11 June 2019
EMA/PRAC/325596/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 11-14 June 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

11 June 2019, 13:00 – 19:30, room 1/C

12 June 2019, 08:30 – 19:30, room 1/C

13 June 2019, 08:30 – 19:30, room 1/C

14 June 2019, 08:30 – 16:00, room 1/C

Organisational, regulatory and methodological matters (ORGAM)

27 June 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.

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the PRAC plenary session to be held 11-14 June 2019. See June 2019 PRAC minutes (to be published post July 2019 PRAC meeting).

1.2. Agenda of the meeting on 11-14 June 2019

Action: For adoption

1.3. Minutes of the previous meeting on 13-16 May 2019

Action: For adoption

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

3.1.1. Leuprorelin (NAP)

Applicant(s): various

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

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

Action: For adoption of a list of questions

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[1]

None

3.5. Others

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Azacitidine – VIDAZA (CAP)

Applicant(s): Celgene Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

Action: For adoption of PRAC recommendation

EPITT 19422 – New signal

Lead Member State(s): NL

4.1.2. Durvalumab – IMFINZI (CAP)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of pemphigoid

Action: For adoption of PRAC recommendation

EPITT 19416 – New signal

Lead Member State(s): NO

[1] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[2] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

4.1.3. Pembrolizumab – KEYTRUDA (CAP)

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of gastrointestinal ulcer

Action: For adoption of PRAC recommendation

EPITT 19427 – New signal

Lead Member State(s): NL

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Dipeptidyl peptidase-4 (DPP-4) inhibitors: alogliptin – VIPIDIA (CAP) - EMEA/H/C/002182/SDA/011; linagliptin – TRAJENTA (CAP) - EMEA/H/C/002110/SDA/017; saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/SDA/043; sitagliptin – JANUVIA (CAP) - EMEA/H/C/000722/SDA/038, RISTABEN (CAP) - EMEA/H/C/001234/SDA/016, TESAVEL (CAP) - EMEA/H/C/000910/SDA/032, XELEVIA (CAP) - EMEA/H/C/000762/SDA/037; vildagliptin – GALVUS (CAP) - EMEA/H/C/000771/SDA/047, JALRA (CAP) - EMEA/H/C/001048/SDA/031, XILIARX (CAP) - EMEA/H/C/001051/SDA/031; Glucagon-like peptide-1 (GLP-1) receptor agonists: albiglutide – EPERZAN[3]; dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/SDA/012; exenatide – BYDUREON (CAP) - EMEA/H/C/002020/SDA/026, BYETTA (CAP) - EMEA/H/C/000698/SDA/046; liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/SDA/018, VICTOZA (CAP) - EMEA/H/C/001026/SDA/037; lixisenatide – LYXUMIA (CAP) - EMEA/H/C/002445/SDA/015; semaglutide – OZEMPIC (CAP) – EMEA/H/C/004174/SDA/006

Applicant(s): AstraZeneca AB (Bydureon, Byetta, Onglyza), Boehringer Ingelheim (Trajenta), Eli Lilly Nederland B.V. (Trulicity), GlaxoSmithKline Trading Services limited (Eperzan), Merck Sharp & Dohme B. V. (Januvia, Ristaben, Tesavel, Xelevia), Novartis Europharm Limited (Galvus, Jalra, Xiliarx), Novo Nordisk A/S (Ozempic, Saxenda, Victoza), Sanofi-aventis groupe (Lyxumia), Takeda Pharma A/S (Vipidia)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of increased risk of cholangiocarcinoma in adults with type 2 diabetes mellitus (T2DM)

Action: For adoption of PRAC recommendation

EPITT 19343 – Follow-up to January 2019

[3] European Commission (EC) decision on the withdrawal of the marketing authorisation(s) dated 29 October 2018

4.3.2. Loperamide (NAP)

Applicant(s): various

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of Brugada syndrome in the context of abuse with loperamide

Action: For adoption of PRAC recommendation

EPITT 19379 – Follow-up April 2019

4.3.3. Propylthiouracil (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of risk of congenital anomalies

Action: For adoption of PRAC recommendation

EPITT 19358 – Follow-up to February 2019

4.3.4. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/SDA/045

Applicant(s): Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of premature ending of the GALILEO[4] study in patients who have received an artificial heart valve through a transcatheter aortic valve replacement (TAVR)

Action: For adoption of PRAC recommendation

EPITT 19294 – Follow-up to September 2018

4.3.5. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/SDA/006

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Signal of dermatitis exfoliative generalised

Action: For adoption of PRAC recommendation

EPITT 19354 – Follow-up to February 2019

4.3.6. Sulfasalazine (NAP)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of interference with dihydronicotinamide-adenine dinucleotide / dihydronicotinamide-adenine dinucleotide phosphate (NADH/NADP) reaction assays

[4] A global multicentre, open-label, randomised, event-driven, active-controlled study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to optimize clinical outcomes

Action: For adoption of PRAC recommendation

EPITT 19351 – Follow-up to February 2019

4.3.7. Temozolomide - TEMODAL (CAP) - EMEA/H/C/000229/SDA/042

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

PRAC Rapporteur: Martin Huber

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

Action: For adoption of PRAC recommendation

EPITT 19332 – Follow-up to January 2019

4.3.8. Topiramate (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of uveitis

Action: For adoption of PRAC recommendation

EPITT 19345 – Follow-up to January 2019

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Azacitidine - EMEA/H/C/005300

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

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

5.1.2. Bortezomib - EMEA/H/C/005074

Scope: Treatment of multiple myeloma

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

5.1.3. Cefiderocol - EMEA/H/C/004829

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

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

5.1.4. Clopidogrel, acetylsalicylic acid - EMEA/H/C/004996

Scope: Secondary prevention of atherothrombotic events

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

5.1.5. Emapalumab - EMEA/H/C/004386, Orphan

Applicant: Novimmune B.V.

Scope: Treatment of paediatric patients with primary haemophagocytic lymphohistiocytosis (HLH)

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

5.1.6. Fostamatinib - EMEA/H/C/005012

Scope: Treatment of thrombocytopenia

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

5.1.7. Lacosamide - EMEA/H/C/005243

Scope: Treatment of epilepsy

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

5.1.8. Netarsudil - EMEA/H/C/004583

Scope: Reduction of elevated intraocular pressure (IOP) in adults with open-angle glaucoma or ocular hypertension

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

5.1.9. Omadacycline tosilate - EMEA/H/C/004715

Scope: Treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults

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

5.1.10. Quizartinib - EMEA/H/C/004468, Orphan

Applicant: Daiichi Sankyo Europe GmbH

Scope: Treatment of acute myeloid leukaemia

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

5.1.11. Replication-competent live recombinant vesicular stomatitis virus (rVSVΔG-ZEBOV-GP, live attenuated) expressing the envelope glycoprotein of the Ebolavirus-Zaire Kikwit strain - EMEA/H/C/004554

Scope (accelerated assessment): Active immunisation of at-risk individuals aged 18 years and older to protect against Ebola virus disease (EVD) caused by Zaire ebolavirus

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

5.1.12. Rituximab - EMEA/H/C/005387

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

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

5.1.13. Rituximab - EMEA/H/C/004807

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

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

5.2. Medicines in the post-authorisation phase – PRAC-led procedures

5.2.1. Adalimumab - HULIO (CAP) - EMEA/H/C/004429/II/0009

Applicant: Mylan S.A.S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 2.2) to modify the post-authorisation measure (listed as a category 3 study in the RMP): a longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies, proposing to use the Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) registry instead of the initially identified British Society for Rheumatology Biologics Register- Rheumatoid Arthritis (BSRBR-RA)

