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Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 12-15 March 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

13 March 2019, 08:30 – 19:30, room 1/C

14 March 2019, 08:30 – 19:30, room 1/C

15 March 2019, 08:30 – 16:00, room 1/C

Organisational, regulatory and methodological matters (ORGAM)

28 March 2019, 09:00 – 12:00, room 6/D, via teleconference

Health and safety information

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

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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 on 12-15 March 2019. See March 2019 PRAC minutes (to be published post April 2019 PRAC meeting).

1.2. Agenda of the meeting on 12-15 March 2019

Action: For adoption

1.3. Minutes of the previous meeting on 11-14 February 2019

Action: For adoption

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

- 3.1.1. Fluorouracil and prodrugs for systemic use:
capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP);
CAPECITABINE TEVA (CAP); ECANSYA (CAP); XELODA (CAP); NAP
5-fluorouracil (5-FU) (NAP)
tegafur (NAP); tegafur, gimeracil, oteracil – TEYSUNO (CAP)

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

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

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

Action: For adoption of a list of questions

3.2. Ongoing procedures

3.2.1. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP); NAP - EMEA/H/A-31/1463

Applicants: Nordic Group B.V. (Nordimet), Therakind Limited (Jylamvo), various

PRAC Rapporteur: Martin Huber; PRAC Co-rapporteur: Željana Margan Koletić

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

Action: For discussion

3.3. Procedures for finalisation

None

3.4. Re-examination procedures¹

None

3.5. Others

None

4. Signals assessment and prioritisation²

4.1. New signals detected from EU spontaneous reporting systems

None

4.2. New signals detected from other sources

4.2.1. Levomethadone (NAP), methadone (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of opioid toxicity in infants exposed to levomethadone and/or methadone via breast milk

Action: For adoption of PRAC recommendation

EPITT 19372 – New signal

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

Lead Member State(s): AT, IE

4.2.2. Natalizumab – TYSABRI (CAP)

Applicant(s): Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of psoriasis

Action: For adoption of PRAC recommendation

EPITT 19365 – New signal

Lead Member State(s): DE

4.2.3. Ondansetron (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications

Action: For adoption of PRAC recommendation

EPITT 19353 – New signal

Lead Member State(s): SI

4.2.4. Pirfenidone – ESBRIET (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of hyponatraemia

Action: For adoption of PRAC recommendation

EPITT 19373 – New signal

Lead Member State(s): UK

4.2.5. Pirfenidone – ESBRIET (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of herpes viral infections

Action: For adoption of PRAC recommendation

EPITT 19374 – New signal

Lead Member State(s): IE, UK

4.2.6. Sodium-glucose co-transporter 2 (SGLT2) inhibitors: canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP); dapagliflozin – EDISTRIDE (CAP); dapagliflozin – FORXIGA (CAP); dapagliflozin,

metformin – EBYMECT (CAP); dapagliflozin, metformin – XIGDUO (CAP); empagliflozin – JARDIANCE (CAP); empagliflozin, metformin – SYNJARDY (CAP); ertugliflozin – STEGLATRO (CAP); ertugliflozin, metformin – SEGLUROMET (CAP)

Applicant(s): AstraZeneca AB (Ebymect, Edistride, Forxiga, Xigduo), Boehringer Ingelheim International GmbH (Jardiance, Synjardy), Janssen-Cilag International NV (Invokana, Vokanamet), Merck Sharp & Dohme B.V. (Segluromet, Steglatro)

PRAC Rapporteur: To be appointed

Scope: New information on the known association between sodium-glucose co-transporter 2 (SGLT2) inhibitors and diabetic ketoacidosis (DKA) in surgical patients

Action: For adoption of PRAC recommendation

EPITT 19355 – New signal

Lead Member State(s): DE, ES, SE, NL, UK

4.2.7. Tocilizumab – ROACTEMRA (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

Action: For adoption of PRAC recommendation

EPITT 19360 – New signal

Lead Member State(s): DE

4.2.8. Tofacitinib - XELJANZ (CAP)

Applicant(s): Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of increased risk of pulmonary embolism and overall mortality arising from a post-authorisation safety study in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily

Action: For adoption of PRAC recommendation

EPITT 19382 – New signal

Lead Member State(s): NL

4.3. Signals follow-up and prioritisation

4.3.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/SDA/032.1

Applicant(s): Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Signal of pancreatitis

Action: For adoption of PRAC recommendation

EPITT 19265 – Follow-up to January 2019

4.3.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/SDA/029.1

Applicant(s): GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of lupus nephritis

Action: For adoption of PRAC recommendation

EPITT 19174 – Follow-up to October 2018

4.3.3. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/SDA/035

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of hypoparathyroidism

Action: For adoption of PRAC recommendation

EPITT 19310 – Follow-up to November 2018

4.3.4. Paracetamol (NAP)

Applicant(s): various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus

Action: For adoption of PRAC recommendation

EPITT 17796 – Follow-up to November 2018

4.3.5. Paracetamol (NAP)

Applicant(s): various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of paracetamol use during pregnancy and premature ductus arteriosus closure in offspring

Action: For adoption of PRAC recommendation

EPITT 19297 – Follow-up to November 2018

4.3.6. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/SDA/053

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of psoriasis

Action: For adoption of PRAC recommendation

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Angiotensin II - EMEA/H/C/004930

Scope: Treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy

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

5.1.2. Ciprofloxacin - EMEA/H/C/004394

Scope: Treatment of non-cystic fibrosis bronchiectasis (NCFBE) patients with chronic lung infection with *Pseudomonas aeruginosa* (P. aeruginosa)

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

5.1.3. L-lysine hydrochloride, L-arginine hydrochloride - EMEA/H/C/004541

Scope: Reduction of renal radiation exposure during peptide-receptor radionuclide therapy (PRRT) with lutetium (¹⁷⁷Lu) oxodotreotide

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

5.1.4. Larotrectinib - EMEA/H/C/004919, Orphan

Applicant: Bayer AG

Scope: Treatment of adult and paediatric patients with locally advanced or metastatic solid tumours

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

5.1.5. Posaconazole - EMEA/H/C/005028

Scope: Treatment of fungal infections in adults

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

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

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

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Update of 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

5.2.2. [Aztreonam - CAYSTON \(CAP\) - EMEA/H/C/000996/II/0075, Orphan](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of the RMP (version 7.1) in order to reflect changes in the categorisation of safety concerns 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. [Cangrelor - KENGREXAL \(CAP\) - EMEA/H/C/003773/II/0015](#)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 2.0) in order to update the requirements for a planned study (listed as a category 3 in the RMP): a multicentre, observational, non-interventional European study of patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

Action: For adoption of PRAC Assessment Report

5.2.4. [Dexamethasone - NEOFORDEX \(CAP\) - EMEA/H/C/004071/II/0008](#)

