1 October 2018
EMA/PRAC/678706/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 01-04 October 2018

Chair: Sabine Straus – Vice-Chair: Martin Huber

01 October 2018, 13:00 – 19:30, room 3/A

02 October 2018, 08:30 – 19:30, room 3/A

03 October 2018, 08:30 – 19:30, room 3/A

04 October 2018, 08:30 – 16:00, room 3/A

Organisational, regulatory and methodological matters (ORGAM)

18 October 2018, 09:00-12:00, room 9/B, via teleconference

Health and safety information

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

Disclaimers

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

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

Note on access to documents

Some documents mentioned in the agenda cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to 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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

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 01-04 October 2018. See October 2018 PRAC minutes (to be published post November 2018 PRAC meeting).

1.2. Agenda of the meeting on 01-04 October 2018

Action: For adoption

1.3. Minutes of the previous meeting on 03-06 September 2018

Action: For adoption

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Methotrexate[1] - JYLAMVO (CAP); NAP - EMEA/H/A-31/1463

Applicants: 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 adoption of a list of outstanding issues (LoOI)

3.3. Procedures for finalisation

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

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

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

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

Action: For adoption of a recommendation to CHMP

3.4. Re-examination procedures[2]

None

3.5. Others

None

[1] For oral use
[2] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Avelumab – BAVENCIO (CAP)

Applicant(s): Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of pancreatitis

Action: For adoption of PRAC recommendation

EPITT 19291 – New signal

Lead Member State(s): DK

4.1.2. Tocilizumab – ROACTEMRA (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of facial paralysis

Action: For adoption of PRAC recommendation

EPITT 19295 – New signal

Lead Member State(s): DE

4.2. New signals detected from other sources

4.2.1. Canagliflozin – INVOKANA (CAP); dapagliflozin - FORXIGA (CAP); empagliflozin - JARDIANCE (CAP); ertugliflozin – STEGLATRO (CAP)

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

PRAC Rapporteur: To be appointed

Scope: Signal of Fournier's gangrene

Action: For adoption of PRAC recommendation

EPITT 19308 – New signal

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

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

4.2.2. Olanzapine – ZALASTA (CAP), ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP); NAP

Applicant(s): Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), Krka, d.d. (Zalasta), various

PRAC Rapporteur: To be appointed

Scope: Signal of gestational diabetes

Action: For adoption of PRAC recommendation

EPITT 19306 – New signal

Lead Member State(s): FI

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab – AMGEVITA (CAP), CYLTEZO (CAP), HUMIRA (CAP), IMRALDI (CAP), SOLYMBIC (CAP); infliximab – FLIXABI (CAP), INFLECTRA (CAP), REMICADE (CAP), REMSIMA (CAP)

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Humira), Amgen Europe B.V. (Amgevita, Solymbic), Boehringer Ingelheim International GmbH (Cyltezo), Celltrion Healthcare Hungary Kft. (Remsima), Janssen Biologics B.V. (Remicade), Pfizer Europe MA EEIG (Inflectra), Samsung Bioepis UK Limited (Flixabi, Imraldi)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of risk of lymphoma in patients with inflammatory bowel disease

Action: For adoption of PRAC recommendation

EPITT 19121 – Follow-up to April 2018

4.3.2. Belimumab – BENLYSTA (CAP)

Applicant(s): Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of lupus nephritis

Action: For adoption of PRAC recommendation

EPITT 19174 – Follow-up to April 2018

4.3.3. Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/SDA/021; dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/SDA/010; elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/SDA/010; glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/SDA/009; ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/SDA/019; ombitasvir, peritеprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/SDA/012; sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/SDA/026; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/SDA/010; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/SDA/003

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Exviera, Maviret, Viekirax), Bristol-Myers Squibb Pharma EEIG (Daklinza), Gilead Sciences Ireland UC (Epclusa, Harvoni, Sovaldi, Vosevi), Merck Sharp & Dohme B.V. (Zepatier)