Action: For adoption of PRAC Assessment Report

5.2.2. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0023

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated the RMP (version 11.0) in order to reclassify and/or rename the known safety concerns associated with the use of Otezla (apremilast) 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)

Action: For adoption of PRAC Assessment Report

5.2.3. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/II/0016

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 4) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the MAH implemented the changes requested in the conclusions of MEA 003.3 adopted at the November 2018 PRAC meeting (held on 29-31 October 2018)

Action: For adoption of PRAC Assessment Report

5.2.4. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0064

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated of the RMP (version 16.0) to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template) and consequential removal of the food interaction and drug-drug interactions (DDI) from the list of important identified risks. In addition, 'drug reaction with eosinophilia and systemic symptoms (DRESS)' is reclassified from important potential risk to important identified risk as requested in the conclusions of PSUSA/00000939/201710 procedure adopted in May 2018. Furthermore, the healthcare professional (HCP) guide is also updated. The MAH took the opportunity to include minor changes throughout the RMP

Action: For adoption of PRAC Assessment Report

5.2.5. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0013

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 4.0-s1) to remove exposure during lactation as missing information based on a literature review

Action: For adoption of PRAC Assessment Report

5.2.6. Human normal immunoglobulin - KIOVIG (CAP) - EMEA/H/C/000628/II/0091

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 9.0) in order to include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as a new indication and update the list of safety concerns to bring it in line with revision 2 of GVP module V on 'Risk management systems'

Action: For adoption of PRAC Assessment Report

5.2.7. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0024

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 11.1) in order to update the study design for study E7080-G000-218 (MEA 007): a randomized, phase 2 trial to assess safety and efficacy of lenvatinib at two different starting doses (18 mg vs. 14 mg one a day (QD)) in combination with everolimus (5 mg QD) in renal cell carcinoma following one prior vascular endothelial growth factor (VEGF)-targeted treatment; from double-blind to open label as requested in the conclusion of MEA 006.1 adopted by the CHMP in February 2019. In addition, the MAH took the opportunity to introduce minor administrative changes to the RMP

Action: For adoption of PRAC Assessment Report

5.2.8. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0051, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 19) in order to reflect deletion/changes in the categorisation of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the RMP is updated to reflect the change of categorisation of posterior reversible encephalopathy syndrome (PRES) as requested in the conclusions of PSUSA/00010128/201712 procedure adopted in July 2018; to correct the categorisation of study AP24534-14-203 ;a randomised, open-label, phase 2 trial of ponatinib in patients with resistant chronic phase chronic myeloid leukaemia to characterize the efficacy and safety of a range of doses, from a category 3 study to category 1 study in the RMP and Annex II and to revise the due date for the submission of its study report to August 2021, as described in the product information and as agreed in the conclusions of ANX 016 procedure adopted by the CHMP in September 2017

Action: For adoption of PRAC Assessment Report

5.2.9. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/II/0034

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 8.0) in order to remove 'bleeding disorders' as an important potential risk as requested in the conclusions of PSUSA/00009282/201805 procedure adopted in January 2019. In addition, the MAH took the opportunity to reflect changes in the categorisation of safety concerns and remove/reclassify additional pharmacovigilance activities (category 4) in line with revision 2 of the guidance on the format of RMP in the EU (template)

Action: For adoption of PRAC Assessment Report

5.2.10. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/II/0031

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 6.0) in order to implement changes in line with revision 2 of the guidance on the format of RMP in the EU (template) and to introduce changes to pre-clinical, clinical and post-marketing exposure information, and to update the due date of drug utilisation study (DUS) Z7219N02: a European multicentre retrospective-prospective cohort study to observe safinamide safety profile and pattern of use in clinical practice during the first post-commercialisation phase; from July 2019 to 28 February 2020

Action: For adoption of PRAC Assessment Report

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

5.3.1. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/X/0019/G

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to introduce a new presentation of 40 mg/0.8 mL solution for injection in vials, to allow the administration to paediatric patients requiring less than a full 40 mg dose; 2) update of the product information for the pre-filled syringe (EU/1/17/1216/001-004) and pre-filled pen (EU/1/17/1216/005-008) presentations in line with the dosage regimen changes introduced with the extension application. The RMP (version 3.0) is updated accordingly. In addition, the applicant took the opportunity to implement minor editorial changes in Module 3.2. Quality - Product

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

5.3.2. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0047, Orphan

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include non-ambulatory patients with Duchenne muscular dystrophy. As supportive data, the variation includes the final results of the long term clinical study PTC-124-GD-019-DMD: an open-label study for previously treated ataluren (PTC124) patients with nonsense mutation dystrophinopathy. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated accordingly

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

5.3.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0062

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include patients aged 5 years and older in the current approved indication for the powder for solution for infusion 120 mg/mL and 400 mg/mL based on the results of study BEL114055: a multicentre, randomised parallel group, placebo-controlled double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of belimumab, a human monoclonal anti-BLyS antibody, plus standard therapy in paediatric patients with systemic lupus erythematosus (SLE). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated with safety and efficacy information. In addition, sections 4.2, 5.1 and 5.2 of the SmPC for the solution for injection in pre-filled pen and pre-filled syringe, 200 mg are updated to reflect the paediatric data available for the intravenous formulation. The package leaflet is updated accordingly. Furthermore, the RMP (version 28.0) is updated accordingly and with revision 2 of the guidance on the format of RMP in the EU (template). Finally, the MAH took the opportunity to introduce some editorial changes in the product information and bring it in line 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

5.3.4. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0067

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.1 of the SmPC based on final results from study BEL115471/HGS1006-C1112 (listed as a category 3 study in the RMP): a phase 3/4, multicentre, randomised, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab in African-American/Black subjects with systemic lupus erythematosus. The RMP (version 31) is updated accordingly

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

5.3.5. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/II/0041

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Extension of indication to include paediatric patients from birth to less than 2 months old based on results from study D3720C00009 (C2661002) an open-label, multicentre study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline in neonates and young infants with late-onset sepsis. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, the package leaflet and the RMP (version 17.0) are updated accordingly

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

5.3.6. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/II/0043

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Update of section 4.2 of the SmPC in order to provide dosing recommendations for a high-dose regimen of ceftaroline fosamil in paediatric patients from 2 months to less than 18 years of age for the treatment of complicated skin and soft tissue infections (cSSTI) for which *Staphylococcus aureus* is known or suspected of having minimum inhibitory concentrations (MIC) of 2 or 4 mg/L based on the final study report of extrapolation study PMAR-EQDD-C266b-DP4-826. The RMP (version 18.0) is updated accordingly

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

5.3.7. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1539/0029; FORXIGA (CAP) - EMEA/H/C/002322/WS1539/0048; dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS1539/0035; XIGDUO (CAP) - EMEA/H/C/002672/WS1539/0046

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Worksharing variations consisting of an update of sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC of Forxiga (dapagliflozin), Edistride (dapagliflozin), Xigduo

(dapagliflozin/metformin) and Ebymect (dapagliflozin/metformin) in order to modify the current indication for improvement of glycaemic control based on final results from study D1693C00001 (DECLARE) (listed as a category 3 study in the RMP): 'dapagliflozin effect on cardiovascular events a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes' for the prevention of new or worsening heart failure (HF) or cardiovascular (CV) death and for the prevention of new or worsening nephropathy. The package leaflets are updated accordingly. The RMPs for Edistride and Forxiga (version 17) and Ebymect and Xigduo (version 11) are updated accordingly. In addition, the MAH took the opportunity to update the warning on lactose in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. The MAH also took the opportunity to introduce minor editorial changes in the product information

