



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 25-28 November 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

26 November 2019, 08:30 – 19:30, room 1/C

27 November 2019, 08:30 – 19:30, room 1/C

28 November 2019, 08:30 – 16:00, room 1/C

Organisational, regulatory and methodological matters (ORGAM)

12 December 2019, 09:00-12:00, room 6/D, 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.

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

### Note on access to documents

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



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## 1. Introduction

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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the PRAC plenary session to be held on 25-28 November 2019. See (current) December 2019 PRAC minutes (to be published post January 2020 PRAC meeting).

### 1.2. Agenda of the meeting on 25-28 November 2019

**Action:** For adoption

### 1.3. Minutes of the previous meeting on 28-31 October 2019

**Action:** For adoption

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

### 2.1. Newly triggered procedures

None

### 2.2. Ongoing procedures

None

### 2.3. Procedures for finalisation

None

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

### 3.1. Newly triggered procedures

None

### 3.2. Ongoing procedures

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

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Applicants: Accord Healthcare S.L.U. (Capecitabine Accord), Krka, d.d., Novo mesto

(Ecansya), Medac Gesellschaft für klinische Spezialpräparate mbH (Capecitabine medac), Nordic Group B.V. (Teysono), Roche Registration GmbH (Xeloda), Teva B.V. (Capecitabine Teva), various

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

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

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

### 3.3. Procedures for finalisation

None

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

None

### 3.5. Others

None

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

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

#### 4.1.1. Idelalisib – ZYDELIG (CAP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

**Action:** For adoption of PRAC recommendation

EPITT 19500 – New signal

Lead Member State(s): DE

#### 4.1.2. Insulin:

insulin aspart – FIASP (CAP), NOVOMIX (CAP), NOVORAPID (CAP); insulin aspart, insulin degludec – RYZODEG (CAP), TRESIBA (CAP); insulin bovine (NAP); insulin degludec, liraglutide – XULTOPHY (CAP); insulin detemir – LEVEMIR (CAP); insulin glulisine – APIDRA (CAP); insulin human – ACTRAPID (CAP), ACTRAPHANE (CAP), INSULATARD (CAP), INSUMAN (CAP), MIXTARD (CAP), PROTAPHANE (CAP), NAP; insulin lispro – HUMALOG (CAP), INSULIN LISPRO SANOFI (CAP), LIPROLOG (CAP); insulin porcine (NAP)

Applicant(s): Eli Lilly Nederland B.V. (Humalog, Liprolog, Liprolog Junior Kwikpen), Novo

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

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

Nordisk A/S (Actraphane, Actrapid, Fiasp, Insulatard, Levemir, Mixtard, NovoMix, NovoRapid, Protaphane, Ryzodeg, Tresiba, Xultophy), Sanofi-Aventis Deutschland GmbH (Apidra, Insuman), Sanofi-aventis groupe (Insulin Lispro Sanofi), various

PRAC Rapporteur: To be appointed

Scope: Signal of cutaneous amyloidosis

**Action:** For adoption of PRAC recommendation

EPITT 19499 – New signal

Lead Member State(s): BE, DK, SE, NL, UK

#### 4.1.3. Nilotinib – TASIGNA (CAP)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of anaphylactic reaction

**Action:** For adoption of PRAC recommendation

EPITT 19497 – New signal

Lead Member State(s): DK

## 4.2. New signals detected from other sources

#### 4.2.1. Andexanet alfa – ONDEXXYA (CAP)

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Applicant(s): Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Signal of erroneous assay results for levels of anti-factor Xa activity with use of andexanet alfa

**Action:** For adoption of PRAC recommendation

EPITT 19493 – New signal

Lead Member State(s): NL

#### 4.2.2. Ifosfamide (NAP)

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Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of increased risk of encephalopathy

**Action:** For adoption of PRAC recommendation

EPITT 19433 – New signal

Lead Member State(s): SE

### 4.3. Signals follow-up and prioritisation

- 4.3.1. Thiazide, thiazide-like diuretics and combinations: bendroflumethiazide (NAP); chlortalidone (NAP); cicletanine (NAP); clopamide (NAP); cyclopenthiiazide (NAP); hydrochlorothiazide (NAP); hydrochlorothiazide, aliskiren – RASILEZ HCT (CAP); hydrochlorothiazide, amlodipine, valsartan - EXFORGE HCT (CAP); hydrochlorothiazide, irbesartan – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); hydrochlorothiazide, telmisartan – ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP); hydrochlorothiazide, valsartan, amlodipine - COPALIA HCT (CAP), DAFIRO HCT (CAP); hydroflumethiazide (NAP); indapamide (NAP); metipamide (NAP); metolazone (NAP); xipamide (NAP)
- 

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

PRAC Rapporteur: Martin Huber

Scope: Signal of choroidal effusion

**Action:** For adoption of PRAC recommendation

EPITT 19468 – Follow-up to October 2019

## 5. Risk management plans (RMPs)

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

#### 5.1.1. Arsenic trioxide - EMEA/H/C/005235

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Scope: Treatment of relapsed acute promyelocytic leukaemia (APL)

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

#### 5.1.2. Azacitidine - EMEA/H/C/004984

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Scope: Treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT)

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

#### 5.1.3. Doxorubicin - EMEA/H/C/005194

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Scope: Treatment of breast cancer, ovarian cancer, progressive multiple myeloma and acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma

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

#### 5.1.4. Influenza vaccine (surface antigen, inactivated) - EMEA/H/C/004993

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Scope: Active immunisation against influenza in the elderly (65 years of age and older) and in children 6 months to less than 6 years of age

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

#### 5.1.5. Isatuximab - EMEA/H/C/004977, Orphan

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Applicant: Sanofi-aventis groupe

Scope: Treatment in combination with pomalidomide and dexamethasone, of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and who have demonstrated disease progression on the last therapy

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

#### 5.1.6. Lifitegrast - EMEA/H/C/004653

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Scope: Treatment of moderate to severe dry eye disease in adults for whom prior artificial tears has not been sufficient

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

#### 5.1.7. Onasemnogene abeparvovec - EMEA/H/C/004750, Orphan

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Applicant: AveXis Netherlands B.V., ATMP<sup>3</sup>

Scope (accelerated assessment): Treatment of spinal muscular atrophy (SMA)

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

#### 5.1.8. Ozanimod - EMEA/H/C/004835

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Scope: Treatment of multiple sclerosis

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

#### 5.1.9. Pexidartinib - EMEA/H/C/004832, Orphan

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Applicant: Daiichi Sankyo Europe GmbH

Scope: Treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT), also referred to as giant cell tumour of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS)

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

#### 5.1.10. Rituximab - EMEA/H/C/004696

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Scope: Treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis (RA)

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<sup>3</sup> Advanced therapy medicinal product

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

#### 5.1.11. Satralizumab - EMEA/H/C/004788, Orphan

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Applicant: Roche Registration GmbH

Scope (accelerated assessment): Treatment of adult and adolescent patients from 12 years of age with neuromyelitis optica spectrum disorders (NMOSD)

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

#### 5.1.12. Semaglutide - EMEA/H/C/004953

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Scope: Treatment of type 2 diabetes mellitus (T2DM)

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

#### 5.1.13. Treprostinil sodium - EMEA/H/C/005207, Orphan

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Applicant: SciPharm Sarl, Hybrid