Applicant: Laboratoires CTRS

PRAC Rapporteur: Ghania Chamouni

Scope: Update of the RMP (version 4.0) in order to propose the 'removal of the score line for subdivision of the 40 mg tablet and consequent deletion of the 20 mg posology' as a category 3 activity. In addition, the MAH updated the other category 3 activity 'development of a 20 mg oral dosage form'. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

Action: For adoption of PRAC Assessment Report

5.2.5. [Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA \(CAP\) - EMEA/H/C/000797/WS1509/0138;](#) [emtricitabine, tenofovir disoproxil - TRUVADA \(CAP\) - EMEA/H/C/000594/WS1509/0158](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Worksharing variation consisting of an update of the RMPs (version 17.1 for Atripla and version 15.5 for Truvada) in order to: 1) reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template); 2) remove the additional risk minimisation measures for tenofovir disoproxil fumarate in the form of education materials regarding renal toxicity and bone events, with the resulting amendment

of Annex II of the product information; 3) add clinical data from study GS-US-104-0352: a phase 3, randomized, open-label study comparing the safety and efficacy of switching stavudine or zidovudine to tenofovir disoproxil fumarate versus continuing stavudine or zidovudine in virologically suppressed human immunodeficiency virus (HIV)-infected children taking highly active antiretroviral therapy; 4) revise the due dates for study GS-US-276-0103 (listed as category 3 study in the RMP): a prospective, observational study of individuals who seroconvert while taking Truvada (emtricitabine/tenofovir disoproxil) for pre exposure prophylaxis (PrEP), and study GS-EU-276-4027 (listed as category 3 study in the RMP): a cross-sectional post authorisation safety study to assess healthcare provider's level of awareness of risk minimisation materials for Truvada (emtricitabine/tenofovir disoproxil) for PrEP in the European Union; 5) implement already approved administrative changes

Action: For adoption of PRAC Assessment Report

5.2.6. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/II/0017

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Update of section 4.4 of the SmPC in order to add a warning on the risk of anaphylactic reaction and update the safety information following a safety review. The package Leaflet and the RMP (version 2.0) are updated accordingly

Action: For adoption of PRAC Assessment Report

5.2.7. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP) - EMEA/H/C/000703/II/0081

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 13.1) in order to update the list of safety concerns by removing all remaining important identified and potential risks and missing information 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

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 5.1) in order to add study 20160176 (listed as category 3 in the RMP): a retrospective cohort study of female breast cancer patients aged 66 years and over selected from the US Surveillance, Epidemiology and End Results (SEER)-Medicare database to investigate the association between granulocyte colony stimulating factor (G-CSF) use and myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML), as a new pharmacovigilance activity. In addition, the MAH submitted a draft protocol for study 20160176

Action: For adoption of PRAC Assessment Report

5.2.9. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0068

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 23.1) in order to discuss the effectiveness of the educational materials put in place for Keytruda (pembrolizumab) at the time of the initial marketing authorisation, to provide a proposal to update these materials and to revise the safety specification as requested in the outcome of the PSUR single assessment procedure (PSUSA/00010403/201803) finalised in October 2018

Action: For adoption of PRAC Assessment Report

5.2.10. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0028

Applicant: Amgen Europe B.V., ATMP³

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 4.0) in order to reflect changes in the categorisation of safety concerns and missing information 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

5.3. 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 40mg 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. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0064/G

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of section 4.4 of the SmPC in order to add a warning on pulmonary events based on post-marketing data. The package leaflet is updated accordingly. Consequently, the important potential risks and the list of target medical events in the RMP (version 4.6) are updated to include pulmonary events and a specific follow-up questionnaire is introduced. The

³ Advanced therapy medicinal product

RMP is also revised in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the due date for submission of the final study report for study Sobi ANAKIN-302 (listed as a category 3 in the RMP): 'a non-interventional study to follow-up long term safety including macrophage activation syndrome (MAS) in paediatric patients with Still's disease (PRINTO/Pharmachild registry)' is proposed to be extended. Furthermore, the MAH took the opportunity to move the text about MAS and malignancies from section 4.8 to section 4.4 of the SmPC

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

5.3.3. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/X/0068

Applicant: Teva B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application to add a new strength of 2 mg/mL (concentrate for solution for solution for infusion) in vials. The RMP (version 2.0) is updated accordingly

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

5.3.4. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0065

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on suicidality and depression based on interim results from study BEL115467 (listed in Annex II): a randomized, double-blind, placebo-controlled 52-week study to assess adverse events of special interest in adults with active, autoantibody-positive systemic lupus erythematosus receiving belimumab. The package leaflet and the RMP (version 30) are updated accordingly. In addition, the MAH is proposing a direct healthcare professional communication (DHPC) and a communication plan

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/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

5.3.6. Ceftolozane, tazobactam - ZERBAXA (CAP) - EMEA/H/C/003772/II/0020

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of nosocomial pneumonia, including ventilator associated pneumonia for Zerbaxa (ceftolozane/tazobactam) based on results from study CXA-NP-11-04 (PN008): a prospective, randomised, double-blind, Phase 3 Study to assess the safety and efficacy of intravenous ceftolozane/tazobactam compared with meropenem in adult patients with ventilated nosocomial pneumonia. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 2.1) are updated accordingly. The MAH also took the opportunity to implement editorial changes in sections 5.2 of the SmPC and to bring section 4.4 of the SmPC and section 2 of the package leaflet in line with the latest Annex to the European Union (EU) 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

5.3.7. [Cinacalcet - MIMPARA \(CAP\) - EMEA/H/C/000570/II/0062/G](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of section 4.4 of the SmPC to provide additional information on switching from etelcalcetide to Mimpara (cinacalcet) as requested by PRAC in the conclusions of the PSUR single assessment procedure for etelcalcetide (PSUSA/00010533/201711) adopted in May 2018; 2) update of section 6.1 of the SmPC to replace the term 'silica, dental type' by 'amorphous silicon dioxide'. The RMP is updated (version 9.0) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

5.3.8. [Collagenase clostridium histolyticum - XIAPEX \(CAP\) - EMEA/H/C/002048/II/0107](#)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update the efficacy and safety information following the final results from study AUX-CC-810 (listed as a category 3 study in the RMP): a long-term safety, curvature deformity, characterization, and immunogenicity over time in subjects previously treated with collagenase clostridium histolyticum (AA4500) for Peyronie's disease in the following studies: 1) study AUX-CC-802: an open-label 9-month phase 3 study including patients with Peyronie's disease from the EU; 2) study AUX-CC-803: a multicentre 12-month phase 3 study including patients with Peyronie's disease from the United States; 3) study AUC-X-CC-804: a multicentre 12-month phase 3 study including patients with Peyronie's disease from Australia; 4) study AUX-CC-806: an open-label phase 3 study to support the results of studies AUX-CC-803 and AUX-CC-804. The RMP (version 14.1) is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to SmPC and package leaflet