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

5.3.8. Docetaxel - DOCETAXEL ZENTIVA (CAP) - EMEA/H/C/000808/WS1550/0058; TAXOTERE (CAP) - EMEA/H/C/000073/WS1550/0131

Applicant: Aventis Pharma S.A.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone, for the treatment of patients with metastatic hormone-sensitive prostate cancer for Taxotere (docetaxel) and Docetaxel Zentiva (docetaxel). As a consequence, sections 4.1, 4.2, 4.4 and 4.8 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly. In addition, the MAH took the opportunity to update information impacting the local representatives in the package leaflet

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

5.3.9. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0017

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include a new indication in adult patients with chronic rhinosinusitis with nasal polyposis. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly

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

5.3.10. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0049

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version

50.0) are updated accordingly

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

5.3.11. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/II/0009/G

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update the safety information based on results from pharmacokinetic (PK) study ELX-PK-01 (listed as a category 3 study in the RMP): a single-dose, open-label, PK study of eluxadoline in healthy subjects with normal renal function and patients with renal impairment; 2) update of sections 4.4 and 4.8 of the SmPC following an update of the company core data sheet (CCDS) based on the review of clinical safety data and post-marketing safety data. In addition, the MAH took the opportunity to introduce minor changes throughout the SmPC, in particular the MAH updated section 4.3 to add clarification in line with section 4.4 as well as section 5.1 to add the pharmacotherapeutic group and anatomical therapeutic chemical (ATC) code. The package leaflet and the RMP (version 3.0) are updated accordingly

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

5.3.12. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/X/0004

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

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

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

5.3.13. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/II/0015

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 4.5 of the SmPC in order to remove the statement on potential drug interactions with drugs that inhibit organic cation transporter 1 (OCT1) based on the final results from study V8953M-SPD503: a non-clinical study on transporter interaction - OCT1 inhibition. The RMP (version 3.0) is updated accordingly

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

5.3.14. Human normal immunoglobulin - FLEBOGAMMA DIF (CAP) - EMEA/H/C/000781/II/0059/G

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC for

Flebogamma DIF (human normal immunoglobulin) 100 mg/mL in order to update the safety information based on the final results from study IG0601: A multicentre, prospective, open-label, clinical trial to assess the safety and the efficacy of a new intravenous immune globulin (IGIV3I Grifols 10%) in patients with idiopathic (immune) thrombocytopenic purpura. The package leaflet is updated accordingly; 2) update of section 4.8 of the SmPC to revise the adverse drug reactions for both strengths based on all completed studies previously submitted. The package leaflet is updated accordingly; 3) update of SmPC according to the 'Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg)' (EMA/CHMP/BPWP/94038/2007 Rev. 5) which came into effect on 01 January 2019. The package leaflet and the RMP (version 7.0) are updated accordingly

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

5.3.15. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0046, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include treatment of adult patients with Waldenström's macroglobulinaemia (WM) in combination with rituximab, based on the results of the final clinical study report of study PCYC-1127-CA: a randomised, double-blind, placebo-controlled, phase 3 study of ibrutinib or placebo in combination with rituximab in subjects with WM (iNNOVATE study). As a consequence, sections 4.1 and 4.8 of the SmPC are updated accordingly. The RMP (version 12) is updated accordingly. In addition, the MAH took the opportunity to update the SmPC and package leaflet with minor editorial/administrative changes

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

5.3.16. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0047, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to extend the existing indication on chronic lymphocytic leukaemia (CLL) to include the combination use with obinutuzumab for the treatment of adult patients with previously untreated CLL, based on the data from study PCYC-1130-CA: a randomised, multicentre, open-label, phase 3 study of the Bruton's tyrosine kinase inhibitor ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in subjects with treatment-naïve CLL or small lymphocytic lymphoma. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 12) are updated accordingly. In addition, the MAH took the opportunity to update the SmPC and package leaflet with minor editorial/administrative changes

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

5.3.17. Insulin aspart - FIASP (CAP) - EMEA/H/C/004046/II/0010

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of children and adolescents aged 1 year and above based on data from study NN1218-4101: a phase 3b study on efficacy and safety of faster-acting insulin aspart compared to Novorapid (insulin aspart) both in combination with insulin degludec in children and adolescents with type 1 diabetes; supported by data from study NN1218-4371: a trial comparing the pharmacokinetic properties of fast-acting insulin aspart between children, adolescents and adults with type 1 diabetes; and study NN1218-3888: a trial investigating the pharmacokinetic properties of Fiasp (insulin aspart) in children, adolescents and adults with type 1 diabetes. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the corresponding sections of the package leaflet are updated accordingly. In addition, the MAH took the opportunity to introduce other non-related minor or editorial changes throughout the product information to increase readability/consistency

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

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

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

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

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

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

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment in combination with metformin of adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or basal insulin, based on phase 3 study EFC13794: a 26-week randomised, open-label, active controlled, parallel-group study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with type 2 diabetes inadequately controlled on glucagon-like peptide-1 (GLP-1) receptor agonist and metformin (alone or with pioglitazone and/or sodium-glucose co-transporter-2 (SGLT2)

inhibitors), followed by a fixed ratio combination single-arm 26-week extension period. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in Denmark, the Netherlands and the UK in the package leaflet and to implement minor editorial changes in the Annexes

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

5.3.20. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0064

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

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

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

5.3.21. Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/II/0073/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.5 and 4.8 of the SmPC in order to include new safety information on cardiac arrhythmias based on safety signal assessment report (SSAR); 2) update of section 4.8 of the SmPC to update the frequency of some adverse events (AEs) based on data obtained from the updated safety pool analysis (Pool DBC-1) which consists of the combined data from SP667, SP754, SP755, and EP0008. All of these studies were randomized, double-blind, placebo-controlled, parallel-group, adjunctive therapy studies in subjects with epilepsy. The package leaflet and the RMP (version 13.0) are updated accordingly

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

5.3.22. Liraglutide - VICTOZA (CAP) - EMEA/H/C/001026/II/0049

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of children and adolescents (age 10-17

years) with type 2 diabetes mellitus (T2DM) based on results from: 1) study NN2211-1800: a phase 1 clinical pharmacology, multicentre, randomised, double-blind placebo controlled trial, and 2) study NN2211-3659: a phase 3a efficacy and safety, multicentre, randomised, parallel group, placebo controlled trial with a 26-week double blind period followed by a 26-week open label period (main part). 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 30) are updated accordingly. Furthermore, the MAH took the opportunity to include a warning on sodium in section 4.4 of the SmPC and the package leaflet in line with the revised European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

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

5.3.23. Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - EMEA/H/C/000739/II/0068

Applicant: Roche Registration GmbH

PRAC Rapporteur: Eva Segovia

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

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

5.3.24. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0026, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

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

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

5.3.25. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0014, Orphan

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study SM202 (EMBRACE or CS7) (listed as a category 3 study in the RMP): a phase 2, randomised, double-blind, sham-procedure-controlled study to assess the safety and tolerability and explore the efficacy of nusinersen

(ISIS 396443 (BIIB058)) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in clinical studies ISIS 396443-CS3B: a phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of nusinersen administered intrathecally in patients with infantile-onset spinal muscular atrophy; or ISIS 396443-CS4: a phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of nusinersen administered intrathecally in patients with later-onset spinal muscular atrophy; due to age at screening and/or survival motor neuron 2 (SMN2) copy number. The RMP (version 10.1) is updated accordingly