Scope: Treatment of thromboembolic pulmonary hypertension (CTEPH)

**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. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0033, Orphan

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Submission of an updated RMP (version 11) in line with revision 2 of GVP module V on 'Risk management systems'. The protocol for study 20150136 (listed as a category 1 in the RMP/Annex II): an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices is updated and the enrolment period extended by 1 year. As a consequence, the milestones in the RMP are updated accordingly. In addition, the RMP includes a proposed update to the milestone of study 20180138 (listed as a category 3 study in the RMP): long-term follow-up of patients enrolled in TOWER study (a phase 3, randomized, open label study investigating the efficacy of the bispecific T-cell engager (BiTE) antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukaemia (ALL))

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

#### 5.2.2. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/II/0015, Orphan

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Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 9.0) in order to remove as missing information drug-drug interaction, use in adolescents, adults and elderly, use in patients with an ethnic origin other than Caucasian, use in patients with hepatic and renal impairment as well as potential harm from overdose



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

### 5.2.3. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/II/0052

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated RMP (version 19.2) in order to update information relating to educational material to include greater emphasis on off label use and the risk of misuse and abuse. In addition, the MAH submitted a synopsis of a protocol for a PASS (as a category 3 study in the RMP) to assess the impact of the updated educational material

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

### 5.2.4. Irinotecan hydrochloride trihydrate – ONIVYDE PEGYLATED LIPOSOMAL (CAP) - EMEA/H/C/004125/II/0015, Orphan

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

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

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

### 5.2.5. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0030

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Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 11.3) as a result of interim analysis and updated final report submission dates for study E7080-G000-307: a multicentre, open-label, randomized, phase 3 trial to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib alone in first-line treatment of subjects with advanced renal cell carcinoma (CLEAR). The protocol is also updated to include an interim analysis for progression-free survival and overall survival

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

### 5.2.6. Lopinavir, ritonavir - ALUVIA (Art 58<sup>4</sup>) - EMEA/H/W/000764/WS1711/0112; KALETRA (CAP) - EMEA/H/C/000368/WS1711/0181

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 9.0) in order to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity

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<sup>4</sup> Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

to review the safety information contained in the RMP, removed an important potential risk of drug interaction with telaprevir and boceprevir (hepatitis C virus (HCV) protease inhibitors) and missing information regarding use of lopinavir/ritonavir (LPV/r) in elderly patients

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

#### 5.2.7. [Lutropin alfa - LUVERIS \(CAP\) - EMEA/H/C/000292/II/0082](#)

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 3.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to remove 'ovarian hyperstimulation syndrome (OHSS)' and 'mild to severe hypersensitivity reactions including anaphylactic reactions and shock' as important identified risks and well as 'thromboembolic (TE) events', 'reproductive system cancer', 'ectopic pregnancy', 'multiple pregnancies', 'congenital anomaly' and 'off label use' as important potential risks. In addition, the age for missing information 'hypogonadotropic hypogonadal women with severe luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency of advanced maternal age (older than 40 years)' is changed from 40 to 42 years. Finally, the sections on epidemiology and non-clinical sections are updated as per the most recent data

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

#### 5.2.8. [Measles, mumps and rubella vaccine \(live\) - M-M-RVAXPRO \(CAP\) - EMEA/H/C/000604/II/0096](#)

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Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 4.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to remove the important potential risk of 'a potential change in the safety profile related to the replacement of human serum albumin (HAS) with recombinant human albumin (rHA)' and to remove the missing information related to 'exposure during pregnancy'

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

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

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 27) in order to update and consolidate within a single RMP the RMPs for pioglitazone-containing product(s), pioglitazone/metformin-fixed dose combination (FDC) and pioglitazone/glimepiride-FDC. The list of safety concerns is revised in line with the conclusions of periodic safety update report

single assessment (PSUSA) procedure PSUSA/00002417/201807 finalised in March 2019 with regards to the discontinuation of the additional risk minimisation measures (aRMMs)

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

#### 5.2.10. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0053, Orphan

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Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 20) in order to remove study AP24534-14-401: a post-marketing observational registry to evaluate the incidence of and risk factors for vascular occlusive events associated with Iclusig (ponatinib) in routine clinical practice in the US (OMNI) from the pharmacovigilance plan. In addition, the MAH took the opportunity to remove the distribution of the educational material in line with the conclusions of variation II/51 adopted in September 2019

**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/II/0134

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of sections 4.8 and 5.1 of the SmPC for the solution for injection in pre-filled syringe and update of section 4.8 of the SmPC for the powder for concentrate for solution for infusion based on the final 24 month-results from study IM101301: an open-label study to assess pharmacokinetics (PK), safety, and efficacy of subcutaneous (SC) abatacept in polyarticular juvenile idiopathic arthritis (pJIA) with no formal hypothesis testing. The package leaflet for the solution for injection in pre-filled syringe is also updated to reflect the removal of the instructions for use (IFU) booklet as requested by the CHMP in the conclusion of procedure X/0117/G adopted in January 2019. The RMP (version 27.0) is updated accordingly. In addition, the MAH took the opportunity to update Annex II and section 4.4 of the SmPC in line with the latest quality review of documents (QRD) template (version 10.1). In addition, the list of local representatives in the package leaflet is updated

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

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

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Annika Folin

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

Spanish product information and to update the list of the local representatives for Austria in the package leaflet

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

### 5.3.3. [Alglucosidase alfa - MYOZYME \(CAP\) - EMEA/H/C/000636/II/0075](#)

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

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

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

### 5.3.4. [Alogliptin, pioglitazone - INCRESYNC \(CAP\) - EMEA/H/C/002178/II/0029](#)

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 10.0) in order to remove additional risk minimisation measures (aRMMs) as requested in the outcome of periodic safety update report single assessment (PSUSA) procedure PSUSA/00002417/201807 for pioglitazone, glimepiride/pioglitazone and metformin/pioglitazone adopted in March 2019 and consequently removal of the drug utilisation study (DUS) on the utilisation of pioglitazone-alogliptin containing medicinal product(s) in clinical practice with regard to diabetic treatment regimen and comorbidities as well as the removal of relevant commitments as per the conclusions of LEG 008 adopted in September 2015. In addition, the RMP is brought in line with revision 2 of the guidance on the format of RMP in the EU (template) reflecting changes in the categorisation of safety concerns. Furthermore, the targeted adverse event (AE) follow-up questionnaires related to AEs of severe hypersensitivity skin reactions, hepatic events, pancreatitis, bladder cancer, malignancies (including pancreatic cancer), bone fractures, and macular oedema are removed. Finally, the RMP is updated to reflect the removal of the additional monitoring inverted black triangle as per the conclusion of the renewal procedure R/0023 finalised in March 2018. Annex II is updated accordingly

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

### 5.3.5. [Andexanet alfa - ONDEXXA \(CAP\) - EMEA/H/C/004108/II/0002](#)

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Applicant: Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report for study ANNEXA-4 (listed as a category 2 study in Annex II and the RMP): an interventional non-randomized, multicentre, prospective, open-label, single-group study in andexanet alfa patients receiving a factor Xa inhibitor with acute major bleeding. The RMP (version 1.1) is updated accordingly