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

5.3.9. [Darbepeotin alfa - ARANESP \(CAP\) - EMEA/H/C/000332/II/0150](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

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

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

5.3.10. 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

5.3.11. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS1461/0017; Linagliptin - TRAJENTA (CAP) - EMEA/H/C/002110/WS1461/0035 Linagliptin, metformin - JENTADUETO (CAP) - EMEA/H/C/002279/WS1461/0047

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC to update the warnings related to acute pancreatitis and bullous pemphigoid as well as the efficacy and safety information based on the final results from study CARMELINA (listed as a category 3 study in the RMP): a multicentre, international, randomised, parallel group, double blind, placebo-controlled Cardiovascular Safety & Renal Microvascular outcome study with LINAgliptin, 5 mg once daily in patients with type 2 diabetes mellitus (T2DM) at high vascular risk. The RMP is updated accordingly (Trajenta and Jentaduetto version 12, Glyxambi version 4.0) 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

5.3.12. [Fluciclovine \(¹⁸F\) - AXUMIN \(CAP\) - EMEA/H/C/004197/II/0011](#)

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include diagnosis and continuing assessment of glioma in adult patients. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 5.1, 5.2 and 11 of the SmPC and Annex II are updated. The package leaflet and the RMP (version 3.0) are updated accordingly

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

5.3.13. [Human papillomavirus vaccine \[types 6, 11, 16, 18\] \(recombinant, adsorbed\) - GARDASIL \(CAP\) - EMEA/H/C/000703/II/0080](#)

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update the information related to the effectiveness and immunogenicity of the immune response of Gardasil (human papillomavirus vaccine [types 6, 11, 16, 18]) based on the final results from the long-term follow-up of study V501-P015-21 (listed as a category 3 study in the RMP): study designed to evaluate the effectiveness, immunogenicity and safety of the quadrivalent human papillomavirus (qHPV) vaccine for at least 10 years. The package leaflet is updated accordingly. The RMP (version 12.1) is also updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH is taking the opportunity to implement minor editorial changes in the product information (SmPC, labelling and package leaflet)

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

5.3.14. [Infliximab - REMSIMA \(CAP\) - EMEA/H/C/002576/X/0062](#)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension application to introduce a solution for injection as a new pharmaceutical form, 120 mg as a new strength and subcutaneous use as a new route of administration. The RMP (version 9.1) is updated accordingly

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

5.3.15. [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

5.3.16. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0014/G, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of 1) submission of the final report of progression free survival (PFS) in fulfilment of study C16019 (SOB004): a phase 3, randomized, placebo-controlled, double-blind study of oral ixazomib citrate maintenance therapy in patients with multiple myeloma following autologous stem cell transplant; 2) request for an extension of the due date for study C16014 (SOB003): a phase 3, randomized, double-blind, multicentre study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma (NDMM). As a result, Annex II is amended. The RMP (version 4.0) is updated accordingly

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

5.3.17. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0102/G, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped applications consisting of: 1) extension of indication to include the treatment in combination with bortezomib and dexamethasone of adult patients with previously untreated multiple myeloma; 2) addition of 7-capsule pack sizes for the 7.5 mg, 20 mg and 25 mg strengths of Revlimid (lenalidomide) to support the proposed posology and lenalidomide dose modification. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated. The package leaflet and the RMP (version 36.1) are updated accordingly. Additionally, minor editorial changes are introduced throughout the product information and Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' on key elements of the risk minimisation measures (RMM) to include information on timing of blood and semen donation in line with section 4.4 of the SmPC

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

5.3.18. 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

5.3.19. [Macitentan - OPSUMIT \(CAP\) - EMEA/H/C/002697/II/0029, Orphan](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), based on: 1) pivotal study MERIT-1 (AC-055E201): a prospective, randomized, placebo-controlled, double-blind, multicentre, parallel-group, 24-week study to assess the efficacy, safety and tolerability of macitentan in subjects with inoperable CTEPH; 2) 6 months of efficacy and safety data (cut-off date 17 October 2017) from its ongoing open-label extension study MERIT-2 (AC-055E202): a long term, multicentre, single-arm, open-label extension study of the merit-1 study, to assess the safety, tolerability and efficacy of macitentan in subjects with inoperable CTEPH; 3) drug-drug interaction (DDI) study AC-055-122: a single-centre, open-label, one-sequence, two-treatment study to investigate the effect of macitentan at steady state on the pharmacokinetics (PK) of rosuvastatin in healthy male subjects; 4) DDI study AC-055-123: a single-centre, open-label, one-sequence, two-treatment study to investigate the effect of macitentan at steady state on the PK of riociguat in healthy male subjects; 5) observational data from the OPUS registry (OPsumit USers Registry; cut-off date of 17 April 2018): safety and tolerability of macitentan in a real-world setting. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 are updated. The package leaflet and the RMP (version 9.2) are updated accordingly. In addition, the MAH took the opportunity to implement editorial changes, to align the annexes with the latest QRD template and to update the contact details of the local representatives in the package leaflet

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

5.3.20. [Mepolizumab - NUCALA \(CAP\) - EMEA/H/C/003860/II/0021](#)

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information based on the final results from study 200363 part B and two open label extension (OLE) studies namely study 201312 and study MEA115666 (listed as category 3 studies in the RMP). These are interventional PASS conducted to assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to patients aged 6 to 11 years old with severe eosinophilic asthma (study 200363 Part B), to describe the long-term safety profile of mepolizumab (MEA115666), and to provide extended treatment to subjects from study MEA115661 and further describe long-term safety in these subjects (study 201312). The RMP (version 5.0) is updated accordingly and brought 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

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

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Amelia Cupelli

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

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

5.3.22. [Niraparib - ZEJULA \(CAP\) - EMEA/H/C/004249/II/0006, Orphan](#)

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to optimise the starting dose of niraparib and clarify dose modification information, modify the existing warning on haematologic adverse reactions, amend the description of thrombocytopenia and amend existing efficacy and pharmacokinetics information, respectively. The changes are based on the integrated population clinical report that contains information from: 1) completed phase 3 study NOVA (submitted as part of the initial application): a phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer; 2) supportive information from ongoing study PR-30-5020-C (QUADRA): a phase 2, open-label, single-arm study to evaluate the safety and efficacy of niraparib in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received three or four previous chemotherapy regimens; 3) study 300-PN-162-01-001 (TOPACIO): a phase 1/2 clinical study of niraparib in combination with pembrolizumab (MK-3475) in patients with advanced or metastatic triple-negative breast cancer and in patients with recurrent ovarian cancer. The package leaflet and the RMP (version 1.1) are updated accordingly. The RMP is also updated in line with revision 2 of the guidance on the format of RMP in the EU (template) and the outcome of the PSUR single assessment procedure (PSUSA/00010655/201803) finalised in October 2018