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

5.3.26. Palbociclib - IBRANCE (CAP) - EMEA/H/C/003853/II/0019/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of section 4.8 of the SmPC in order to include interstitial lung disease (ILD)/pneumonitis as adverse drug reactions (ADRs) based on a safety cumulative review together with a reclassification of the risk from potential to be identified in the RMP. The package leaflet and the RMP (version 1.6) are updated accordingly. The MAH also submitted the updated RMP in order to remove long term use from missing information in the list of safety concerns. In addition, the MAH proposes to change the due date for the submission of the final clinical study report (CSR) of study A5481027 (listed as a category 3 study in the RMP): a multicentre, randomized, double-blind phase 3 study of palbociclib (oral cyclin-dependent kinase (CDK) 4/6 inhibitor) plus letrozole versus placebo plus letrozole for the treatment of previously untreated Asian post-menopausal women with estrogen receptor (ER) (+), human epidermal growth factor receptor 2 (HER2) (-) advanced breast cancer

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

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

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

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

5.3.28. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0029

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to reflect the outcome of study D5160C00035 (listed as a category 3 study in the RMP): an open-label, phase 1 study to

assess the pharmacokinetics, safety and tolerability of osimertinib following a single oral 80 mg dose to patients with advanced solid tumours and normal renal function or severe renal impairment. The RMP (version 13) is updated accordingly

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

5.3.29. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0027

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Cyramza (ramucirumab) as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alfa fetoprotein (AFP) ≥ 400 ng/mL, after prior sorafenib therapy. 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 8.1) are updated accordingly

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

5.3.30. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0076

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated with. The package leaflet and the RMP (version 19.0) are updated accordingly

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

5.3.31. Rufinamide - INOVELON (CAP) - EMEA/H/C/000660/II/0052, Orphan

Applicant: Eisai GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section 4.2 of the SmPC in order to include an additional method of administration via feeding tube for Inovelon (rufinamide) oral suspension, as requested in the conclusions of variation II/45 adopted by CHMP in June 2018. The RMP (version 11) is updated accordingly

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

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC with information on the glycaemic efficacy and renal safety of dapagliflozin in patients with type 2 diabetes mellitus (T2DM) and moderate renal impairment (chronic kidney disease (CKD) 3A) based on final results from study D1690C00024 (DERIVE) (dapagliflozin): a multicentre, Double-blind, placebo-controlled, parallel group, randomised, phase 3 study to evaluate the glycaemic efficacy and

renal safety of dapagliflozin in patients with T2DM and CKD 3A who have inadequate glycaemic control, and to reflect a change in renal cut-off value for saxagliptin. The package leaflet and the RMP (version 4.1) are updated accordingly. In addition, the MAH took the opportunity to update section 2, 4.8, 5.2 of the SmPC and Annex II to include the required excipient information in relation to sodium levels and lactose following the update to the Annex to the European Commission (EC) guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', as well as to bring the product information in line with EMA guidance on 'Compilation of quality review of documents (QRD) decisions on stylistic matters in product information' (EMA/25090/2002 Rev.18)

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

5.3.33. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/II/0022

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Update of Sections 4.2, 4.4 and 4.5 of the SmPC in order to update the safety information based on the final results from study AC-065-117 (listed as a category 3 study in the RMP): clinical pharmacology drug-drug interaction (DDI) study evaluating the effect of clopidogrel a moderate inhibitor of CYP2C8[5], on the pharmacokinetics of selexipag and its active metabolite ACT-333679. The package leaflet and the RMP (version 6.1) are updated accordingly. In addition, the MAH took the opportunity to correct minor discrepancies in the SmPC

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

5.3.34. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS1518/0055; sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/WS1518/0077; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS1518/0034; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/WS1518/0025

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Worksharing variation to update sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Epclusa (sofosbuvir/velpatasvir) and Harvoni (sofosbuvir/ledipasvir), sections 4.2, 4.4, 5.1 and 5.2 for Sovaldi (sofosbuvir) and sections 4.2, 4.8 and 5.2 for Vosevi (sofosbuvir/velpatasvir/voxilaprevir) in order to add new information regarding the use of sofosbuvir-containing products in patients with renal impairment, based on the final results from studies: 1) GS-US-342-4062 (listed as a category 3 study in the RMP): a phase 2, multicentre, open-label study to evaluate the efficacy and safety of sofosbuvir/velpatasvir for 12 weeks in subjects with chronic hepatitis C virus (HCV) infection who are on dialysis for end stage renal disease; 2) GS-US-337-4063 (listed as a category 3 study in the RMP): a phase 2, multicentre, open-label study to evaluate the efficacy and safety of ledipasvir/sofosbuvir in subjects with genotype 1, 4, 5 and 6 chronic HCV infection who are on dialysis for end stage renal disease; 3) GS-US-334-0154 (listed as a category 3 study in the RMP): a phase 2b, open label study of 200 mg or 400 mg Sofosbuvir+ribavirin for 24 weeks in genotype 1 or 3 HCV infected subjects with renal insufficiency; 4) study GS-US-

[5] Cytochrome P450 2C8

338-1125: a phase 1, open-label, parallel-group, single-dose study to evaluate the pharmacokinetics of voxilaprevir in subjects with normal renal function and severe renal impairment. The package leaflet is updated accordingly. The RMPs for Epclusa (version 4.1), Harvoni (version 5.1), Sovaldi (version 8.1) and Vosevi (version 2.1) are updated accordingly

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

5.3.35. Teriparatide - MOVYMIA (CAP) - EMEA/H/C/004368/II/0010

Applicant: Stada Arzneimittel AG

PRAC Rapporteur: Ronan Grimes

Scope: Submission of the final clinical study report from study RGB1023O31: a phase 3, multicentre, randomised, active-controlled, parallel-group, comparative study to evaluate the efficacy and safety of Movymia (teriparatide) to the originator medicinal product containing teriparatide in patients with osteoporosis at high risk of fracture. The RMP (version 1.3) is updated accordingly

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

5.3.36. Teriparatide - TERROSA (CAP) - EMEA/H/C/003916/II/0009

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ronan Grimes

Scope: Submission of the final clinical study report from study RGB1023O31: a phase 3, multicentre, randomised, active-controlled, parallel-group, comparative study to evaluate the efficacy and safety of Terrosa (teriparatide) to the originator medicinal product containing teriparatide in patients with osteoporosis at high risk of fracture. The RMP (version 1.3) is updated accordingly

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

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

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

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

5.3.38. Trifluridine, tipiracil - LONSURF (CAP) - EMEA/H/C/003897/II/0012

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been

previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, platinum-, and either a taxane- or irinotecan-based chemotherapy. 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 is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. The RMP (version 6.1) is also 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

5.3.39. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0071

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to include treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies. As a consequence, the SmPC, package leaflet and RMP (version 15.0) are updated

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

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

Applicant: Correvio

PRAC Rapporteur: Menno van der Elst

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

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

6. Periodic safety update reports (PSURs)

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

6.1.1. Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201811

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.2. Aflibercept[6] - EYLEA (CAP) - PSUSA/00010020/201811

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.3. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/201811

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. Autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - PSUSA/00010505/201811

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[7]

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CAT and CHMP

6.1.5. Benralizumab - FASENRA (CAP) - PSUSA/00010661/201811

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

[6] Ophthalmological indication(s) only
[7] Advanced therapy medicinal product

Action: For adoption of recommendation to CHMP

6.1.6. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201812

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.7. Cabozantinib - CABOMETYX (CAP); COMETRIQ (CAP) - PSUSA/00010180/201811 (with RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.8. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/201811

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.9. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/201811

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.10. Darifenacin - EMSELEX (CAP) - PSUSA/00000933/201810

Applicant: Merus Labs Luxco II S.a.r.l.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.11. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/201811

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.12. Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/201811

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.13. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/201812

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.14. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/201811

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.15. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/201811

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.16. Empagliflozin, linagliptin - GLYXAMBI (CAP) - PSUSA/00010539/201811

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.17. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/201811

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.18. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/201811

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.19. Fluciclovine (^{18}F) - AXUMIN (CAP) - PSUSA/00010594/201811