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

#### 5.3.6. [Apalutamide - ERLEADA \(CAP\) - EMEA/H/C/004452/II/0001](#)

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) based on the results of study 56021927PCR3002 (TITAN study): a randomised, double-blind, placebo-controlled phase 3 study comparing apalutamide plus ADT versus ADT in patients with mHSPC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add a warning on ischaemic cardiovascular events and to reflect new safety and efficacy information. The package leaflet 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 and to make editorial update to the product information

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

#### 5.3.7. [Belimumab - BENLYSTA \(CAP\) - EMEA/H/C/002015/II/0073](#)

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study BEL116027 (listed as a category 3 study in the RMP): a multicentre, open-label, non-randomized, efficacy and safety study to evaluate treatment holidays and rebound phenomenon after treatment with belimumab 10 mg/kg in subjects with low systemic lupus erythematosus (SLE) disease activity. The RMP (version 34) is updated accordingly

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

#### 5.3.8. [Budesonide - JORVEZA \(CAP\) - EMEA/H/C/004655/X/0007/G, Orphan](#)

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Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Grouped application consisting of: 1) extension application to add a new strength of 0.5 mg for budesonide orodispersible tablets; 2) extension of indication to include the maintenance of remission for the 0.5 mg and 1 mg orodispersible tablets. As a consequence, sections 4.2, 4.8 and 5.1 of the SmPC are updated to reflect the recommended daily dose and duration of treatment of Jorveza (budesonide) for the maintenance of remission, to update the list of adverse reactions and the clinical efficacy and safety information based on the results of study BUL-2/EER: a double-blind, randomized, placebo-controlled, phase 3 study on the efficacy and tolerability of a 48-week

treatment with two different doses of budesonide effervescent tablets vs. placebo for maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis. The package leaflet is updated accordingly. In addition, the RMP (version 2.0) is updated accordingly and is brought in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH also took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1); 3) addition of a new pack-size of 200 x 1 orodispersible tablets (unit dose) in a blister for Jorveza (budesonide) 1 mg orodispersible tablet

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

#### 5.3.9. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/X/0032, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension application to introduce a new pharmaceutical form (solution for injection), a new strength (1800 mg) and a new route of administration (subcutaneous route). The RMP (version 7.0) is updated accordingly

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

#### 5.3.10. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/II/0021/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped variations consisting of: 1) submission of the final report from study GS-US-311-1717 (listed as a category 3 study in the RMP): a randomized, double-blind, active-controlled study to evaluate the safety and efficacy of switching to emtricitabine/tenofovir alafenamide (F/TAF) versus continuing abacavir/lamivudine (ABC/3TC) in human immunodeficiency virus type 1 (HIV-1) infected subjects who were virologically suppressed (HIV-1 ribonucleic acid (RNA) < 50 copies/mL) on a stable regimen containing ABC/3TC after 96 weeks. The RMP (version 6.1) is updated accordingly; 2) Submission of an updated RMP (version 6.1) in order to postpone the due date of the final report from study GS-US-292-0109: a phase 3, open-label study to evaluate switching from a tenofovir disoproxil fumarate (TDF)-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed HIV-1 positive subjects, from Q4 2019 to Q2 2021

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

#### 5.3.11. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/II/0044

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study GS-US-311-1717 (listed as a category 3 in the RMP): a phase 3b, randomized, double-blind, switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in human immunodeficiency virus type 1 (HIV-1) infected subjects who are virologically suppressed on regimens containing

abacavir/lamivudine (ABC/3TC). The RMP (version 4.1) is updated accordingly

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

#### 5.3.12. Fidaxomicin - DIFICLIR (CAP) - EMEA/H/C/002087/X/0034/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

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

#### 5.3.13. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/II/0003

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.8 of the SmPC in order to update the safety information based on final results from study TV48125-CNS-30051 (listed as a category 3 study in the RMP): a multicentre, randomized, double-blind, parallel-group study evaluating the long-term safety, tolerability, and efficacy of subcutaneous administration of TEV-48125 (fremanezumab) for the preventive treatment of migraine. 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

#### 5.3.14. Granisetron - SANCUSO (CAP) - EMEA/H/C/002296/II/0056/G

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Grouped variations consisting of: 1) update of section 5.2 of the SmPC to add pharmacokinetic (PK) information following the completion of paediatric PK study 392MD/44/C: an open-label, cross-over, pharmacokinetic study to assess the safety and pharmacokinetics of transdermal granisetron (Sancuso patch) and intravenous (IV) granisetron in a paediatric oncology population (aged 13 to 17 years). The RMP (version 4.0) is updated accordingly; 2) update of the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to update the pregnancy information in section 4.6 to align with the quality review document (QRD) template

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

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

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Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.2, 4.6, 4.8 and 5.1 of the SmPC in order to update the safety and immunogenicity information based on final results from study V503-P004 (listed as a category 3 study in the RMP): an open-label phase 3 clinical trial to study the immunogenicity and tolerability of Gardasil 9 in adult women (27 to 45 year-olds) compared to young adult women (16 to 26 year-olds) (in fulfilment of MEA 007). The package leaflet and the RMP (version 4.1) are updated accordingly. In addition, the MAH took the opportunity to update section 4.4 of the SmPC in line with the 'Guideline on quality aspects included in the product information for vaccines for human use (EMA/CHMP/BWP/133540/2017)' and to include editorial changes in section 5.1 of the SmPC

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

### 5.3.16. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/II/0030

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with active axial spondyloarthritis. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 10.1) are updated accordingly. The product information is also brought in line with the latest quality review of documents (QRD) template (version 10.1)

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

### 5.3.17. Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/II/0030

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Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Change in the legal status from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription' in view of the safety profile of Fortacin (lidocaine/prilocaine), the post-marketing experience already available with other medicinal products containing amide local anaesthetics and in view of making the medicinal product more accessible to the target population. The RMP (version 3.1) is updated accordingly. Furthermore, the product information is also brought in line with the latest quality review of documents (QRD) template (version 10.1)

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

### 5.3.18. Necitumumab - PORTRAZZA (CAP) - EMEA/H/C/003886/II/0017

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Submission of the exploratory biomarker analysis from 4 clinical studies (listed as a



category 3 studies in the RMP) namely: 1) study I4X-MC-JFCU: a single-arm, multicentre, phase 1b study with an expansion cohort to evaluate safety and efficacy of necitumumab in combination with abemaciclib in treatment of patients with stage IV non-small cell lung cancer (NSCLC); 2) study I4X-MC-JFCQ: an open-label, multicentre, phase 1b study with an expansion cohort to evaluate safety and efficacy of the combination of necitumumab with pembrolizumab in patients with stage IV NSCLC; 3) study I4X-MC-JFCP: a single-arm, multicentre, open-label, phase 2 study of nab-paclitaxel and carboplatin chemotherapy plus necitumumab (LY3012211) in the first-line treatment of patients with stage IV NSCLC; 4) study I6A-MC-CBBE: a phase 2 study of the combination of LY3023414 (oral phosphatidylinositol-3-kinase (PI3K)/ mammalian target of rapamycin (mTOR) dual inhibitor) and necitumumab after first-line chemotherapy for metastatic squamous non-small cell carcinoma of the lung. The RMP (version 8.1) is updated accordingly

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

### 5.3.19. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0027, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype based on the results of pharmacology studies and the double-blind, randomised, placebo-controlled phase 3 trial (INBUILD). 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 9.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor formatting changes in the product information. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