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

5.3.23. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/II/0060/G](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of an update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include information from the following studies: 1) study CA209171: a phase 2, single-arm, open-label, multicentre clinical trial with nivolumab monotherapy in subjects with advanced or metastatic squamous (Sq) cell non-small cell lung cancer (NSCLC) who have received at least one prior systemic regimen for the treatment of stage IIIb/IV Sq NSCLC; 2)

study CA209172: a phase 2, single-arm, open-label, multicentre clinical trial with nivolumab monotherapy in subjects with histologically confirmed stage III (unresectable) or stage IV melanoma progressing after prior treatment containing an anti-CTLA-4 monoclonal antibody. In addition, the MAH took the occasion to update Annex II to reflect the already fulfilled requirement regarding biomarkers data (ANX 005.3, ANX 006, ANX 023, ANX 024, ANX 026 and ANX 027). The RMP (version 13.4) is updated accordingly

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

5.3.24. [Omalizumab - XOLAIR \(CAP\) - EMEA/H/C/000606/II/0093](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.6 of the SmPC based on the data from the Xolair Pregnancy Registry (EXPECT): an observational study of the use and safety of Xolair (omalizumab) during pregnancy; and the final study report for study Q2952g (listed as a category 3 study in the RMP): an observational study to evaluate pregnancy outcomes and estimate the incidence of spontaneous foetal loss in pregnant women exposed to omalizumab prenatally and to explore the potential risk to newborn infants exposed via breast milk. The package leaflet and the RMP (version 14.0) are updated accordingly

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

5.3.25. [Pembrolizumab - KEYTRUDA \(CAP\) - EMEA/H/C/003820/II/0065](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include Keytruda (pembrolizumab) as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults; based on the results from KEYNOTE-048: a randomized, multicentre, open-label phase 3 study investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line recurrent or metastatic HNSCC. 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 22.1) are updated accordingly

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

5.3.26. [Pitolisant - WAKIX \(CAP\) - EMEA/H/C/002616/II/0017, Orphan](#)

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.4, 4.5 and 4.6 of the SmPC in order to reflect available information of co-administration of pitolisant with cytochrome P450 3A4 (CYP3A4) substrates based on the results from the following studies: 1) study R-B478-2.649: a drug-drug interaction in-vitro study of CYP450 3A induction: effect of BF2.649 (pitolisant), BP2.951 (pitolisant metabolite), BP1.8054(pitolisant metabolite) and BP1.4787 (modafinil); 2) study R.BF2.649-SK-005: evaluation of the induction potential of CYP3A4 by BF2.649, P2.951 and BP1.8054 gene expression analysis in human primary hepatocytes; 3) study R-B472-1.11413: quantification

of 4 β -hydroxycholesterol (BP1.11413) in human serum from a two-part, open label, one sequence, cross-over pharmacokinetic study to evaluate: study part I: at steady-state, the pitolisant (40 mg) interaction (as inducer) on both a single dose of midazolam and of bupropion in eighteen healthy male volunteers; study to assess the tolerance and pharmacokinetic profile of repeated 20 mg oral doses of BF2.649, in healthy elderly subjects and a young adult control group; a study to assess the potential impact of drug-drug interaction of rifampicin on the relative bioavailability of BF2.649 in healthy male subjects; B28-day repeated dose study, to evaluate pharmacokinetic parameters and accumulation rate of BF2.649, administered once a day, in six ambulatory healthy male volunteers. The MAH took the opportunity to update section 5.2 of the SmPC to more accurately reflect information previously assessed during procedure II/0004/G finalised in 2017. The RMP (version 6.0) is updated accordingly. In addition, the MAH took the opportunity to clarify details on the manufacturers of the finished product in the package leaflet

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

5.3.27. [Ramucirumab - CYRAMZA \(CAP\) - EMEA/H/C/002829/II/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) of ≥ 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

5.3.28. [Smallpox vaccine \(live modified vaccinia virus Ankara\) - IMVANEX \(CAP\) - EMEA/H/C/002596/II/0035](#)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information and to add urticaria as an adverse reaction following the final results from study POX-MVA-037 (listed as a category 3 study in the RMP (post-authorisation measure MEA 007)): a phase 2, randomized, open-label, multicentre trial designed to evaluate the safety and immunogenicity of Imvanex (modified vaccinia Ankara-Bavarian Nordic (MVA-BN) live virus smallpox vaccine) when increasing the dose or the number of injections compared with the standard 2-dose regimen in a population of adult, vaccinia naive, immunocompromised subjects with human immunodeficiency virus (HIV) infection. The RMP (version 7.1) is updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10)

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

5.3.29. [Ulipristal acetate - ESMYA \(CAP\) - EMEA/H/C/002041/II/0045/G](#)

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of final study reports from five mechanistic in vitro studies, namely: 1) 3083-N03-050: inhibition of multidrug resistance-associated protein 2 (MRP2) in vitro in membrane vesicles (PAM MEA 020); 2) 3083-N04-050: cell viability in 3D spheroid micro-tissues (PAM MEA 021); 3) 3083-N05-050: cell viability in 'sandwich' (PAM MEA 022); 4) 3083-N01-050: effects of ulipristal acetate (UPA) and its main metabolite PGL4002 on mitochondrial function and cell health markers in vitro in HepG2⁴ cells (PAM REC), 4) 3083-N02-050: in vitro interaction studies of UPA and PGL4002 test articles with human bile salt export pump (BSEP), MRP3 (multidrug resistance-associated protein 3) and multidrug resistance-associated protein 4 (MRP4) efflux (ABC) transporters and with the human sodium/taurocholate co-transporting polypeptide (NTCP) uptake transporter (PAM REC), as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMA/H/A-20/1460). The RMP (version 16.1) is updated accordingly

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

5.3.30. Varenicline - CHAMPIX (CAP) - EMA/H/C/000699/II/0074

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to reflect results of paediatric study A3051073 (MEA 047): a phase 4, twelve-week, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study with follow-up, evaluating the safety and efficacy of varenicline for smoking cessation in healthy adolescent smokers. The package leaflet and the RMP (version 11.0) are updated accordingly

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

6. Periodic safety update reports (PSURs)

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

6.1.1. Agalsidase alfa - REPLAGAL (CAP) - PSUSA/00000069/201808

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.2. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (Δ LNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS (CAP) - PSUSA/00010530/201808

Applicant: MolMed S.p.A, ATMP⁵

⁴ Human liver cancer cell line

⁵ Advanced therapy medicinal product

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CAT and CHMP

6.1.3. [Asenapine - SYCREST \(CAP\) - PSUSA/00000256/201808](#)