PRAC Rapporteur: Julie Williams

Scope: Signal of dysglycaemia

Action: For adoption of PRAC recommendation

EPITT 19234 – Follow-up to May 2018

4.3.4. Dolutegravir – TIVICAY (CAP) – EMEA/H/C/002753/SDA/009; abacavir sulfate, dolutegravir sodium, lamivudine – TRIUMEQ (CAP); dolutegravir, rilpivirine – JULUCA (CAP)

Applicant(s): ViiV Healthcare B.V. (Tivicay), ViiV Healthcare UK Limited (Juluca, Triumeq)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women

Action: For adoption of PRAC recommendation

EPITT 19244 – Follow-up to June 2018

4.3.5. Hormonal contraceptives: Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol[4] (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, nomegestrol acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene[5] (NAP); ethinylestradiol, gestodene[6] (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol[7] (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP)

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

PRAC Rapporteur: Menno van der Elst

[4] Contraception indication
[5] All route of administrations except transdermal
[6] Transdermal application
[7] Combination pack

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

Action: For adoption of PRAC recommendation

EPITT 19143 – Follow-up to July 2018

4.3.6. Hormonal contraceptives: Chlormadinone, estradiol (NAP); chlormadinone acetate, ethinylestradiol (NAP); conjugated estrogens, medrogestone (NAP); conjugated estrogens, medroxyprogesterone acetate (NAP); conjugated estrogens, norgestrel (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel ,ethinylestradiol (NAP); dienogest, estradiol[8] (NAP); dienogest, ethinylestradiol (NAP); drospirenone, estradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, estriol, levonorgestrel (NAP); estradiol, gestodene (NAP); estradiol, levonorgestrel (NAP); estradiol, medroxyprogesterone acetate (NAP); estradiol, nomegestrol acetate (NAP); estradiol, norethisterone (NAP); estradiol, norgestimate (NAP); estradiol (17-beta), progesterone (NAP); estradiol (17-beta), trimegestone (NAP); estradiol valerate, norgestrel (NAP); ethinylestradiol, etonogestrel (NAP); ethinylestradiol, etynodiol (NAP); ethinylestradiol, gestodene[9] (NAP); ethinylestradiol, gestodene[10] (NAP); ethinylestradiol, levonorgestrel (NAP); ethinylestradiol, lynestrenol (NAP); ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol[11] (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); mestranol, norethisterone (NAP); nomegestrol (NAP); nomegestrol acetate, estradiol – ZOELY (CAP); norelgestromin, ethinyl estradiol – EVRA (CAP), NAP; norethisterone (NAP)

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

PRAC Rapporteur: Doris Stenver

Scope: Signal of suicidality with hormonal contraceptives following a recent publication

Action: For adoption of PRAC recommendation

EPITT 19144 – Follow-up to May 2018

4.3.7. Oxybutynin – KENTERA (CAP), NAP; carbamazepine (NAP)

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

PRAC Rapporteur: Laurence de Fays

Scope: Signal on drug interaction between oxybutynin and carbamazepine resulting in seizures and carbamazepine overdose secondary to carbamazepine plasma level variations

Action: For adoption of PRAC recommendation

EPITT 19233 – Follow-up to May 2018

[8] Contraception indication
[9] All route of administrations except transdermal
[10] Transdermal application
[11] Combination pack

4.3.8. Teriflunomide – AUBAGIO (CAP) - EMEA/H/C/002514/SDA/004

Applicant(s): Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Signal of dyslipidaemia

Action: For adoption of PRAC recommendation

EPITT 19227 – Follow-up to May 2018

4.3.9. Trastuzumab – HERCEPTIN (CAP) - EMEA/H/C/000278/SDA/101, HERZUMA (CAP) - EMEA/H/C/002575/SDA/002, ONTRUZANT (CAP) - EMEA/H/C/004323/SDA/003; trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/SDA/020; pertuzumab – PERJETA (CAP) - EMEA/H/C/002547/SDA/013