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

### 5.3.20. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/II/0051

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 9.1) as requested in the outcome of the imposed PASS protocol adopted by the PRAC in June 2019 for a prospective observational study to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the risk of VTE in users of combined oral contraceptives (COCs)-containing levonorgestrel. The RMP is also updated in line with revision 2 of the guidance on the format of RMP in the EU (template) including an update of the due date for the PASS (from June 2020 to April 2021). As a consequence, Annex II is updated. The MAH also took the opportunity to amend the package leaflet in order to update the list of local representatives in The Netherlands and Portugal

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

### 5.3.21. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0036, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.8 and 5.1 of the SmPC based on data from the final clinical study report (CSR) of pivotal study GA04753g/GO01297 (GADOLIN) (listed as category 3 study in the RMP): an open-label, multicentre, randomized, phase 3 Study to investigate the efficacy and safety of bendamustine compared with bendamustine+ obinutuzumab (RO5072759 (GA101)) in patients with rituximab-refractory, indolent non-Hodgkin's lymphoma. The package leaflet and the RMP (version 6.0) are updated accordingly

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

#### 5.3.22. [Pemetrexed - ALIMTA \(CAP\) - EMEA/H/C/000564/WS1704/0058; PEMETREXED LILLY \(CAP\) - EMEA/H/C/004114/WS1704/0010](#)

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section 4.8 of the SmPC to reorganise the section as requested in the conclusions of periodic safety update report single assessment (PSUSA) procedure PSUSA/00002330/201802 finalised in October 2018. The package leaflet is updated accordingly. The product information is also brought in line with the latest quality review of documents (QRD) template (version 10.1). In addition, the RMP (version 6.1) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

#### 5.3.23. [Perampanel - FYCOMPA \(CAP\) - EMEA/H/C/002434/II/0047](#)

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Applicant: Eisai GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include adjunctive treatment in paediatric patients from 2 to 11 years of age in partial-onset (focal) seizures with or without secondary generalisation and primary generalised tonic-clonic seizures with idiopathic generalised epilepsy. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.3) are updated accordingly

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

#### 5.3.24. [Propranolol - HEMANGIOL \(CAP\) - EMEA/H/C/002621/II/0019](#)

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Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

Scope: Submission of the results of a drug utilisation study (DUS) performed in Germany and France to evaluate off-label use and effectiveness of risk minimisation measures (RMM) in a real-life clinical setting (in fulfilment of MEA 002). As a consequence, the package leaflet is updated to strengthen the warning on hypoglycaemia and bronchospasm. The RMP (version 3.1) is updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes in section 4.4 of the SmPC as well as changes in the package leaflet in accordance with the latest quality review document (QRD) template (version 10.0)

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

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

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Cyramza (ramucirumab) in combination with erlotinib for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 9.0) are updated accordingly

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

#### 5.3.26. Regadenoson - RAPISCAN (CAP) - EMEA/H/C/001176/II/0034/G

Applicant: GE Healthcare AS

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC regarding myocardial ischaemia (myocardial infarction, ventricular arrhythmias and cardiac arrest) based on a review of the safety database and company core safety datasheet (CCDS) update; 2) update of sections 4.4, 4.5, 4.8, 4.9 and 5.1 of the SmPC regarding co-administration with methylxanthine due to the risk of seizure and hypersensitivity including anaphylaxis based on a review of the safety database and CCDS update; 3) update of section 5.1 of the SmPC regarding the use of regadenoson in patients with inadequate stress test based on results from study 3606-CL-3004: a phase 3b, open-label, parallel group, randomized, multicentre study to assess regadenoson administration following an inadequate exercise stress test as compared to regadenoson alone for myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT); and CCDS update. The RMP (version 11.1) is updated accordingly (in fulfilment of LEG 016)

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

#### 5.3.27. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/II/0038

Applicant: AstraZeneca AB

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated RMP (version 19) to amend the list of safety concerns and remove additional risk minimisation measures (aRMM) as advised by PRAC in November 2018. In addition, the RMP is brought in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template) leading to a reclassification of safety concerns. As a consequence, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated. The MAH took the opportunity to introduce minor changes in section 4.4 of the SmPC and in the package leaflet in line with the latest quality review of documents (QRD) template (version 10.1)

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

### 5.3.28. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0053/G

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of non-radiographic axial spondyloarthritis (nr-axSpA)/axial spondyloarthritis (axSpA) without radiographic evidence. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 of the SmPC are amended. The package leaflet and the RMP (version 5.0) are updated accordingly; 2) change in the due date of the psoriasis registry (listed as a category 3 study in the RMP)

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

### 5.3.29. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/II/0076

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include adolescents and children older than 7 years to the existing indication of treatment of narcolepsy with cataplexy in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 9.0) are updated accordingly

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

### 5.3.30. Sodium zirconium cyclosilicate - LOKELMA (CAP) - EMEA/H/C/004029/II/0013

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Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to update the clinical information based on final results from study DIALIZE: a Phase 3b, multicentre, prospective, randomised, double-blind, placebo-controlled study to reduce incidence of pre-dialysis hyperkalaemia with sodium zirconium cyclosilicate. The package leaflet, labelling and the RMP (version 2.1) are updated accordingly. In addition, the MAH took the opportunity to reflect information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, minor editorial changes were introduced in the package leaflet

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

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

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (61 mg soft capsules, pack-size of 30 and 90 capsules) including an extension of indication to include treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related

hospitalisation (ATTR-CM); 2) update of section 4.6 of the SmPC of 20 mg soft capsules to reflect some wording pertaining to the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme. The RMP (version 9.0) is updated accordingly, including proposed new dosage/indication, review of the additional data collected from the ATTR-CM clinical programme and post marketing reporting, a reclassification of the safety concerns and the removal of healthcare professional (HCP) educational leaflet. Annex II is updated in accordance. In addition, the MAH proposed to update the information in Braille of Annex III-A on 'labelling' to differentiate between the dosage forms

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

### 5.3.32. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/II/0013/G, Orphan

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Applicant: Novartis Europharm Limited, ATMP<sup>5</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC to implement 24 month follow-up results from study CCTL019C2201: a phase 2, single arm, multicentre trial to determine the efficacy and safety of CTL019 (tisagenlecleucel) in adult patients with relapsed or refractory diffuse large b-cell lymphoma (DLBCL); 2) update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC based on interim results from study CCTL019B2202: a phase 2, single arm, multicentre trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory b-cell acute lymphoblastic leukaemia; 3) update of section 5.2 of the SmPC based on interim results from study CCTL019B2205J: a phase 2, single arm, multicentre trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory b-cell acute lymphoblastic leukaemia. Annex II, the package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to clarify the wording of the indication in order to reflect that patients of 25 years of age are being included and to introduce some minor editorial corrections throughout the SmPC and the package leaflet

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

### 5.3.33. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/II/0048/G

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC in order to update the safety information on the risk of left ventricular dysfunction (LVD) based on the final results from study BO39807 (listed as a category 3 study in the RMP): an observational study of cardiac events in patients with epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer who have a left ventricular ejection fraction (LVEF) between 40%-49% prior to initiating treatment with Kadcyla (trastuzumab emtansine). The RMP (version 10.0) is updated accordingly; 2) submission of the final report from study BO28408 (listed as a category 3 study in the RMP): a randomised, multicentre, open-label, two-arm, phase 3 neoadjuvant study evaluating the efficacy and safety of trastuzumab emtansine plus pertuzumab compared with chemotherapy plus trastuzumab and