Applicant: N.V. Organon

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.4. [Baricitinib - OLUMIANT \(CAP\) - PSUSA/00010578/201808](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.5. [Bedaquiline - SIRTURO \(CAP\) - PSUSA/00010074/201809](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.6. [Burosumab - CRYSVITA \(CAP\) - PSUSA/00010669/201808](#)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.7. [Ceftazidime, avibactam - ZAVICEFTA \(CAP\) - PSUSA/00010513/201808](#)

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.8. [Chlormethine - LEDAGA \(CAP\) - PSUSA/00010587/201808](#)

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.9. [Cobicistat - TYBOST \(CAP\) - PSUSA/00010081/201808](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.10. [Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD \(CAP\) - PSUSA/00010082/201808](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.11. [Cobimetinib - COTELLIC \(CAP\) - PSUSA/00010450/201808](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.12. [Copper \(⁶⁴Cu\) chloride - CUPRYMINA \(CAP\) - PSUSA/00010040/201808](#)

Applicant: Sparkle S.r.l.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.13. [Dabrafenib - TAFINLAR \(CAP\) - PSUSA/00010084/201808](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.14. [Deferiprone - FERRIPROX \(CAP\) - PSUSA/00000940/201808](#)

Applicant: Apotex Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.15. [Diphtheria, tetanus, pertussis \(acellular, component\), hepatitis B \(rDNA\), poliomyelitis \(inactivated\), haemophilus type b conjugate vaccine \(adsorbed\) - VAXELIS \(CAP\) - PSUSA/00010469/201808](#)

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.16. [Eliglustat - CERDELGA \(CAP\) - PSUSA/00010351/201808](#)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.17. [Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR \(CAP\) - PSUSA/00010352/201808](#)

Applicant: Chiesi Farmaceutici S.p.A., ATMP⁶

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CAT and CHMP

6.1.18. [Ferric maltol - FERACCRU \(CAP\) - PSUSA/00010476/201808](#)

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.19. [Fluticasone, salmeterol⁷ - AERIVIO SPIROMAX \(CAP\); AIREXAR SPIROMAX \(CAP\) - PSUSA/00010531/201808](#)

Applicant: Teva B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

⁶ Advanced therapy medicinal product

⁷ Centrally authorised product(s) only

6.1.20. Glimepiride, pioglitazone hydrochloride - TANDEMACT (CAP); metformin, pioglitazone - COMPETACT (CAP), GLUBRAVA (CAP); pioglitazone - ACTOS (CAP), GLUSTIN (CAP) - PSUSA/00002417/201807 (with RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.21. Human alpha₁-proteinase inhibitor⁸- RESPREEZA (CAP) - PSUSA/00010410/201808

Applicant: CSL Behring GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.22. Human coagulation factor VIII, human von Willebrand factor⁹ - VONCENTO (CAP) - PSUSA/00010102/201808

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.23. Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/201808

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.24. Interferon beta-1b - BETAFERON (CAP); EXTAVIA (CAP) - PSUSA/00001759/201807

Applicant(s): Bayer AG (Betaferon), Novartis Europharm Limited (Extavia)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.25. Linaclotide - CONSTELLA (CAP) - PSUSA/00010025/201808

Applicant: Allergan Pharmaceuticals International Limited

⁸ Centrally Authorised Product(s) only

⁹ Centrally Authorised Product(s) only

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.26. [Loxapine¹⁰ - ADASUVE \(CAP\) - PSUSA/00010113/201808](#)

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.27. [Maraviroc - CELSENTRI \(CAP\) - PSUSA/00001934/201808](#)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.28. [Mecasermin - INCRELEX \(CAP\) - PSUSA/00001942/201808](#)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.29. [Nonacog alfa - BENEFIX \(CAP\) - PSUSA/00002183/201808](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.30. [Pandemic influenza vaccine \(H5N1\) \(whole virion, vero cell derived, inactivated\) - PANDEMIC INFLUENZA VACCINE H5N1 BAXTER \(CAP\); prepandemic influenza vaccine \(H5N1\) \(whole virion, vero cell derived, inactivated\) - VEPACEL \(CAP\) - PSUSA/00002282/201808](#)

Applicant: Ology Bioservices Ireland Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

¹⁰ Pre-dispensed inhalation powder only

6.1.31. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/201808

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.32. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201809

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.33. Pyronaridine, artesunate - PYRAMAX (Art 58¹¹) - EMEA/H/W/002319/PSUV/0020

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUR procedure

Action: For adoption of recommendation to CHMP

6.1.34. Reslizumab - CINQAERO (CAP) - PSUSA/00010523/201808

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.35. Rolapitant - VARUBY (CAP) - PSUSA/00010592/201808

Applicant: Tesaro UK Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.36. Safinamide - XADAGO (CAP) - PSUSA/00010356/201808

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

¹¹ 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)

Action: For adoption of recommendation to CHMP

6.1.37. Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/201808

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.38. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/201808

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.39. Telotristat ethyl - XERMELO (CAP) - PSUSA/00010639/201808

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.40. Tivozanib - FOTIVDA (CAP) - PSUSA/00010636/201808

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.41. Vemurafenib - ZELBORAF (CAP) - PSUSA/00009329/201808

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

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. Eflornithine - VANIQA (CAP), NAP - PSUSA/00001202/201807

Applicants: Almirall S.A (Vaniqa), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.2. Human protein c - CEPROTIN (CAP); NAP - PSUSA/00002563/201807

Applicants: Baxter AG (Ceprotrin), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

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. Adapalene (NAP) - PSUSA/00000058/201807

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.2. Alprostadil¹² (NAP) - PSUSA/00010021/201807

Applicant(s): various

PRAC Lead: Daniela Philadelphly

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.3. Amlodipine, rosuvastatin (NAP) - PSUSA/00010434/201807

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.4. Atorvastatin, ezetimibe (NAP) - PSUSA/00010385/201807

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

¹² Indicated for maintaining the patency of the ductus arteriosus

6.3.5. Benperidol (NAP) - PSUSA/00000329/201807

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.6. Budesonide, salmeterol (NAP) - PSUSA/00010511/201807

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.7. Colchicine (NAP) - PSUSA/00000858/201807

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.8. Everolimus¹³ (NAP) - PSUSA/00010269/201807

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.9. Fluticasone propionate, formoterol fumarate dihydrate (NAP) - PSUSA/00010339/201807

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.10. Inosine dimepranol acedoben (NAP) - PSUSA/00010425/201808

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

¹³ Indicated for the prevention of rejection of transplanted organs only

Action: For adoption of recommendation to CMDh

6.3.11. [Landiolol \(NAP\) - PSUSA/00010570/201808](#)

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.12. [Magnesium sulfate, sodium sulfate, potassium sulfate \(NAP\) - PSUSA/00010239/201808](#)

Applicant(s): various

PRAC Lead: Jana Lukačšínová

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.13. [Miglitol \(NAP\) - PSUSA/00002061/201808](#)