Applicant(s): Celltrion Healthcare Hungary Kft. (Herzuma), Roche Registration GmbH (Herceptin, Kadcyla, Perjeta), Samsung Bioepis UK Limited (SBUK) (Ontruzant)

PRAC Rapporteur: Doris Stenver

Scope: Signal of multiple sclerosis relapse

Action: For adoption of PRAC recommendation

EPITT 19208 – Follow-up to May 2018

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Botulinum toxin type A - EMEA/H/C/004587

Scope: Temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows

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

5.1.2. Dapivirine - Art 58[12] - EMEA/H/W/002168

Scope: Reduction of the risk of human immunodeficiency virus-1 (HIV-1) infection via vaginal intercourse in sexually active HIV-uninfected women

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

5.1.3. Lorlatinib - EMEA/H/C/004646

Scope: Treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

[12] 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 PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.4. Lusutrombopag - EMEA/H/C/004720

Scope: Treatment of thrombocytopenia

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

5.1.5. Tobramycin - EMEA/H/C/005086

Scope: Management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF)

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

5.1.6. Treosulfan - EMEA/H/C/004751, Orphan

Applicant: Medac Gesellschaft fur klinische Spezialpraparate mbH

Scope: Conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (allo-HSCT)

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

5.1.7. Zanamivir - EMEA/H/C/004102

Scope: Treatment of influenza A or B virus infection

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. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/II/0030

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

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

Action: For adoption of PRAC Assessment Report

5.2.2. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/II/0148

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' to implement information on education material proposal to address the incorrect self-administration of Aranesp (darbepoetin alfa) via the SureClick pre-filled pen and associated dosing errors. The RMP (version 9.1) 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

5.2.3. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/WS1441/0034; elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/WS1441/0051; emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - EMEA/H/C/004156/WS1441/0035; tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/WS1441/0016

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 3.1 for Vemlidy, Descovy and Odefsey, as well as version 3.3 for Genvoya) 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) in order to revise the safety concerns in alignment with the approved RMP for Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide). In addition, the MAH took the opportunity to update the deliverable milestones for study GS-US-311-1269 (listed as a category 3 study in the RMP): a phase 2/3, open-label, multi-cohort switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in human immunodeficiency virus 1 (HIV-1) infected children and adolescents virologically suppressed on a 2-nucleoside reverse transcriptase inhibitor (NRTI)-containing regimen as well as to amend the address of the MAH

Action: For adoption of PRAC Assessment Report

5.2.4. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0028

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of the RMP (version 5.0) in order to provide the final results of study 20120332 (GAUSS-3, part C) (listed as a category 3 study in the RMP): a 3-part, phase 3, multicentre, randomized, double-blind, ezetimibe-controlled, parallel-group study. Part C was a 2-year, open-label extension that evaluated the long-term safety and efficacy of evolocumab in hypercholesterolemic subjects unable to tolerate an effective dose of a statin. As a consequence, the MAH proposes to remove missing information of use in patients with severe hepatic impairment (Child-Pugh class C) and use in patients with hepatitis C

Action: For adoption of PRAC Assessment Report

5.2.5. Human fibrinogen, human thrombin - EVICEL (CAP) - EMEA/H/C/000898/II/0063

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 14.2) in order bring it in line with revision 2 of the guidance on the format of RMP in the EU (template) to update exposure data, and reflect the PRAC outcome for procedure PSUSA/00010297/201706 adopted in January 2018 (removal of lack of efficacy as identified risk, reclassification and/or removal of risk from the safety specification)

Action: For adoption of PRAC Assessment Report

5.2.6. Panobinostat - FARYDAK (CAP) - EMEA/H/C/003725/II/0013, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 5.0) in order to remove the commitment to conduct a study LBH589D2408 (listed as a category 3 study in the RMP): a non-interventional PASS of panobinostat use in relapsed or relapsed/refractory multiple myeloma patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent in a real-world setting according to the current EU prescribing information and document adherence to dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of the medication error events