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<sup>5</sup> Advanced therapy medicinal product

pertuzumab for patients with HER2-positive breast cancer

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

#### 5.3.34. [Trifluridine, tipiracil - LONSURF \(CAP\) - EMEA/H/C/003897/II/0016](#)

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update information on patients with severe renal impairment based on final results from study TO-TAS-102-107: a phase 1, open-label study to evaluate the safety, tolerability, and pharmacokinetics of TAS-102 (trifluridine/tipiracil) in patients with advanced solid tumours and varying degrees of renal impairment. The package leaflet and the RMP (version 6.3) are updated accordingly. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

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

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

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

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

#### 5.3.36. [Vedolizumab - ENTYVIO \(CAP\) - EMEA/H/C/002782/X/0040](#)

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (108 mg) and a new route of administration (subcutaneous use). The RMP (version 5.0) is updated accordingly

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

## 6. Periodic safety update reports (PSURs)

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

#### 6.1.1. Anakinra - KINERET (CAP) - PSUSA/00000209/201905

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.2. Apixaban - ELIQUIS (CAP) - PSUSA/00000226/201905

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Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.3. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/201905

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.4. Benralizumab - FASENRA (CAP) - PSUSA/00010661/201905

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Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.5. Brigatinib - ALUNBRIG (CAP) - PSUSA/00010728/201904

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.6. Brinzolamide, timolol - AZARGA (CAP) - PSUSA/00000433/201904

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Applicant: Novartis Europharm Limited

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

#### 6.1.7. Cerliponase alfa - BRINEURA (CAP) - PSUSA/00010596/201904

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

#### 6.1.8. Cetrotorelix - CETROTIDE (CAP) - PSUSA/00000633/201904

Applicant: Merck Europe B.V.  
PRAC Rapporteur: Martin Huber  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.9. Darunavir, cobicistat - REZOLSTA (CAP) - PSUSA/00010315/201905

Applicant: Janssen-Cilag International NV  
PRAC Rapporteur: Ilaria Baldelli  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.10. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/201905

Applicant: EUSA Pharma (Netherlands) B.V.  
PRAC Rapporteur: Brigitte Keller-Stanislawski  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.11. Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/201905

Applicant: ViiV Healthcare B.V.  
PRAC Rapporteur: Adrien Inoubli  
Scope: Evaluation of a PSUSA procedure  
**Action:** For adoption of recommendation to CHMP

#### 6.1.12. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/201904

Applicant: AstraZeneca AB  
PRAC Rapporteur: David Olsen



Scope: Evaluation of a PSUSA procedure

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

#### 6.1.13. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/201905

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.14. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/201905

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.15. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58<sup>6</sup>) - EMEA/H/W/002320/PSUV/0001

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUR procedure

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

#### 6.1.16. Gemtuzumab ozogamicin - MYLOTARG (CAP) - PSUSA/00010688/201905

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.17. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/201905

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

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<sup>6</sup> Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

#### 6.1.18. [Letermovir - PREVYMIS \(CAP\) - PSUSA/00010660/201905](#)

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.19. [Lidocaine, prilocaine<sup>7</sup> - FORTACIN \(CAP\) - PSUSA/00010110/201905](#)

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Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.20. [Lumacaftor, ivacaftor - ORKAMBI \(CAP\) - PSUSA/00010455/201905](#)

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.21. [Meningococcal group B vaccine \(recombinant, adsorbed\) - TRUMENBA \(CAP\) - PSUSA/00010607/201904](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.22. [Midostaurin - RYDAPT \(CAP\) - PSUSA/00010638/201904](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.23. [Padeliporfin - TOOKAD \(CAP\) - PSUSA/00010654/201905](#)

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Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

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<sup>7</sup> Centrally authorised product(s) only

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

6.1.24. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - PSUSA/00010501/201905

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Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

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

6.1.25. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP); prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - PREPANDRIX (CAP) - PSUSA/00002281/201905

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

6.1.26. Pixantrone - PIXUVRI (CAP) - PSUSA/00009261/201905

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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

6.1.27. Prasterone<sup>8</sup> - INTRAROSA (CAP) - PSUSA/00010672/201905

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Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

6.1.28. Radium (<sup>223</sup>Ra) dichloride - XOFIGO (CAP) - PSUSA/00010132/201905

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Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

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

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<sup>8</sup> Pessary, for vaginal use only

#### 6.1.29. Rurioctocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/201905

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.30. Shingles (herpes zoster) vaccine (live) - ZOSTAVAX (CAP) - PSUSA/00009289/201905

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Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.31. Sunitinib - SUTENT (CAP) - PSUSA/00002833/201904

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.32. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/201905

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.33. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/201905

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.34. Temoporfin - FOSCAN (CAP) - PSUSA/00002885/201904

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Applicant: Biolitec Pharma Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.35. Tilmanocept - LYMPHOSEEK (CAP) - PSUSA/00010313/201905

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Applicant: Norgine B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.36. Tolvaptan<sup>9</sup> - JINARC (CAP) - PSUSA/00010395/201905

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.37. Tolvaptan<sup>10</sup> - SAMSCA (CAP) - PSUSA/00002994/201905

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.38. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/201905

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

#### 6.1.39. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/201905

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Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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

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<sup>9</sup> Indicated for adults with autosomal dominant polycystic kidney disease (ADPKD) only

<sup>10</sup> Indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) only

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

### 6.2.1. Bortezomib - BORTEZOMIB ACCORD (CAP); BORTEZOMIB HOSPIRA (CAP); BORTEZOMIB SUN (CAP); VELCADE (CAP); NAP - PSUSA/00000424/201904

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Applicant(s): Accord Healthcare S.L.U. (Bortezomib Accord), Janssen-Cilag International NV (Velcade), Pfizer Europe MA EEIG (Bortezomib Hospira), Sun Pharmaceutical Industries Europe B.V. (Bortezomib Sun), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

### 6.2.2. Efavirenz - STOCRIN (CAP); SUSTIVA (CAP), NAP - PSUSA/00001200/201904

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Applicant(s): Merck Sharp & Dohme B.V. (Stocrin), Bristol-Myers Squibb Pharma EEIG (Sustiva), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

### 6.2.3. Hydrochlorothiazide, telmisartan - KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP); telmisartan - KINZALMONO (CAP), MICARDIS (CAP), PRITOR (CAP); NAP - PSUSA/00002882/201904

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Applicant(s): Bayer AG (Kinzalkomb, Kinzalmono, Pritor, PritorPlus), Boehringer Ingelheim International GmbH (Micardis, MicardisPlus), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

### 6.2.4. Mycophenolate mofetil - CELLCEPT (CAP), MYCLAUSEN (CAP), MYCOPHENOLATE MOFETIL TEVA (CAP), MYFENAX (CAP); NAP; mycophenolic acid (NAP) - PSUSA/00010550/201905

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Applicant(s): Passauer Pharma GmbH (Myclausen), Roche Registration GmbH (CellCept), Teva B.V. (Mycophenolate mofetil Teva, Myfenax), various