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.20. Follitropin alfa - BEMFOLA (CAP); GONAL-F (CAP); OVALEAP (CAP) - PSUSA/00001463/201810

Applicant(s): Gedeon Richter Plc. (Bemfola), Merck Europe B.V. (Gonal-f), Theramex Ireland Limited (Ovaleap)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.21. Follitropin alfa, lutropin alpha - PERGOVERIS (CAP) - PSUSA/00001464/201810

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.22. Follitropin delta - REKOVELLE (CAP) - PSUSA/00010554/201811

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.23. Fondaparinux - ARIXTRA (CAP) - PSUSA/00001467/201812

Applicant: Aspen Pharma Trading Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.24. Glibenclamide[8] - AMGLIDIA (CAP) - PSUSA/00010690/201811

Applicant: Ammtek

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.25. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - PSUSA/00009175/201811

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.26. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/201811

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.27. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/201811

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.28. Ixazomib - NINLARO (CAP) - PSUSA/00010535/201811

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.29. Ketoconazole[9] - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201811

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

[8] Centrally authorised product(s) only
[9] Centrally authorised product(s) only

Action: For adoption of recommendation to CHMP

6.1.30. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/201811

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.31. Metformin, saxagliptin - KOMBOGLYZE (CAP) - PSUSA/00002686/201811

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.32. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/201811

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.33. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - PSUSA/00010296/201811

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.34. Necitumumab - PORTRAZZA (CAP) - PSUSA/00010471/201811

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.35. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/201811

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.36. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/201811

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.37. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/201811

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.38. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/201811

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.39. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/201811

Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.40. Pentosan polysulfate sodium[10] - ELMIRON (CAP) - PSUSA/00010614/201812

Applicant: bene-Arzneimittel GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.41. Prasterone[11] - INTRAROSA (CAP) - PSUSA/00010672/201811

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

[10] Centrally authorised product(s) only
[11] Pessary, vaginal use only

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.42. Rituximab - BLITZIMA (CAP); MABTHERA (CAP); RITEMVIA (CAP); RITUZENA (CAP); RIXATHON (CAP); RIXIMYO (CAP); TRUXIMA (CAP) - PSUSA/00002652/201811

Applicant(s): Roche Registration GmbH (MabThera), Sandoz GmbH (Rixathon, Riximyo), Celltrion Healthcare Hungary Kft. (Blitzima, Ritemvia, Rituzena, Truxima)

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.43. Rotavirus vaccine pentavalent (live, oral) - ROTATEQ (CAP) - PSUSA/00002666/201811

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.44. Rurioctocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/201811

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.45. Sapropterin - KUVAN (CAP) - PSUSA/00002683/201812

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.46. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/201812

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.47. Semaglutide - OZEMPIC (CAP) - PSUSA/00010671/201811

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.48. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201812

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.49. Susoctocog alpha - OBIZUR (CAP) - PSUSA/00010458/201811

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.50. Tenofovir alafenamide - VEMLIDY (CAP) - PSUSA/00010575/201811

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.51. Tolvaptan[12] - JINARC (CAP) - PSUSA/00010395/201811

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.52. Venetoclax - VENCLYXTO (CAP) - PSUSA/00010556/201812

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

[12] Treatment of adults with autosomal dominant polycystic kidney disease (ADPKD) to slow the progression of cyst development and renal insufficiency

Action: For adoption of recommendation to CHMP

6.1.53. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/201811

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

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

6.2.1. Bosentan - STAYVEER (CAP), TRACLEER (CAP); NAP - PSUSA/00000425/201811

Applicant(s): Janssen-Cilag International NV (Stayveer, Tracleer), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.2. Eslicarbazepine acetate - ZEBINIX (CAP); NAP - PSUSA/00001267/201810

Applicant(s): Bial - Portela & Cª, S.A. (Zebinix), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.3. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP); NAP - PSUSA/00002014/201810

Applicant(s): Nordic Group B.V. (Nordimet), Therakind (Europe) Limited (Jylamvo), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.4. Sevelamer - RENAGEL (CAP), RENVELA (CAP), SEVELAMER CARBONATE WINTHROP (CAP); NAP - PSUSA/00002697/201810

Applicant(s): Genzyme Europe BV (Renagel, Renvela, Sevelamer carbonate Winthrop), various

PRAC Rapporteur: Laurence de Fays

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. Acitretin (NAP) - PSUSA/00000051/201810

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.2. Azelastine, fluticasone (NAP) - PSUSA/00010067/201810

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.3. Benzydamine (NAP) - PSUSA/00000375/201810

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.4. Bromocriptine (NAP) - PSUSA/00000438/201810

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.5. Ceftazidime (NAP) - PSUSA/00000608/201810

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.6. Clindamycin (NAP) - PSUSA/00000795/201810

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.7. Dexketoprofen (NAP) - PSUSA/00000997/201810

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.8. Dextromethorphan (NAP) - PSUSA/00001009/201811

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.9. Didanosine (NAP) - PSUSA/00001054/201810

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.10. Flutamide (NAP) - PSUSA/00001453/201810

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.11. Human coagulation factor VIII, human von Willebrand factor (NAP) - PSUSA/00001621/201810

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.12. Letrozole (NAP) - PSUSA/00001842/201810

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.13. Meningococcal group C polysaccharide conjugate vaccine (NAP) - PSUSA/00001971/201810

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.14. Methoxyflurane (NAP) - PSUSA/00010484/201811

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.15. Methylphenidate (NAP) - PSUSA/00002024/201810

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.16. Milrinone (NAP) - PSUSA/00002064/201810

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.17. Nimodipine (NAP) - PSUSA/00002166/201811

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.18. Piretanide (NAP) - PSUSA/00002433/201810

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/LEG 066.3

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to LEG 066.1 [detailed study report of the retrospective analysis of extended interval dosing (EID) versus standard interval dosing (SID), a proposal for further investigation of efficacy and safety in terms of progressive multifocal leukoencephalopathy (PML) risk reduction with EID relative to SID, and updated pharmacokinetic/pharmacodynamic (PK/PD) modelling taking into account body weight and extended dosing intervals, as requested in the conclusions of PSUSA/00002127/201708 adopted by PRAC in March 2018] as per the request for supplementary information (RSI) adopted in January 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)[13]

7.1.1. Aclidinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - EMEA/H/C/PSA/S/0037

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Substantial amendment to the previously agreed common protocol in July 2013 on 'aclidinium bromide PASS to evaluate the risk of cardiovascular endpoints, potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for aclidinium bromide-containing products

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

7.1.2. Dexketoprofen, tramadol (NAP) - EMEA/H/N/PSP/S/0062.2

Applicant: Menarini International Operations Luxembourg S.A. (Dextradol, Enanplus, Lenizak, Takudex)

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to PSP/J/0062.1 [protocol for a drug utilisation study (DUS) on dexketoprofen-tramadol (DKP-TRAM) fixed combination to evaluate the pattern of prescriptions of DKP-TRAM and assess the risk of adverse events (AE) (e.g. nausea, vomiting, diarrhoea, vertigo) in DKP-TRAM *vs.* tramadol monotherapy (including tramadol-paracetamol combinations) users, with a special focus on patients 75 years old and over] as per the request for supplementary information (RSI) adopted in January 2019

[13] In accordance with Article 107n of Directive 2001/83/EC

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

7.1.3. Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/J/0067.1

Applicant(s): Fresenius Kabi Deutschland GmbH, B. Braun Melsungen AG

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to PSP/J/0067 [protocol for a joint retrospective, multinational, drug utilisation study (DUS) to assess the non-adherence of physicians in hydroxyethyl starch (HES) accredited hospitals to the approved European product information regarding indication for use, contraindications and posology (dosage) for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures, as required in the outcome of the referral procedure under Article 107i of Directive 2001/83/EC for HES completed in 2018 (EMEA/H/A-107i/1457)] as per the request for supplementary information (RSI) adopted in January 2019