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.14. [Montelukast \(NAP\) - PSUSA/00002087/201807](#)

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.15. [Opium \(NAP\) - PSUSA/00010670/201808](#)

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.16. [Paracetamol, tramadol \(NAP\) - PSUSA/00002310/201808](#)

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.17. Poliovirus type 1, poliovirus type 3 (oral, live, attenuated) vaccine (NAP) - PSUSA/00010642/201807

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.18. Tiapride (NAP) - PSUSA/00002944/201807

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/LEG 010.2

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to LEG 010.1 [overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the effectiveness of each measure in place to minimise any risk (including educational material and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017] as per the request for supplementary information (RSI) adopted in September 2018

Action: For adoption of advice to CHMP

6.4.2. Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/LEG 086.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to LEG 086.1 [overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the effectiveness of each measure in place to minimise any risk (including educational material and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017] as per the request for supplementary information (RSI) adopted in September 2018

Action: For adoption of advice to CHMP

6.4.3. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/LEG 014

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Review of cases of meningioma associated with estradiol/nomegestrol use including a thorough discussion on whether the individual dose of each component and interactions between oestrogens and progestogens could limit the extrapolation from nomegestrol monocomponent to Zoely (estradiol/nomegestrol acetate) in relation to this risk, as requested in the conclusions of PSUSA/00002182/201801 adopted in October 2018

Action: For adoption of advice to CHMP

6.4.4. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/LEG 057

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Detailed analysis of cases of hypofibrinogenaemia and whether these cases observed in tocilizumab-exposed patients are related to a disorder of liver protein synthesis performance, as requested in the conclusions of PSUSA/00002980/201804 adopted at the November 2018 PRAC

Action: For adoption of advice to CHMP

6.4.5. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/LEG 027

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Reviews of cases of 'medication errors', 'vomiting' and 'blurred vision' as requested in the conclusions of PSUSA/00003103/201802 adopted in October 2018

Action: For adoption of advice to CHMP

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)¹⁴

7.1.1. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/PSP/S/0063.2

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to PSP/S/0063.1 [protocol for study 190-504 (replacing study 190-501): a non-interventional PASS (observational drug study) in order to evaluate the long-term safety of cerliponase alfa, including the occurrence of serious hypersensitivity reactions and anaphylaxis in patients with neuronal ceroid lipofuscinosis type 2 (CLN2)] as per the request for supplementary information (RSI) adopted at the November 2018 PRAC

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

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

7.1.2. Radium (Ra223) dichloride - XOFIGO (CAP) - EMEA/H/C/PSP/S/0076

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Protocol for a PASS to estimate the incidence rate of symptomatic bone fractures among users of Xofigo (Ra-223) in routine clinical practice

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

7.1.3. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/PSP/S/0077

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a study evaluating the long-term safety of Adynovi (rurioctocog alfa pegol) in adults and adolescents ≥ 12 years of age with haemophilia A

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

7.1.4. Umeclidinium bromide – INCRUSE ELLIPTA (CAP), ROLUFTA ELLIPTA (CAP); umeclidinium bromide, vilanterol – ANORO ELLIPTA (CAP), LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/PSA/S/0032.1

Applicant: Glaxo Group Limited

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to PSA/S/0032 [amendment to a protocol initially endorsed by PRAC in March 2015 (EMEA/H/C/PSP/J/003.1) for study 201038: a post-authorisation safety (PAS) observational cohort study to quantify the incidence of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients using inhaled umeclidinium bromide/vilanterol (UMEC/VI) combination, inhaled UMEC, or tiotropium] as per the request for supplementary information (RSI) adopted in October 2018

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)¹⁵

7.2.1. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 011.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 011.2 [revised statistical analysis plan (SAP) and submission of protocol for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a

¹⁵ 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

randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in October 2018

Action: For adoption of advice to CHMP

7.2.2. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMA/H/C/003833/MEA 003.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 003.2 [revised statistical analysis plan (SAP) and submission of protocol for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in October 2018

Action: For adoption of advice to CHMP

7.2.3. Empagliflozin, metformin - SYNJARDY (CAP) - EMA/H/C/003770/MEA 007.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 007.2 [revised statistical analysis plan (SAP) and submission of protocol for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with

heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in October 2018

Action: For adoption of advice to CHMP

7.2.4. Ertugliflozin - STEGLATRO (CAP) - EMA/H/C/004315/MEA 002

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023] (from initial opinion/MA)

Action: For adoption of advice to CHMP

7.2.5. Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMA/H/C/004314/MEA 002

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023] (from initial opinion/MA)

Action: For adoption of advice to CHMP

7.2.6. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMA/H/C/004313/MEA 002

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023] (from initial opinion/MA)

Action: For adoption of advice to CHMP

7.2.7. Niraparib - ZEJULA (CAP) - EMA/H/C/004249/MEA 002.2

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 002.1 [protocol for study 3000-04-001: a non-interventional PASS to evaluate the risks of myelodysplastic syndrome/acute myeloid leukaemia and secondary primary malignancies in adult patients with relapsed ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula (niraparib)] as per the request for supplementary information (RSI) adopted in October 2018

Action: For adoption of advice to CHMP

7.2.8. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.1 [PASS protocol for a safety surveillance programme using existing EU rheumatoid arthritis (RA) registries conducted in four countries: Germany (German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (OBS15180)), Spain (Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER) (6R88-RA-1720)), Sweden (Register for Antirheumatic Therapies in Sweden (ARTIS) (OBS15220)) and UK (British Society for Rheumatology Biologicals Register (BSRBR) (6R88-RA-1634)) (from initial MAA/opinion)] as per the request for supplementary information (RSI) adopted in September 2018

Action: For adoption of advice to CHMP

7.2.9. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/MEA 008.1

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 008 [protocol for a study to evaluate the effectiveness of risk minimisation measures (RMM): a survey among healthcare professionals to assess their knowledge on dosing and administration of Obizur (susoctocog alfa) in six European countries] as per the request for supplementary information (RSI) adopted in September 2018

Action: For adoption of advice to CHMP

7.3. Results of PASS imposed in the marketing authorisation(s)¹⁶

7.3.1. Valproate (NAP) - EMEA/H/N/PSI/J/0003

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSI/J/0003 [third interim result report for a joint drug utilisation study (DUS) of valproate and related substances conducted in Europe aiming at describing the prescribing practices before and after the dissemination of risk minimisation measures (RMM) (i.e. educational materials and direct healthcare professional communication (DHPC)) and assessing the effectiveness of these measures using databases, as requested in the outcome of the referral procedure on valproate and related substances (EMEA/H/A-31/1387) concluded in 2014] as per the request for supplementary information (RSI) adopted at the November 2018 PRAC