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

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

### 6.2.5. Olanzapine - OLAZAX DISPERZI (CAP); ZALASTA (CAP); ZYPADHERA (CAP); ZYPREXA (CAP); ZYPREXA VELOTAB (CAP); NAP - PSUSA/00010540/201903

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Applicant(s): Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), Glenmark

Pharmaceuticals s.r.o. (Olazax Disperzi), Krka, d.d., Novo mesto (Zalasta), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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

#### 6.2.6. Pramipexole - MIRAPEXIN (CAP); SIFROL (CAP); NAP - PSUSA/00002491/201904

Applicant: Boehringer Ingelheim International GmbH (Mirapexin, Sifrol), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

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

#### 6.2.7. Tacrolimus<sup>11</sup> - PROTOPIC (CAP); NAP - PSUSA/00002840/201903

Applicant: LEO Pharma A/S (Protopic), various

PRAC Rapporteur: Rhea Fitzgerald

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. Carteolol (NAP) - PSUSA/00000574/201903

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.2. Carvedilol, ivabradine (NAP) - PSUSA/00010586/201904

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.3. Cytarabine (NAP) - PSUSA/00000911/201903

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

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<sup>11</sup> Topical formulation(s) only

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

#### 6.3.4. Deoxycholic acid (NAP) – PSUSA/00010525/201904

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.5. Ethinylestradiol, levonorgestrel (NAP) - PSUSA/00001309/201904

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.6. Isotretinoin<sup>12</sup> (NAP) - PSUSA/00010488/201905

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.7. Ivermectin<sup>13</sup> (NAP) - PSUSA/00010377/201904

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.8. Ivermectin<sup>14</sup> (NAP) - PSUSA/00010376/201904

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

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

#### 6.3.9. Nefopam (NAP) - PSUSA/00002131/201903

Applicant(s): various

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<sup>12</sup> Oral formulation(s) only

<sup>13</sup> Systemic use only

<sup>14</sup> Topical use only



PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

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

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6.3.10. Sulfametrole, trimethoprim (NAP); sulfadiazine, trimethoprim (NAP); sulfamethoxazole, trimethoprim (co-trimoxazole) (NAP) - PSUSA/00010593/201903

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Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

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

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6.3.11. Triamcinolone<sup>15</sup> (NAP) - PSUSA/00010292/201903

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Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

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

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6.3.12. Varicella vaccine (live) (NAP) - PSUSA/00010473/201903

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Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

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

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

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6.4.1. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/LEG 005

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Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Review of all available data from clinical trials, spontaneous reports and published literature relating to the risk of inflammatory bowel disease (IBD) and potential mechanism/biological plausibility of the occurrence of IBD as requested in the conclusions of PSUSA/00010341/201812 for secukinumab adopted in July 2019

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

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6.4.2. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/LEG 004

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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<sup>15</sup> Intraocular formulation(s) only

Scope: Review of all available data from clinical trials, spontaneous reports and published literature relating to the risk of inflammatory bowel disease (IBD) and potential mechanism/biological plausibility of the occurrence of IBD as requested in the conclusions of PSUSA/00010341/201812 for secukinumab adopted in July 2019

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

#### 6.4.3. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/LEG 007

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Review of cases of inflammatory bowel disease (IBD) in order to revise the existing warning on IBD in the product information as requested in the conclusions of PSUSA/00010341/201812 adopted in July 2019

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

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

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>16</sup>

#### 7.1.1. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/PSP/S/0070.2

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Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSP/S/0070.1 [protocol for an observational study to assess the effectiveness and long term safety of prophylaxis with damoctocog alfa pegol in real-world settings through the collection of total bleeding events and analysis of the annualised bleeding rate (ABR) in the different prophylaxis regimens (following approved local label or any other regimen prescribed by the physician as part of normal clinical practice) in patients with haemophilia A] as per the request for supplementary information (RSI) adopted in July 2019

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

#### 7.1.2. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/PSA/S/0039.1

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to PSA/S/0039 [amendment to a protocol initially endorsed by PRAC in April 2017 (EMEA/H/C/PSP/S/0049.2) for a post-marketing, observational safety study in patients with cystic fibrosis to evaluate the long-term safety of Quinsair (levofloxacin) over a five-year period (2017 to 2021) compared to other inhaled approved antibiotic therapies in cystic fibrosis (CF) patients who are enrolled in the United Kingdom (UK) CF registry. The primary objective is extended to evaluate the safety profile of Quinsair (levofloxacin) over a three-year period (2019 to 2021) compared to other inhaled approved antibiotic therapies in CF patients who are enrolled in the German CF registry] as per the request for

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<sup>16</sup> In accordance with Article 107n of Directive 2001/83/EC

supplementary information (RSI) adopted in July 2019

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

### 7.1.3. Radium (Ra<sup>223</sup>) – XOFIGO (CAP) - EMEA/H/C/PSP/S/0076.2

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's response to PSP/S/0076.1 [protocol for a PASS to estimate the incidence rate of symptomatic bone fractures among users of Xofigo (radium-223) in routine clinical practice] as per the request for supplementary information (RSI) adopted in July 2019

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

### 7.1.4. Valproate (NAP) - EMEA/H/N/PSP/J/0072.2

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0072.1 [protocol for a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in July 2019

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

### 7.1.5. Valproate (NAP) - EMEA/H/N/PSP/J/0073.2

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope MAH's response to PSP/J/0073.1 [protocol for a survey among healthcare professionals (HCP) to assess the knowledge of HCP and behaviour with regard to the pregnancy prevention programme (PPP), the receipt/use of direct healthcare professional communication (DHPC) and educational materials as well as for a survey among patients to assess the knowledge of patients with regards to PPP and receipt/use of educational materials, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in July 2019

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

### 7.1.6. Valproate (NAP) - EMEA/H/N/PSP/J/0075.2

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0075.1 [protocol for a drug utilisation study (DUS) to assess the effectiveness of the new risk minimisation measures (RMMs) and to further characterise the prescribing patterns for valproate as required in the outcome of the referral

procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in July 2019

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

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>17</sup>

### 7.2.1. Cangrelor - KENGREXAL (CAP) - EMA/H/C/003773/MEA 002.1

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ilaria Baldelli

Scope: MAH's response to MEA 002 [Protocol for study DFIDM-1801 (ARCANGELO (Italian prospective study on CANGRELOr)): a multicentre prospective observational study of acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor] as per the request for supplementary information (RSI) adopted in July 2019

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

### 7.2.2. Empagliflozin - JARDIANCE (CAP) - EMA/H/C/002677/MEA 004.4

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 004.3 [amendment to a previously agreed protocol in September 2016 for study 1245.97: a study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 mellitus diabetes (T2DM): a multi-database European study to add Finnish national registries to the study as additional data sources to evaluate the main study outcomes] as per the request for supplementary information (RSI) adopted in June 2019

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

### 7.2.3. Empagliflozin, metformin - SYNJARDY (CAP) - EMA/H/C/003770/MEA 006.4

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 006.3 [amendment to a previously agreed protocol in September 2016 for study 1245.97: a study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 mellitus diabetes (T2DM): a multi-database European study to add Finnish national registries to the study as additional data sources to evaluate the main study outcomes] as per the request for supplementary information (RSI) adopted in June 2019

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

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<sup>17</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