Action: For adoption of PRAC Assessment Report

5.2.7. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS1364/0092; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS1364/0021

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of the RMP (version 12.0) in order to include the changes requested in the conclusions of EMEA/H/C/PSUSA/00002511/201701 procedure finalised in September 2017, updating the safety specifications and risk minimisation measures. The pharmacovigilance plan is also updated. The draft protocol for a non-interventional non-imposed PASS (A0081359) entitled 'a population-based cohort study of pregabalin to characterize pregnancy outcomes' is submitted. The MAH took the opportunity to include minor updates and to align 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

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

5.3.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0042

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease based on the final study report of study EFC11570: a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an acute coronary syndrome. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet and RMP (version 4.0) are updated accordingly

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

5.3.2. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0106/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of: 1) update of section 5.1 of the SmPC to reflect final overall survival data from the long-term follow-up study JO25567 (erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer (NSCLC) harbouring epidermal growth factor receptor (EGFR) mutations: an open-label, randomised, multicentre, phase 2 study) in order to fulfil ANX 085 for study JO29424 (survival follow up of JO25567); 2) change in the deadline for the fulfilment of ANX 086 (discussion on any further outcome data on the combination of bevacizumab and erlotinib in the first-line treatment of patients with non-squamous NSCLC harbouring EGFR activating mutations) from Q4 2018 to Q2 2019. Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 29.0) are updated accordingly. The RMP is submitted in line with revision 2 of the guidance on the format of RMP in the EU (template) and consolidates the approved versions (versions 27.1 and 28.1)

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

5.3.3. Cetuximab - ERBITUX (CAP) - EMEA/H/C/000558/II/0082

Applicant: Merck KGaA

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4 and 4.8. of the SmPC regarding the existing warning on interstitial lung disease (ILD) by specifying potentially fatal ILD outcome, patients with contributory factors at risk of fatal events and need for close monitoring of these patients. The RMP (version 19.0) is updated accordingly including further changes as per the conclusions of the latest PSUSA procedure (PSUSA/00000635/201739) finalised in May 2018. The MAH also took the opportunity to update Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' to delete an obsolete sentence referring to a RMP to be submitted in 2014

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

5.3.4. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1344/0025; FORXIGA (CAP) - EMEA/H/C/002322/WS1344/0044

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include the treatment of insufficiently controlled type 1 diabetes mellitus (T1DM) as an adjunct to insulin, when insulin does not provide adequate glycaemic control, for Forxiga and Edistride (dapagliflozin). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and RMP (version 16) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the SmPC and package leaflet

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

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

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

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

5.3.6. Efmoroctocog alfa - ELOCTA (CAP) - EMEA/H/C/003964/II/0026

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to add a statement for a once-weekly prophylaxis dose and to update the safety information based on the final results from study 8HA01EXT (listed as a category 3 study in the RMP): an interventional study that evaluated the long-term safety (particularly immunogenicity) and efficacy of Elocta (efmoroctocog alfa) in the prevention and treatment of bleeding episodes and for perioperative management. The RMP (version 2.1) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

5.3.7. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include routine prophylaxis of bleeding episodes in patients with haemophilia A without factor VIII (FVIII) inhibitors. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information of the following pivotal trials: 1) study BH30071 (HAVEN 3): an ongoing, multicentre, open-label, randomized phase 3 clinical study evaluating the efficacy, safety and pharmacokinetic (PK) of emicizumab prophylaxis at doses of 1.5 mg/kg/week (QW) and 3 mg/kg/every 2 weeks (Q2W) versus no prophylaxis in adults and adolescent patients (age of 12 or above) with haemophilia A without inhibitors against FVIII; 2) study BO39182 (HAVEN 4): an ongoing multicentre, open-label, non-randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab given as the dose of 6 mg/kg/every 4 weeks (Q4W) in adults and adolescent patients (age of 12 or above) with haemophilia A with or without FVIII inhibitors; 3) study BH29992 (HAVEN 2): a multicentre, open-label, non-randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab at the QW dose in paediatric patients (<12 years old or 12-17 years old and <40kg) with haemophilia A with FVIII inhibitors. The package leaflet and the RMP (version.2.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor corrections and clarity to sections 4.4, 4.5 and 4.6 of the SmPC

