018

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**Action:** For information

### 12.8.4. PRAC workload statistics – Q2 2018

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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 single assessment (PSUSA) – update on follow-up procedures (PSUFU) for nationally approved products (NAPs) and CMDh table on other considerations

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PRAC lead: Menno van der Elst

**Action:** For discussion

12.10.2. Periodic safety update reports

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None

12.10.3. Granularity and Periodicity Advisory Group (GPAG)

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PRAC lead: Menno van der Elst, Maia Uusküla

**Action:** For discussion

12.10.4. PSURs repository

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None

12.10.5. Union reference date list – consultation on the draft list

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**Action:** For adoption

## 12.11. Signal management

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

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PRAC lead: Sabine Straus

**Action:** For discussion

## 12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

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None

12.12.2. Additional monitoring

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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

12.13.2. EudraVigilance (EV) - Clarification for MAHs on recording of individual case safety reports (ICSRs) accessed in EV

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**Action:** For adoption

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

12.14.1. Risk management systems

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None

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

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None

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

12.15.1. Post-authorisation Safety Studies – imposed PASS

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None

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

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None

**12.16. Community procedures**

12.16.1. Referral procedures for safety reasons

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None

**12.17. Renewals, conditional renewals, annual reassessments**

None



## 12.18. Risk communication and transparency

### 12.18.1. Public participation in pharmacovigilance

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None

### 12.18.2. Safety communication

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None

## 12.19. Continuous pharmacovigilance

### 12.19.1. Incident management

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None

## 12.20. Others

### 12.20.1. Centrally authorised products (CAP) - abolition of signature(s) for divergent position(s) in procedures adopted by majority

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**Action:** For discussion

### 12.20.2. EMA relocation to Amsterdam, the Netherlands - update

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**Action:** For discussion

### 12.20.3. Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population-specific considerations IV: 'Paediatric pharmacovigilance'

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**Action:** For adoption

### 12.20.4. Medical device and in vitro diagnostic regulation - EMA implementation plan of the new legislation

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**Action:** For discussion

### 12.20.5. Strategy on measuring the impact of pharmacovigilance - update on prioritised impact research topics

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**Action:** For adoption

## **13. Any other business**

Next meeting on: 03-06 September 2018

## 14. Explanatory notes

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

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

(Items 2 and 3 of the PRAC agenda)

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

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

### **Signals assessment and prioritisation**

(Item 4 of the PRAC agenda)

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

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

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

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

(Item 5 of the PRAC agenda)

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

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

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

(Item 6 of the PRAC agenda)

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

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

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

(Item 7 of the PRAC agenda)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC agenda)

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

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