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

7.1.4. Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/S/0068.1

Applicant: Serumwerk Bernburg AG

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to PSP/S/0068 [protocol for a retrospective, multinational, drug utilisation study (DUS) to assess the non-adherence of physicians in hydroxyethyl starch (HES) accredited hospitals to the approved European product information regarding indication for use, contraindications and posology (dosage) for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures, as required in the outcome of the referral procedure under Article 107i of Directive 2001/83/EC for HES completed in 2018 (EMEA/H/A-107i/1457)] as per the request for supplementary information (RSI) adopted in January 2019

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

7.1.5. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064.2

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

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0064.1 [protocol for a multicentre, observational, prospective PASS to evaluate the safety concerns of long-term cardiovascular and psychiatric risks within the adult attention deficit/hyperactivity disorder (ADHD) population taking Medikinet Retard (methylphenidate hydrochloride) according to normal standard clinical practice] as per the request for supplementary information (RSI) adopted in January 2019

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

7.1.6. Nomegestrol acetate, estradiol – ZOELY (CAP) - EMEA/H/C/PSA/S/0038

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Protocol 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

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

7.1.7. Oral retinoids: acitretin (NAP), alitretinoin (NAP), isotretinoin (NAP) - EMEA/H/N/PSP/J/0069.1

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

PRAC Rapporteur: Ana Sofia Diniz Martins

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

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[14]

7.2.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/MEA 003

Applicant: Kite Pharma EU B.V., ATMP[15]

PRAC Rapporteur: Anette Kirstine Stark

Scope: Protocol for study KT-EU-471-0116: a prescriber survey to assess the prescribers' understanding of serious neurologic adverse reactions and cytokine release syndrome (CRS) (from initial opinion/MA)

Action: For adoption of advice to CAT and CHMP

7.2.2. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 035 [protocol for study 20180204: a registry study to evaluate the incidence and risk of hypocalcaemia in paediatric patients treated with cinacalcet with secondary hyperparathyroidism receiving maintenance dialysis within the International Pediatric Dialysis Network (IPDN) registry] as per the request for supplementary information (RSI) adopted in October 2018

Action: For adoption of advice to CHMP

[14] 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
[15] Advanced therapy medicinal product

7.2.3. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/MEA 042

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 20190038 V1: a retrospective cohort study assessing the incidence of cardiovascular and cerebrovascular events among postmenopausal women and men with osteoporosis who initiated treatment with denosumab or zoledronic acid

Action: For adoption of advice to CHMP

7.2.4. Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/MEA 019.4

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 019.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.5. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 008.2

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Updated protocol for study 109MS402: Biogen multiple sclerosis pregnancy exposure registry to prospectively evaluate pregnancy outcomes in women with multiple sclerosis (MS) who were exposed to a registry-specified Biogen MS product during the eligibility window for that product

Action: For adoption of advice to CHMP

7.2.6. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 007.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 007.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.7. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/REC 001.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: MAH's response to REC 001.1 [protocol for study R668-AD-1225: a non-imposed, interventional PASS: an open-label study of dupilumab in patients with atopic dermatitis who participated in previous dupilumab clinical trials, five year open label extension study] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.8. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/MEA 004.4

Applicant: Merck Sharp & Dohme B.V

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 004.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.9. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 002.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 002 [protocol for study BO40853: a PASS based on healthcare professional (HCP) and patient/carer survey to evaluate the awareness, knowledge and compliance of HCPs and patients/carers to the additional risk minimisation measures (guide for HCPs, patient/carer guide, patient alert card), in relation to the safety concerns of thromboembolic events, thrombotic microangiopathy as well as life-threatening bleeding due to misinterpretation of the standard coagulation tests [final study report due date: 30/04/2021] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.10. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 004.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: 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

Action: For adoption of advice to CHMP

7.2.11. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: 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

Action: For adoption of advice to CHMP

7.2.12. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 047.2

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 047.1 [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 at the November 2018 PRAC meeting

Action: For adoption of advice to CHMP

7.2.13. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58[16]) - EMEA/H/W/002320/MEA 002

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study FEXINC09395: a prospective observational study of the safety of fexinidazole for human African trypanosomiasis [final clinical study report expected in September 2023] (from initial opinion/MA)

Action: For adoption of advice to CHMP

7.2.14. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/MEA 006.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

[16] 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)

Scope: MAH's response to MEA 006.2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.15. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/MEA 004.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 004.1 [protocol for study CSIMM000265: a retrospective cohort study using health administrative claims databases to assess adverse pregnancy and infant outcomes in women with psoriasis who were exposed to guselkumab versus other biologic therapies during pregnancy] as per the request for supplementary information (RSI) adopted in February 2019

Action: For adoption of advice to CHMP

7.2.16. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.1

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001 [protocol for a retrospective chart review for evaluating adherence to and effectiveness of the proposed platelet monitoring schedule, proposed cut-off points, dose adaptation, and initiation of corticosteroids on thrombocyte recovery] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.17. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 002.1

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002 [protocol for a study to evaluate and further characterize the events of thrombocytopenia, glomerulonephritis and retinal toxicity/eye disease related to vitamin A deficiency when Tegsedi (inotersen) is prescribed in normal clinical practice] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.18. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 017.4

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 017.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.19. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 007.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 007.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.20. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/MEA 024.4

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 024.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.21. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/MEA 008.4

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 008.3 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.22. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/MEA 002.3

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 002.1 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.23. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/MEA 002.1

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 002 [protocol for study VX17-661-117 (study 117) (listed as a category 3 study in the RMP): an observational cohort study on utilisation patterns and real-world effects of tezacaftor and ivacaftor combination therapy (TEZ/IVA) in patients with cystic fibrosis (CF) [final report expected in December 2023] as per the request for supplementary information (RSI) adopted in February 2019

Action: For adoption of advice to CHMP

7.2.24. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 024.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH Response to MEA-024 [Protocol for study PGL18-002: a retrospective, multi-national, comparative, non-interventional cohort study to investigate the risk of liver injury possibly associated with Esmya (ulipristal acetate) use based on data from various national electronic health record based databases in Europe [final study report expected by Q4 2019] as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.25. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 028.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 028 [protocol for study PGL18-001: a retrospective drug utilisation study (DUS) through a chart review across four major EU countries [final study report expected by Q2 2020], as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.2.26. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.4

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Amendment to the previously agreed protocol in February 2017 (MEA 044.2) for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)

Action: For adoption of advice to CHMP

7.2.27. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Amendment to protocol (version 3.0) for study P16-562: a prospective observational study to assess the long term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients [final clinical study report (CSR) planned in December 2025]

Action: For adoption of advice to CHMP

7.2.28. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/MEA 001.1

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 001 [protocol for study VON (BAX0111) VWF-500 COL (listed as a category 3 study in the RMP): a real world safety and effectiveness study of factor replacement for clinically severe von Willebrand disease (VWD) [interim report due date: 30/06/2019; final report due date: 30/06/2022]] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.3. Results of PASS imposed in the marketing authorisation(s)[17]

7.3.1. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/PSR/S/0020

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to PSR/S/0020 [results of an observational 5 year safety study to assess the identified and potential risks of Bronchitol (mannitol) in cystic fibrosis (CF) through a comparison between Bronchitol-exposed patients and unexposed patients matched for key characteristics] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of PRAC Assessment Report