#### 7.2.4. [Emtricitabine, tenofovir disoproxil - TRUVADA \(CAP\) - EMEA/H/C/000594/MEA 047.3](#)

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 047.2 [protocol for study No GS EU 276 4487: a prospective, longitudinal, observational registry of emtricitabine/tenofovir disoproxil fumarate for human immunodeficiency virus 1 (HIV-1) pre-exposure prophylaxis (PrEP) in the European Union] as per the request for supplementary information (RSI) adopted in June 2019

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

#### 7.2.5. [Estrogens conjugated, bazedoxifene - DUAVIVE \(CAP\) - EMEA/H/C/002314/MEA 002.13](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 02.12 [Substantial amendment to a protocol previously agreed in May 2015 for ongoing US study B2311060 (listed as a category 3 study in the RMP): a study to estimate the incidence and to compare the risks of endometrial hyperplasia and endometrial cancer in postmenopausal women initiating either Duavive (estrogens conjugated/bazedoxifene) or estrogen + progestin (E+P) combination hormone replacement therapy (HRT)] as per the request for supplementary information (RSI) adopted in July 2019

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

#### 7.2.6. [Lenalidomide - REVLIMID \(CAP\) - EMEA/H/C/000717/MEA 046.3](#)

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Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Substantial amendment (version 4.0) to a protocol previously endorsed in November 2017 for study CC-5013-MCL-005 to further investigate and characterise the association of lenalidomide and tumour flare reaction (TFR)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL) [final clinical study report (CSR) expected in December 2022]

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

#### 7.2.7. [Naldemedine - RIZMOIC \(CAP\) - EMEA/H/C/004256/MEA 001](#)

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Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for an observational PASS of patients with chronic opioid use for non-cancer and cancer pain who have opioid-induced constipation (OIC) [final clinical study report (CSR) expected in January 2026]] (from opinion/MA)

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

### 7.2.8. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 002.2

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Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002.1 [protocol for study ALN-TTR02-0009: a prospective observational study to monitor and assess the safety of Onpattro (patisiran) in a real-world cohort of hereditary transthyretin amyloidosis (hATTR) patients] as per the request for supplementary information (RSI) adopted in July 2019

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

### 7.2.9. Ropeginterferon alfa-2b - BESREMI (CAP) - EMEA/H/C/004128/MEA 001.1

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Applicant: AOP Orphan Pharmaceuticals AG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 001 [protocol for EUPAS29462 study: a prospective, multicentre, non-interventional observational PASS to further investigate the safety and tolerability of ropeginterferon alfa-2b in polycythaemia vera patients with a special focus on hepatotoxicity to evaluate the effectiveness of risk minimisation measures and to evaluate cardiovascular safety during titration phase [final study report expected in Q3 2023]] as per the request for supplementary information (RSI) adopted in July 2019

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

## 7.3. Results of PASS imposed in the marketing authorisation(s)<sup>18</sup>

None

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

### 7.4.1. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0009

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of the final clinical study report (CSR) for study EMR700568-012 (PREMIERE registry) (listed as a category 3 study in the RMP): a prospective, observational, long-term safety registry of multiple sclerosis (MS) patients who have participated in cladribine clinical studies. It collected long-term safety data from patients previously participating in 1 out of 5 clinical trials, namely: 1) study 25643 (CLARITY): a phase 3, randomized, double-blind, three-arm, placebo-controlled, multi-center study to evaluate the safety and efficacy of oral cladribine in subjects with relapsing-remitting multiple sclerosis (RRMS); 2) study 26593 (ONWARD): a phase 2, multicentre, randomized, double blind, placebo controlled, safety, tolerability and efficacy study of add-on cladribine tablet therapy with interferon-beta (IFN- $\beta$ ) treatment in MS subjects with active disease; 3) study 27820: a phase 3b, double-blind, placebo-controlled, multicentre, parallel group, extension trial to evaluate the safety and tolerability of oral cladribine in subjects with relapsing-remitting

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<sup>18</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>19</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

multiple sclerosis who have completed trial 25643 (CLARITY); 4) study 27967: an open-label, cross over study, to assess the interactions of pantoprazole with oral cladribine administered in subjects with MS; 5) study 28821: a phase 3, randomized, double-blind, placebo-controlled, multicentre clinical trial of oral cladribine in subjects with a first clinical event at high risk of converting to MS

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

#### 7.4.2. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0033, Orphan

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of final study results of non-interventional study L01XC24 investigating the effectiveness of the educational materials of Darzalex (daratumumab) concerning the potential risk of daratumumab to interfere with blood typing analysis. This commitment was requested as PAM 001. The RMP (version 5.4) is updated accordingly

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

#### 7.4.3. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0079

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final clinical study report (CSR) for study C1231002 (PERSIST): an observational cohort study designed to evaluate real life drug persistence in biologic naive rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis patients receiving CT-P13 (infliximab biosimilar) or those switched to CT-P13 from stable treatment with the reference medicinal product containing infliximab

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

#### 7.4.4. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0080

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final clinical study report (CSR) for study C1231001 (CONNECT-IBD): a non-interventional study designated as a PASS conducted voluntarily to capture data from real-world clinical practice to characterise the population and document drug utilisation patterns. In addition, available safety data and data on the effectiveness of CT-P13 (infliximab biosimilar) was collected in patients with Crohn's disease or ulcerative colitis in the context of standard of care utilisation of the reference medicinal product containing infliximab

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

#### 7.4.5. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0073

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Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final clinical study report (CSR) for study C1231001 (CONNECT-IBD): a non-interventional study designated as a PASS conducted voluntarily to capture data from real-world clinical practice to characterise the population and document drug utilisation patterns. In addition, available safety data and data on the effectiveness of CT-P13 (infliximab biosimilar) was collected in patients with Crohn's disease or ulcerative colitis in the context of standard of care utilisation of the reference medicinal product containing infliximab

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

#### 7.4.6. [Infliximab - REMSIMA \(CAP\) - EMEA/H/C/002576/II/0074](#)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final clinical study report (CSR) for study C1231002 (PERSIST): an observational cohort study designed to evaluate real life drug persistence in biologic naive rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis patients receiving CT-P13 (infliximab biosimilar) or those switched to CT-P13 from stable treatment with the reference medicinal product containing infliximab

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

#### 7.4.7. [Linaclotide - CONSTELLA \(CAP\) - EMEA/H/C/002490/II/0043](#)

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study 'linaclotide utilisation study in selected European populations' (listed as a category 3 study in the RMP): a drug utilisation study (DUS) addressing the potential for off-label use and abuse/excessive use, the extent of use in pregnancy and lactation, and male patients as well as assessing the extent of off-label use and the extent of use in males and in pregnant females

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

#### 7.4.8. [Nalmefene - SELINCRO \(CAP\) - EMEA/H/C/002583/II/0025](#)

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

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

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



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

### 7.5.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 046.9

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Tenth annual interim report for study P10-262, a registry study in juvenile idiopathic arthritis (JIA) patients: a long term, multicentre, longitudinal post-marketing, observational study to assess long term safety and effectiveness of Humira (adalimumab) in children with moderately to severely active polyarticular or polyarticular-course JIA – STRIVE [final study report due date: 31 December 2024]