¹⁶ In accordance with Article 107p-q of Directive 2001/83/EC

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

7.4. Results of PASS non-imposed in the marketing authorisation(s)¹⁷

7.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0124/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped variations consisting of: 1) submission of the final reports from studies (listed as category 3 studies in the RMP), namely: study IM101125: a nationwide post-marketing study on the safety of abatacept treatment in Sweden Using the 'Antirheumatic Therapies in Sweden (ARTIS)' register, study IM101127: a long-term observation of treatment with biologics in rheumatoid arthritis (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)), study IM101211: a multinational surveillance of abatacept-treated patients during disease registries, study IM101213: a post-marketing observational study assessing the long-term safety of abatacept using a population-based cohort of rheumatoid arthritis patients in the province of British Columbia, Canada, as well as the interim report from study IM101121: Abatacept Pregnancy Exposure Registry 'Organization of Teratology Information Specialists (OTIS)' autoimmune diseases in pregnancy project an extension study. These are biologic registries and pharmacoepidemiology studies to assess the risk associated with the use of abatacept during post-marketing in geographically diverse populations and subgroups; 2) submission of the final study report from study IM101488: a retrospective cohort study assessing the long-term safety of abatacept; 3) The deadline for submission of the final study report from study IM101121 (pregnancy registry) is proposed to be extended. The RMP (version 26) is updated accordingly and also include the addition of two epidemiological studies as category 3 studies in the RMP, namely: study IM101803: a nationwide post-marketing study on the safety of abatacept treatment in Denmark using the DANBIO¹⁸ register and IM101W52: a nationwide post-marketing study on the safety of abatacept treatment in Sweden using the ARTIS register. In addition, the RMP is updated to remove the following missing information: combination therapy, including biologic therapy, and elderly patients

Action: For adoption of PRAC Assessment Report

7.4.2. 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)

¹⁷ 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

¹⁸ A nationwide registry of biological therapies in Denmark

Action: For adoption of PRAC Assessment Report

7.4.3. [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

7.4.4. [Etanercept - ENBREL \(CAP\) - EMEA/H/C/000262/WS1526/0223; LIFMIOR \(CAP\) - EMEA/H/C/004167/WS1526/0018](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) register cohort 2 (listed as a category 3 study in the RMP): a prospective, non-interventional, observational, long-term cohort Germanic biologics register to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor (TNF)-inhibitor therapies in the treatment of rheumatoid arthritis (RA) in comparison to cohorts of RA patients treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic (b)DMARDs

Action: For adoption of PRAC Assessment Report

7.4.5. [Filgrastim - FILGRASTIM HEXAL \(CAP\) - EMEA/H/C/000918/MEA 006.6](#)

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 006.4 [submission of the final results for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase 4 study based on data collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients were followed-up for a total of five years (one year in the SCN study and four years within the registry)] as per the request for supplementary information (RSI) adopted in October 2018

Action: For adoption of advice to CHMP

7.4.6. [Filgrastim - ZARZIO \(CAP\) - EMEA/H/C/000917/MEA 006.6](#)

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 006.4 [submission of the final results for study EP006-401:

safety follow-up of severe chronic neutropenia (SCN) patients included in phase 4 study based on data collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients were followed-up for a total of five years (one year in the SCN study and four years within the registry)] as per the request for supplementary information (RSI) adopted in October 2018

Action: For adoption of advice to CHMP

7.4.7. [Idelalisib - ZYDELIG \(CAP\) - EMEA/H/C/003843/II/0046](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for study GS-EU-313-4226 (listed as a category 3 study in the RMP): a cross-sectional PASS to assess healthcare provider awareness of risks associated with Zydelig (idelalisib) in the European Union. The study assesses the effectiveness of additional risk minimisation measures (RMM) by determining the level of knowledge of haematologists and oncologists on the infection risks associated with Zydelig (idelalisib) treatment and the corresponding recommendation to minimise these risks (fulfilment of post-authorisation measures (PAM) MEA 016)

Action: For adoption of PRAC Assessment Report

7.4.8. [Indacaterol, glycopyrronium - ULTIBRO BREEZHALER \(CAP\) - EMEA/H/C/002679/WS1543/0029; ULUNAR BREEZHALER \(CAP\) - EMEA/H/C/003875/WS1543/0029; XOTERNA BREEZHALER \(CAP\) - EMEA/H/C/003755/WS1543/0033](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final study report for study CQVA149A2402 (listed as a category 1 study): a multinational database cohort study in Europe in chronic obstructive pulmonary disease (COPD) patients, to assess the incidence rates and hazard ratios of various safety outcomes in new users of indacaterol/glycopyrronium compared to new users of comparator drugs (at the drug-class level). The product information is updated to remove the black triangle and to amend Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' to remove the obligation to conduct the study. The RMP (version 5.0) is updated accordingly

Action: For adoption of PRAC Assessment Report

7.4.9. [Pegvisomant - SOMAVERT \(CAP\) - EMEA/H/C/000409/II/0089](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final clinical study report (CSR) from A6291010 (ACROSTUDY) (listed as a category 3 study in the RMP): an open-label, global, non-interventional PASS performed to monitor the long-term safety and outcomes of pegvisomant treatment in clinical practice (fulfilment of post-authorisation measures (PAM) MEA 059)

Action: For adoption of PRAC Assessment Report

7.4.10. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/WS1557/0120; PROMETAX (CAP) - EMEA/H/C/000255/WS1557/0121

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final report for study CENA713D2409: a drug utilisation study (DUS) aimed to assess the extent of inappropriate use of Exelon/Prometax (rivastigmine) (fulfilment of post-authorisation measures (PAM) Exelon MEA 034 and Prometax MEA 035)

Action: For adoption of PRAC Assessment Report

7.4.11. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/II/0078

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final clinical study report (CSR) for study NA0001: a PASS on the effectiveness of the educational materials for Xyrem (sodium oxybate)

Action: For adoption of PRAC Assessment Report

7.4.12. Vardenafil - LEVITRA (CAP) - EMEA/H/C/000475/WS1536/0064; VIVANZA (CAP) - EMEA/H/C/000488/WS1536/0060

Applicant: Bayer AG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final clinical study report (CSR) for study 12912: (listed as category 3 study in the RMP) a non-interventional PASS to investigate the risk of non-arteritic anterior ischemic optic neuropathy (NAION) associated with phosphodiesterase type 5 (PDE5) inhibitors. The RMP (version 6.0) is updated accordingly

Action: For adoption of PRAC Assessment Report

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

7.5.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017.3

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Second interim report for study ALIROC07997: a PASS using healthcare databases, in order to monitor the safety of Praluent (alirocumab) in patients affected with the human immunodeficiency virus (HIV) (from initial opinion/MA)

Action: For adoption of advice to CHMP

7.5.2. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 053.1

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Interim report for study M07-001: a prospective registry for an observational, multicentre, multinational study of patients with paroxysmal nocturnal haemoglobinuria (PNH)