7.4. Results of PASS non-imposed in the marketing authorisation(s)[18]

7.4.1. Aflibercept - ZALTRAP (CAP) - EMEA/H/C/002532/II/0051

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from study OBS13597 (OZONE) (listed as a category 3 study in the RMP): a prospective international observational cohort non-comparative study describing the safety and effectiveness of Zaltrap (aflibercept) administered in combination with folinic acid, fluorouracil and irinotecan (FOLFIRI) for the treatment of patients with metastatic colorectal cancer in current clinical practice. The RMP (version 4.0) is updated accordingly and 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)

Action: For adoption of PRAC Assessment Report

7.4.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/LEG 011

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First interim results of a national, post-registration observational study of the long-term safety and health outcome of patients treated with Defitelio (defibrotide), including patients with severe hepatic veno-occlusive disease (VOD) after hematopoietic stem-cell transplantation (HSCT) (DEFIFRANCE registry) as requested in the conclusions of EMEA/H/C/002393/S/0038 adopted in March 2019

Action: For adoption of advice to CHMP

7.4.3. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0035

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Eva Segovia

[17] In accordance with Article 107p-q of Directive 2001/83/EC
[18] 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

Scope: Submission of the final report from study CMO-EPI-EYE-0522 (listed as a category 3 study in the RMP): an observational, cross-sectional study conducted in France, Germany, Spain, and the UK aiming at assessing the effectiveness of the educational material provided to treating physicians

Action: For adoption of PRAC Assessment Report

7.4.4. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/II/0020, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study ELIGLC06912 (listed as a category 3 study in the RMP) (MEA006): a drug utilisation study (DUS) of eliglustat in the United States (US) population using MarketScan database and the International Collaborative Gaucher Group Registry. The RMP (version 6) is updated accordingly and 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)

Action: For adoption of PRAC Assessment Report

7.4.5. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS1568/0043; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS1568/0041

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report for study HZC102972 (listed as a category 3 study in the RMP): a PASS to further characterise the important potential risk of decreased bone mineral density (BMD) and associated fractures with fluticasone furoate (FF)/vilanterol (VI) in the treatment of chronic obstructive pulmonary disease (COPD) by evaluating the effect of the inhaled corticosteroid fluticasone furoate (FF) on bone mineral density by comparing FF/VI treatment with VI treatment in subjects with moderate COPD

Action: For adoption of PRAC Assessment Report

7.4.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0085

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study CNTO148ART4002 (listed as a category 3 study in the RMP): an observational phase 4 study using the Optum Research Database (ORD) to estimate the long-term safety profile in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) who are initiating Simponi (golimumab) treatment and/or other types of biologic and non-biologic treatments. The RMP (version 19.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems' in order to reflect changes in the categorisation of safety concerns

Action: For adoption of PRAC Assessment Report

7.4.7. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0218

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final study report from the Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) cohort 2 portion of the registry: a German rheumatoid arthritis (RA) registry established as a prospective observational cohort study on the long-term safety and effectiveness of biologic disease-modifying anti-rheumatic drugs (DMARDs) in patients with RA. The RMP (version 19) is updated accordingly. The MAH also revised the RMP list of safety concerns as requested in the conclusions of procedure LEG 156 adopted in October 2017

Action: For adoption of PRAC Assessment Report

7.4.8. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/WS1596/0172; LIPROLOG (CAP) - EMEA/H/C/000393/WS1596/0133

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from an on-going review of adverse drug events related to Humalog (insulin lispro) (MEA 028) and Liprolog (insulin lispro) (MEA 021) (listed as a category 3 study in the RMP): a post approval safety surveillance programme for lot-specific adverse event review to evaluate any potential change in frequency of hypersensitivity, immunogenicity, and lack of drug effect (LODE) events for insulin lispro synthesized via streamlined lispro drug substance process (sKPB)

Action: For adoption of PRAC Assessment Report

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

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

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

Action: For adoption of PRAC Assessment Report

7.4.10. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/II/0030

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from drug utilisation study AMDC-204-403 EU (listed as a category 3 study in the RMP): a multinational retrospective medical record review to evaluate utilisation patterns of Adasuve (loxapine) for inhalation in agitated persons in

routine clinical care. The RMP (version 9.1) is updated accordingly

Action: For adoption of PRAC Assessment Report

7.4.11. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/II/0030

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report for study 178-PV-002: a drug utilisation study (DUS) of mirabegron using real-word healthcare databases from Finland, the Netherlands (NL) and the United Kingdom (UK) (in fulfilment of post-approval commitment MEA 009.2)

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. Autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/ANX 004.1

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[19]

PRAC Rapporteur: Menno van der Elst

Scope: 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 50th patient has 15 year follow-up visit - Q4 2037]

Action: For adoption of advice to CAT and CHMP

7.5.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.13

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Sixth annual interim report for study BEL116543/HGS1006-C1124: a long-term controlled safety registry evaluating the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus followed for a minimum of 5 years

Action: For adoption of advice to CHMP

7.5.3. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 010.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third monitoring interim report for PASS study 1245.97: a non-interventional PASS

[19] Advanced therapy medicinal product

assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]

Action: For adoption of advice to CHMP

7.5.4. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third monitoring interim report for PASS study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]

Action: For adoption of advice to CHMP

7.5.5. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.11

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Fourth interim report for the ongoing US non-interventional PASS (study B2311060) (listed as a category 3 study in the RMP) including data through the fourth year of PASS to estimate the incidence and compare the risks of endometrial hyperplasia and endometrial cancer among postmenopausal women initiating either Duavive (estrogens conjugated/bazedoxifene) or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT)

Action: For adoption of advice to CHMP

7.5.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 005.7

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eighth annual report from the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT): a long-term observational study of the safety of biologic treatments in rheumatoid arthritis [final clinical study report (CSR) expected in December 2022]

Action: For adoption of advice to CHMP

7.5.7. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.10

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual interim report for the passive enhanced safety surveillance study (ESS) D2560C00008: a postmarketing non-interventional cohort study of the safety of live

attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age for the 2018-2019 influenza season in England

Action: For adoption of advice to CHMP

7.5.8. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 041.2

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Third interim report for the Insuman implantable registry HUBIN-C-06380: a European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman implantable 400 IU/mL (insulin human) in Medtronic MiniMed implantable pump

Action: For adoption of advice to CHMP

7.5.9. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/ANX 041.7

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Interim descriptive report for study CC-5013-MDS-012 (listed as a category 1 study in Annex II (PSA/S/0016)): a post-authorisation, non-interventional, retrospective, drug-utilisation study (DUS) to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)

Action: For adoption of advice to CHMP

7.5.10. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 023.2

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third progress report for study V72_82OB 'Bexsero pregnancy registry': an observational study of the safety of Bexsero (meningococcal group B vaccine (recombinant, component, adsorbed)) exposure in pregnant women and their offspring

Action: For adoption of advice to CHMP

7.5.11. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

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

Action: For adoption of advice to CHMP

7.5.12. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.5

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

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

Action: For adoption of advice to CHMP

7.5.13. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

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

Action: For adoption of advice to CHMP

7.5.14. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.2

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

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

Action: For adoption of advice to CHMP

7.5.15. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Second annual interim report for PASS AC-065A401 (EXPOSURE): an observational cohort study of pulmonary arterial hypertension (PAH) patients newly treated with either Uptravi (selexipag) or any other PAH-specific therapy in routine clinical practice [final study report expected in 2023]

Action: For adoption of advice to CHMP

7.5.16. Somatropin - OMNITROPE (CAP) - EMEA/H/C/000607/MEA 012.3

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH Response to MEA 012.3 [second interim report for study EP00-501 (PATRO Children): a non-interventional post-marketing surveillance study to collect long-term safety and efficacy of Omnitrope (somatropin) in infants, children and adolescents with growth hormone deficiency and treated within routine clinical practice inEurope] as per the request for supplementary information (RSI) adopted in December 2018