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

5.3.8. Eptacog alfa (activated) - NOVOSEVEN (CAP) - EMEA/H/C/000074/II/0104

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to extend patient population of NovoSeven (eptacog alfa) for use in patients with Glanzmann's thrombasthenia without antibodies to platelets, or where platelets are not readily available, based on a prospective observational registry and literature references. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in section 4.8 of the SmPC and in package leaflet

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

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

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

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

(version 13.0) are updated accordingly

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

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

Applicant: Roche Registration GmbH

PRAC Rapporteur: Eva Segovia

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

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

5.3.11. Modified vaccinia Ankara virus - 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 QRD template (version 10)

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

5.3.12. Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/II/0036

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 provide confirmation in terms of immunogenicity based on the results from study POX-MVA-006 (listed as an obligation in Annex II (ANX 004)): a randomized, open-label phase 3 non-inferiority trial to compare indicators of efficacy for smallpox vaccine to the US licensed replicating smallpox vaccine in 18-42 year old healthy vaccinia-naïve subjects. The package leaflet and the RMP (version 7.2) are updated accordingly

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

5.3.13. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/II/0092

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 4.4, 4.6 and 6.6 of the SmPC for Xolair (omalizumab) solution for injection in pre-filled syringe (PFS) to allow for home use in severe allergic asthma and chronic spontaneous urticaria. Consequential updates are applied to the SmPC for powder and solvent for solution for injection. Artwork for the outer box, the blister and the syringe label for Xolair (omalizumab) solution for injection in PFS are updated to ensure that patients/lay caregiver can more easily distinguish the two strengths of Xolair PFS. The package leaflet, labelling and the RMP (version 13) are updated accordingly

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

5.3.14. Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/II/0016/G

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of an update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC with the final results from 2 studies, namely: 1) study DFCI 11-001 (listed as a category 3 study in the RMP): a phase 2, open-label, randomized, multicentre study to determine the safety and feasibility of administering an investigational asparaginase product (asparaginase formulation) compared with Oncaspar (pegaspargase) in subjects aged 1 to <22 years with newly diagnosed acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma; 2) study AALL07P4 (listed as a category 3 study in the RMP): a multicentre, open label, randomized, active-controlled, parallel design clinical pilot study conducted to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, immunogenicity and efficacy of an investigational asparaginase product in comparison with Oncaspar (pegaspargase) in patients aged 1 to <31 years newly diagnosed with high risk B-precursor ALL. 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

5.3.15. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0046

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning and safety information on 'anaphylaxis'. The RMP is updated accordingly (version 3.2)

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

5.3.16. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0057

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include first line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) tumours expressing programmed death-ligand 1 (PD-L1) with a ≥1% tumour proportion score (TPS) based on data from study KEYNOTE-042: an international, randomized, open-label phase 3 study investigating Keytruda (pembrolizumab) monotherapy compared to standard of care platinum-based chemotherapy in patients with locally advanced or metastatic PD-L1 positive (TPS ≥ 1%) NSCLC, and on supportive data from the final planned analysis of KEYNOTE-024: a phase 3 randomized open-label study of Keytruda (pembrolizumab) monotherapy compared to platinum-based chemotherapy in metastatic NSCLC with PD-L1 TPS ≥50%. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The RMP is updated accordingly (version 18.1)

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

5.3.17. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0058

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.4 of the SmPC to include in the existing warning regarding immune-related adverse reactions the fact that these reactions may be fatal in patients treated with pembrolizumab. The package leaflet is updated accordingly, and for consistency with the already existing statement in SmPC section 4.4, the package leaflet also includes that immune-related adverse reactions can occur after discontinuation of pembrolizumab treatment. The RMP is updated accordingly (version 19.1)