Action: For adoption of advice to CHMP

7.5.3. [Florbetaben \(¹⁸F\) - NEURACEQ \(CAP\) - EMEA/H/C/002553/MEA 001.8](#)

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Martin Huber

Scope: Interim report for study FBB-01_03_13 (PASS 2): a non-interventional, prospective observational multicentre, multi-country registry to observe usage pattern, safety and tolerability of the diagnostic agent NeuraCeq (florbetaben (¹⁸F)) in clinical practice [final clinical study report (CSR) expected in Q2/2020]

Action: For adoption of advice to CHMP

7.5.4. [Infliximab - REMICADE \(CAP\) - EMEA/H/C/000240/MEA 133.13](#)

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eleventh annual paediatric inflammatory bowel disease (IBD) registry (DEVELOP) report on long-term safety and efficacy of infliximab and other therapies, safety and efficacy of variable infliximab dosing intervals, episodic therapy, monotherapy (initiated de novo or following discontinuation of concomitant immunomodulators), combined infliximab and immunomodulator therapy (azathioprine/6-mercaptopurine (AZA/6-MP) or methotrexate (MTX))

Action: For adoption of advice to CHMP

7.5.5. [Insulin glargine, lixisenatide - SULIQUA \(CAP\) - EMEA/H/C/004243/MEA 005.1](#)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Second annual progress report for a patient registry of lixisenatide use in adult patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and databases in Italy and Belgium [final report due date: December 2020] (from initial MAA/opinion)

Action: For adoption of advice to CHMP

7.5.6. [Lixisenatide - LYXUMIA \(CAP\) - EMEA/H/C/002445/MEA 008.3](#)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Second annual progress report for a patient registry of lixisenatide use in adult patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer

and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and databases in Italy and Belgium [final report due date: December 2020] (from initial MAA/opinion)

Action: For adoption of advice to CHMP

7.5.7. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 001.7

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Interim results for study 178-CL-114: a non-imposed, non-interventional, safety long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (individual and composite outcomes) in patients administered mirabegron and other treatments for overactive bladder

Action: For adoption of advice to CHMP

7.5.8. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 009.2

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Annual progress study report for study D3820R00008: a US post-marketing, comparative, observational study in order to evaluate the cardiovascular safety of naloxegol in patients with non-cancer pain in comparison to other treatments for opioid induced constipation [final study report: December 2023]

Action: For adoption of advice to CHMP

7.5.9. Voriconazole - VFEND (CAP) - EMEA/H/C/000387/MEA 091.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Interim report for study A1501103: a non-interventional PASS, an active safety surveillance programme to monitor selected events in patients with long-term voriconazole use

Action: For adoption of advice to CHMP

7.6. Others

7.6.1. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/LEG 087.6

Applicant: Roche Registration GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Sixth annual review on pregnancy cases

Action: For adoption of advice to CHMP

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

8.1.1. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0038 (with RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.2. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0047 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.2. Conditional renewals of the marketing authorisation

8.2.1. Pixantrone - PIXUVRI (CAP) - EMEA/H/C/002055/R/0046 (with RMP)

Applicant: CTI Life Sciences Deutschland GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3. Renewals of the marketing authorisation

8.3.1. Canakinumab - ILARIS (CAP) - EMEA/H/C/001109/R/0062 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.2. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/R/0028

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.3. Flutemetamol (¹⁸F) - VIZAMYL (CAP) - EMEA/H/C/002557/R/0017 (without RMP)

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.4. Insulin degludec, liraglutide - XULTOPHY (CAP) - EMEA/H/C/002647/R/0028 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.5. Insulin glargine - ABASAGLAR (CAP) - EMEA/H/C/002835/R/0023 (without 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. Tacrolimus - ENVARUSUS (CAP) - EMEA/H/C/002655/R/0014 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ronan Grimes

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. Ibrutinib – IMBRUVICA (CAP) – EMEA/H/C/003791/II/0048

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Update of section 4.4 of the SmPC in order to add a warning under 'bleeding-related events' based on the final clinical study report results for study PCYC-PMR-2060-4 (listed as a category 3 study in the RMP): a non-interventional PASS exploring the risk of serious haemorrhage. In addition, the MAH took the opportunity to include minor editorial changes in the list of local representatives in the package leaflet

Action: For adoption of advice to CHMP

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Carbetocin (NAP) - UK/H/PSUFU/000546/201706

Applicant(s): Ferring Pharmaceuticals (Pabal 100 micrograms/ml solution for injection), Laboratorios GP Pharm (Carbetocin 100 micrograms solution for injection in pre-filled syringe)

PRAC Lead: Julie Williams

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on the review of the risk of myocardial ischaemia, arrhythmia and angina pectoris and on the review of the risk of anaphylaxis in patients with latex allergy as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on tramadol (PSUSA/00000546/201706) concluded in March 2018, on request of the United Kingdom

Action: For adoption of advice to Member States

11.2.2. Levonorgestrel (NAP) - DE/H/PSUFU/00001856/201712/I

Applicants: Bayer AG (Mirena, Jaydess/Luadei, Kyleena), Mithra Pharmaceuticals (Levosert)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on detailed analyses on the effectiveness of the current educational material for levonorgestrel-containing intrauterine device (IUDs) and reviews of the educational material safety concerns and key elements' as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on levonorgestrel (PSUSA/00001856/201712) concluded in September 2018, on request of Germany

Action: For adoption of advice to Member States

11.2.3. Levonorgestrel (NAP) - DE/H/PSUFU/00001856/201712/II

Applicants: Bayer AG (Mirena, Jaydess/Luadei, Kyleena), Mithra Pharmaceuticals (Levosert)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on detailed analyses of the 'risk of expulsion of levonorgestrel-containing intrauterine device (IUDs) in obese women' as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on levonorgestrel (PSUSA/00001856/201712) concluded in September 2018, on request of Germany

Action: For adoption of advice to Member States

11.2.4. Tramadol (NAP) - UK/H/PSUFU/00003002/201705

Applicants: various

PRAC Lead: Julie Williams

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on the review of cases of anorgasmia reported with tramadol therapy as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on tramadol (PSUSA/00003002/201705) concluded in January 2018, on request of the United Kingdom

Action: For adoption of advice to Member States

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. Brexit – Rapporteurship transfer and EMA knowledge sharing package to support UK portfolio transfer

Action: For discussion

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Handling of confidential information within the EU network

Action: For discussion

12.4.2. PRAC Strategic Review and Learning Meeting (SRLM) under the Romanian presidency of the European Union (EU) Council – Bucharest, Romania, 22-23 May 2019 - agenda

PRAC lead: Roxana Stroe, Alexandra Spurni

Action: For discussion

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

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. PSURs repository

None

12.10.4. 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 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

12.16. 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

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/