Action: For adoption of advice to CHMP

7.5.17. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018.2

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Third yearly progress report for study PGL14-001: a prospective, multinational, multicentre, non-interventional study to evaluate the long-term safety of Esmya (ulipristal acetate) in particular the endometrial safety and the current prescription and management patterns of Esmya (ulipristal acetate) in a long-term treatment setting [final clinical study report (CSR) expected in 2023]

Action: For adoption of advice to CHMP

7.5.18. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.3

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: First interval safety report for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)

Action: For adoption of advice to CHMP

7.6. Others

7.6.1. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/MEA 004

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Feasibility assessment for a prospective, observational safety study to characterise the risks of the use of apalutamide in non-metastatic castration-resistant prostate cancer (NM-CRPC) patients on androgen deprivation therapy (ADT) with clinically significant cardiovascular conditions [final report expected in 2023]

Action: For adoption of advice to CHMP

7.6.2. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/MEA 013.2

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Annual report (integrated safety analysis report) for clinical studies: 1) study BRF113683 (BREAK-3): a two-arm, open-label, randomized phase 3 pivotal study comparing oral dabrafenib with intravenous dacarbazine (DTIC), 2) study MEK115306 (COMBI-d): a two-arm, double-blinded, randomized, phase 3 study comparing dabrafenib and trametinib combination therapy with dabrafenib administered with a trametinib placebo (dabrafenib monotherapy); 3) study MEK116513 (COMBI-v): a 2-arm, randomized, open-label, phase 3 study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma on secondary malignancies in patients treated with dabrafenib in randomised controlled trials to comply with the additional pharmacovigilance activity as requested in the RMP; 4) study BRF115531 (COMBI-AD): a 2-arm, randomized, double-blind, phase 3 study of dabrafenib in combination with trametinib versus two matching placebos in the adjuvant treatment of melanoma after surgical resection

Action: For adoption of advice to CHMP

7.6.3. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 025.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 025 [feasibility report for a retrospective case control study utilising medical records of transplantation centres in at least five EU Member States as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.6.4. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 026.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 026 [feasibility report for an observational study using EU registries with biomarker data, as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.6.5. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 027.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 027 [feasibility report for a genetic analysis (human

leukocyte antigen (HLA)) study using data from EU registries with biomarker data in patients with severe drug-induced liver injury (DILI), as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in January 2019

Action: For adoption of advice to CHMP

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

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

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

None

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

8.1. Annual reassessments of the marketing authorisation

8.1.1. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0064 (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

8.1.2. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0029 (without RMP)

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.3. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0063 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.4. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/S/0004 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

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. Nalotimagene carmaleucel - ZALMOXIS (CAP) - EMEA/H/C/002801/R/0015 (with RMP)

Applicant: MolMed S.p.A, ATMP[20]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CAT and CHMP

8.3. Renewals of the marketing authorisation

8.3.1. Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/R/0026 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.2. Aclidinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/R/0026 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.3. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/R/0062 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

[20] Advanced therapy medicinal product

8.3.4. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/R/0027 (without RMP)

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.5. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/R/0036 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.6. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/R/0021 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.7. Nintedanib - VARGATEF (CAP) - EMEA/H/C/002569/R/0025 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.8. Nonacog gamma - RIXUBIS (CAP) - EMEA/H/C/003771/R/0029 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.9. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/R/0029 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.10. Paliperidone - TREVICTA (CAP) - EMEA/H/C/004066/R/0022 (with RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.11. Rasagiline - RASAGILINE RATIOPHARM (CAP) - EMEA/H/C/003957/R/0014 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.12. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/R/0050 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

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. Tacrolimus – ADVAGRAF (CAP), MODIGRAF (CAP) - EMEA/H/C/WS1511/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: PRAC consultation on a grouped variations consisting of: 1) update of sections 4.5 and 4.8 of the SmPC to add the drug-drug interaction with letemovir and to add the febrile neutropenia with a frequency unknown, based on a cumulative review of the MAH's safety database; 2) update of section 4.6 of the SmPC to add information on pregnancy and lactation following the cumulative review of the cases reported in the MAH's global safety database, published literature and the transplantation pregnancy exposure registry. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes throughout the product information and to implement the wording from the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

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

10.3.1. Direct-acting oral anticoagulants (DOACs): apixaban – ELIQUIS (CAP); dabigatran etexilate – PRADAXA (CAP); rivaroxaban – XARELTO (CAP) - EMEA/H/A-5(3)/1478

Applicant(s): Bayer AG (Xarelto), Boehringer Ingelheim (Pradaxa), Bristol-Myers Squibb Pharma EEIG (Eliquis)

PRAC Rapporteur: Ulla Wändel-Liminga

Scope: PRAC consultation on the review under Article 5(3) of Regulation (EC) No 726/2004 of the results of a study (EU PAS register 16014) commissioned by the EMA: an observational study assessing the risk of major bleedings with direct oral anticoagulants (DOACs): Eliquis (apixaban), Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban) when used to prevent blood clotting in patients with non-valvular atrial fibrillation (irregular rapid contractions of the heart), in comparison with other oral anticoagulants, using databases available in the EU

Action: For adoption of advice to CHMP

10.3.2. Doxorubicin hydrochloride

PRAC Rapporteur: Eva Jirsová

Scope: PRAC consultation on mitigating the risk of medication error due to possible confusion between liposomal formulations and non-liposomal formulations

Action: For adoption of advice to CHMP

10.3.3. Gadoversetamide – OPTIMARK[21] - EMEA/H/C/000745/ANX 014.11

Applicant(s): Guerbet (Optimark) on behalf of a consortium

PRAC Rapporteur: Patrick Batty

Scope: PRAC consultation on the assessment of the interim analysis report for study ALS-Gd64/001: exploratory evaluation of the potential for long-term retention in the bone of gadolinium (Gd) in the bones of patients who have received Gd-based contrast agents (GdCAs): gadoversetamide, gadoteric acid-, gadobutrol-, gadoxetic acid-, gadopentetic acid- and gadodiamide-containing medicinal products, according to their medical history

Action: For adoption of advice to CHMP

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Fingolimod - FI/H/1028/001/DC

PRAC Lead: Kirsti Villikka

Scope: PRAC consultation on the evaluation of initial marketing authorisation application(s) under the decentralised procedure for generic fingolimod-containing medicinal products, on request of Finland

Action: For adoption of advice to Member States

11.2.2. Iron complex[22]: Ferric carboxymaltose (NAP); iron (III) isomaltosid 1000 (NAP); iron(III)-hydroxide sucrose (NAP)

Applicant(s): Vifor France (Ferinject, Monofer, Venofer)

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on the evaluation of annual reports of hypersensitivity reactions,

[21] Marketing authorisation(s) expired on 25 July 2017
[22] For intravenous (I.V.) use only

fatal cases and pregnancy cases, as required in the conclusions of the referral procedure on iron-containing products under Article 31 of Directive 2001/83/EC concluded in 2013, on request of Sweden

Action: For adoption of advice to Member States

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

Action: For discussion

12.10.3. Periodic safety update reports single assessment (PSUSA) – Joint PRAC/CMDh Action Group on 'other consideration' section – call for volunteers

Action: For discussion

12.10.4. PSURs repository

None

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

Action: For adoption

12.11. Signal management

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

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

None

12.12.2. Additional monitoring

None

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

Action: For adoption

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.15.3. Post-authorisation Safety Studies - Guidance for assessors to request the conduct of a PASS

PRAC lead: Ulla Wändel Liminga

Action: For discussion

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Strategy on measuring the impact of pharmacovigilance - PRAC interest group (IG) Impact – update on activities

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

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/