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

5.3.18. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0031/G, Orphan

Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: Grouped applications consisting of: 1) extension of indication to include treatment with Imnovid (pomalidomide) in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 15.0) are updated accordingly; 2) addition of 14-capsule pack sizes for the 1 mg, 2 mg, 3 mg and 4 mg strengths to support the proposed posology and pomalidomide dose modification. The SmPC, labelling and package leaflet are updated accordingly; 3) update of section 5.1 of the SmPC in order to update the information on pomalidomide mechanism of action based on literature data

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

5.3.19. Regadenoson - RAPISCAN (CAP) - EMEA/H/C/001176/II/0027

Applicant: GE Healthcare AS

PRAC Rapporteur: Patrick Batty

Scope: Extension of indication to include use in the measurement of fractional flow reserve (FFR) during invasive coronary angiography (ICA) in patients presenting a coronary artery stenosis based on results from study 060912001: a comparison of Rapiscan (regadenoson) and central intravenous adenosine for measurement of fractional flow reserve and data from published literature. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 10.0) are updated accordingly

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

5.3.20. Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/X/0006/G

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to add new strengths of 2500 IU, 3000 IU and 4000 IU, powder and solvent for solution for injection; 2) update of sections 4.2, 4.8 and 5.1 of the SmPC to reflect available data from previously untreated patients (PUP) from GENA-05 (immunogenicity, efficacy and safety of treatment with human cell line-derived recombinant factor VIII (human-cl rhFVIII) in previously untreated patients with severe haemophilia A) (interim report) study; 3) update of the RMP (version 10) to align the content in a single harmonised worldwide version for simocotocg alfa (recombinant factor VIII (rFVIII)); 4) update of the product information as per the outcome of the referral procedure under Article 31 of Directive 2001/83/EC finalised in 2017 (EMEA/H/A-31/1448)

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

5.3.21. Thalidomide - THALIDOMIDE CELGENE (CAP) - EMEA/H/C/000823/II/0056, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Update of the RMP (version 19) 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) to propose the reclassification and/or renaming of known safety concerns associated with the use of thalidomide. Consequently, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product', section 4.4 and 4.6 of the SMPC as well as the package leaflet are updated accordingly

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

5.3.22. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0027

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 4.8 of the SmPC in order to add safety information based on the final results from study 16099 (listed as a post-authorisation efficacy study (PAES) in the RMP): a prospective, randomized, open-label, active-controlled, multicentre study to evaluate the efficacy and safety of tedizolid in Japanese patients with methicillin-resistant Staphylococcus aureus (MRSA) infections (skin and soft tissue infection (SSTI) and SSTI-related bacteraemia). The RMP (version 4.0) is updated accordingly in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

5.3.23. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/II/0028

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Update of sections 4.1, 4.4 and 5.1 of the SmPC in order to delete the information regarding rearranged during transfection (RET) mutation. The application fulfils SOB 001 and includes a proposal to revert from conditional to marketing authorisation to standard marketing authorisation. Annex II, the package leaflet and the RMP (version 12.2) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

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

5.3.24. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0034

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 5.1 of the SmPC in order to provide the final efficacy results up to week 348 regarding clinical study c13008 (listed as a category 3 study in the RMP): a phase 3, open-label study to determine the long-term safety and efficacy of vedolizumab in subjects with ulcerative colitis and Crohn's disease. The RMP is updated accordingly (version 4.0)

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. 5-aminolevulinic acid[13] - GLIOLAN (CAP) - PSUSA/00000009/201803

Applicant: Medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

[13] Indicated in the treatment of glioma

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.2. Albiglutide - EPERZAN (CAP) - PSUSA/00010175/201803

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.3. Apremilast - OTEZLA (CAP) - PSUSA/00010338/201803