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

### 7.5.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 075.8

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Seventh annual interim study report for Humira ulcerative colitis registry P11-282: a long-term non-interventional post-marketing study to assess safety and effectiveness of Humira (adalimumab) in patients with moderately to severely active ulcerative colitis (UC)

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

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

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Applicant: Orchard Therapeutics (Netherlands) BV, ATMP<sup>20</sup>

PRAC Rapporteur: Menno van der Elst

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

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

### 7.5.4. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.6

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Third annual interim report for study CA209234 (listed as a category 3 study in the RMP): a PASS exploring the pattern of use, safety, and effectiveness of nivolumab in routine

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<sup>20</sup> Advanced therapy medicinal product

oncology practice [final clinical study report (CSR) expected in December 2024]

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

#### 7.5.5. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/MEA 004.5

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Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date expected in 2020]

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

#### 7.5.6. Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/MEA 004.4

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Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date expected in 2020]

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

#### 7.5.7. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 023.12

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 023.11 [ninth annual interim report for study CNTO1275PSO4005 (Nordic database initiative): a prospective cohort registry, five-year observational study of adverse events (AEs) observed in patients exposed to ustekinumab] as per the request for supplementary information (RSI) adopted in July 2019

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

#### 7.5.8. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.13

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 024.12 [ninth annual interim report for study CNTO1275PSO4007 (Nordic 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] as per the request for supplementary information (RSI) adopted in July 2019

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

### 7.5.9. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 006.1

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: MAH's reponse to MEA 006 [interim study report for study M12-175: a phase 1 study evaluating the safety and pharmacokinetics of venetoclax (ABT-199) in subjects with relapsed or refractory chronic lymphocytic leukaemia and non-Hodgkin lymphoma] as per the request for supplementary information (RSI) adopted in July 2019

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

## 7.6. Others

### 7.6.1. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/MEA 009.1

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Feasibility/futility report for study 20150162 (listed as a category 3 study in the RMP) with a protocol previously agreed in March 2016: a multi-national observational study to evaluate the safety of Repatha (evolocumab) in pregnancy [final report expected in Q2 2027] (from initial opinion/MA)

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

## 7.7. New Scientific Advice

None

## 7.8. Ongoing Scientific Advice

None

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

None

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

## 8.1. Annual reassessments of the marketing authorisation

### 8.1.1. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0041 (without RMP)

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual reassessment of the marketing authorisation

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

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

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

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. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/R/0039 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

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

### 8.2.2. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0022 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

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

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

### 8.3.1. Aripiprazole - ARIPIPRAZOLE MYLAN PHARMA (CAP) - EMEA/H/C/003803/R/0013 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.2. Atazanavir, cobicistat - EVOTAZ (CAP) - EMEA/H/C/003904/R/0031 (without RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

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

### 8.3.3. Duloxetine - DULOXETINE MYLAN (CAP) - EMEA/H/C/003981/R/0021 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.4. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/R/0023 (with RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.5. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/R/0031 (with RMP)

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

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

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

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.7. Lutetium (<sup>177</sup>Lu) chloride - LUMARK (CAP) - EMEA/H/C/002749/R/0014 (with RMP)

Applicant: I.D.B. Holland B.V.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.8. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/R/0074 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

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

#### 8.3.9. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/R/0081 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

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

#### **8.3.10. Pregabalin - PREGABALIN MYLAN (CAP) - EMEA/H/C/004078/R/0014 (without RMP)**

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Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

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

#### **8.3.11. Pregabalin - PREGABALIN MYLAN PHARMA (CAP) - EMEA/H/C/003962/R/0012 (without RMP)**

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Applicant: Mylan S.A.S

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

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

#### **8.3.12. Voriconazole - VORICONAZOLE HIKMA (CAP) - EMEA/H/C/003737/R/0010 (with RMP)**

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Applicant: Hikma Farmaceutica (Portugal), S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

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

## **9. Product related pharmacovigilance inspections**

### **9.1. List of planned pharmacovigilance inspections**

None

### **9.2. Ongoing or concluded pharmacovigilance inspections**

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

### **9.3. Others**

None

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

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

#### 10.1.1. Nomegestrol acetate, estradiol – ZOELY (CAP) – EMEA/H/C/001213/II/0050

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: PRAC consultation on a type II variation updating sections 4.3 and 4.4 of the SmPC in order to add a new contraindication and a new warning regarding meningioma, as requested in the conclusions of LEG 014 finalised in March 2019. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Netherlands and Portugal in the package leaflet

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

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

None

### 10.3. Other requests

None

### 10.4. Scientific Advice

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

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

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

None

### 11.2. Other requests

None

## 12. Organisational, regulatory and methodological matters

### 12.1. Mandate and organisation of the PRAC

None

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

None

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

### **12.3.1. Scientific advice working party (SAWP) – re-nomination of PRAC representative(s)**

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**Action:** For adoption

## **12.4. Cooperation within the EU regulatory network**

### **12.4.1. European Network Training Centre (EU NTC) - Pharmacoepidemiology - Training curriculum (TC)**

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**Action:** For discussion

## **12.5. Cooperation with International Regulators**

None

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

None

## **12.7. PRAC work plan**

### **12.7.1. PRAC work plan 2020 – preparation**

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PRAC lead: Sabine Straus, Martin Huber

**Action:** For discussion

## **12.8. Planning and reporting**

None

## **12.9. Pharmacovigilance audits and inspections**

### **12.9.1. Pharmacovigilance systems and their quality systems**

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None

### **12.9.2. Pharmacovigilance inspections**

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None

### **12.9.3. Pharmacovigilance audits**

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None



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

### **12.10.1. Periodic safety update reports**

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None

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

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PRAC lead: Menno van der Elst, Maia Uusküla

**Action:** For discussion

### **12.10.3. PSURs repository**

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None

### **12.10.4. Union reference date list – consultation on the draft list**

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**Action:** For adoption

### **12.10.5. Periodic safety update reports single assessment (PSUSA) – updates to the assessment report template**

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PRAC lead: Ulla Wändel Liminga, Menno van der Elst (NL), Jana Lukačičinová (CZ), Ana Sofia Martins (PT)

**Action:** For adoption

## **12.11. Signal management**

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

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PRAC lead: Menno van der Elst

**Action:** For discussion

## **12.12. Adverse drug reactions reporting and additional monitoring**

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

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None

### **12.12.2. Additional monitoring**

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None

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

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**Action:** For adoption

## **12.13. EudraVigilance database**

### **12.13.1. Activities related to the confirmation of full functionality**

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None

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

### **12.14.1. Risk management systems**

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None

### **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

### **12.18.3. Direct healthcare professional communication (DHPC) – proposal for publication on the EMA website**

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**Action:** For discussion

## 12.19. Continuous pharmacovigilance

### 12.19.1. Incident management

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None

## 12.20. Others

### 12.20.1. Biosimilar medicines and identification – update

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**Action:** For discussion

### 12.20.2. EMA – future proofing exercise

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**Action:** For discussion

### 12.20.3. EMA relocation, Amsterdam, the Netherlands – move to the new building

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**Action:** For discussion

### 12.20.4. Strategy on measuring the impact of pharmacovigilance - PRAC interest group (IG) Impact – impact guidance

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PRAC Lead: Antoine Pariente

**Action:** For discussion

## 13. Any other business

## 14. Explanatory notes

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

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

(Items 2 and 3 of the PRAC agenda)

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

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