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.4. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/201803

Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.5. Belimumab - BENLYSTA (CAP) - PSUSA/00009075/201803

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.6. Bosutinib - BOSULIF (CAP) - PSUSA/00010073/201803

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.7. Canagliflozin - INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/201803

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.8. Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/201803

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.9. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/201803

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.10. Cholic acid[14] - KOLBAM (CAP) - PSUSA/00010182/201803

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.11. Ciclosporin[15] - IKERVIS (CAP) - PSUSA/00010362/201803

Applicant: Santen Oy

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

[14] Indicated in the treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7α-hydroxylase (CYP7A1) deficiency

[15] Topical use only

6.1.12. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/201803

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.13. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - PSUSA/00010646/201803

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.14. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/201803

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.15. Eftrenonacog alfa - ALPROLIX (CAP) - PSUSA/00010499/201803

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.16. Eluxadoline - TRUBERZI (CAP) - PSUSA/00010528/201803

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.17. Ferric citrate coordination complex - FEXERIC (CAP) - PSUSA/00010418/201803

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.18. Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP) - PSUSA/00010653/201803

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.19. Glycopyrronium[16] - SIALANAR (CAP) - PSUSA/00010529/201803

Applicant: Proveca Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.20. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/201803

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.21. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/201803

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.22. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/201803

Applicant: Bio Products Laboratory Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

[16] Centrally authorised product(s) only, indicated for the treatment of severe sialorrhea

6.1.23. Influenza vaccine[17] (split virion, inactivated) - INTANZA[18] (CAP) - PSUSA/00001743/201803

Applicant: Sanofi Pasteur Europe

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.24. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/201803

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.25. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201803

Applicant: Basilea Medical Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.26. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/201803

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.27. Lapatinib - TYVERB (CAP) - PSUSA/00001829/201803

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.28. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201803

Applicant: GlaxoSmithKline Trading Services Limited

[17] Centrally authorised product(s) only
[18] European Commission (EC) decision on the MA withdrawal of Intanza dated 3 August 2018

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.29. Midostaurin - RYDAPT (CAP) - PSUSA/00010638/201803

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.30. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/201803

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.31. Niraparib - ZEJULA (CAP) - PSUSA/00010655/201803

Applicant: Tesaro UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.32. Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/201803

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.33. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201803

Applicant: Rempex London Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.34. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201803

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

6.1.35. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[19]) - EMEA/H/W/002300/PSUV/0033

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUR procedure

Action: For adoption of recommendation to CHMP

6.1.36. Tobramycin[20] - VANTOBRA (CAP) - PSUSA/00010370/201803

Applicant: Pari Pharma GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.37. Tolcapone - TASMAR (CAP) - PSUSA/00002985/201803

Applicant: Meda AB

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.38. Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/201803

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

[19] 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)
[20] Centrally authorised product(s) only, nebuliser solution only

6.1.39. Velaglucerase alpha - VPRIV (CAP) - PSUSA/00003103/201802

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.40. Vildagliptin - GALVUS (CAP); JALRA (CAP); XILIARX (CAP); vildagliptin, metformin - EUCREAS (CAP); ICANDRA (CAP) ; ZOMARIST (CAP) - PSUSA/00003113/201802

Applicant: Novartis Europharm Limited

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. Atosiban - TRACTOCILE (CAP); NAP - PSUSA/00000264/201801

Applicants: Ferring Pharmaceuticals A/S (Tractocile), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.2. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/201802

Applicants: Clinigen Healthcare Ltd (Savene), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.3. Estradiol, nomegestrol acetate - ZOELY (CAP); NAP - PSUSA/00002182/201801

Applicants: Teva B.V. (Zoely), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.4. Pemetrexed - ALIMTA (CAP); ARMISARTE (CAP); NAP - PSUSA/00002330/201802

Applicants: Actavis Group PTC ehf (Armisarte), Eli Lilly Nederland B.V. (Alimta), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.5. Trientine - CUPRIOR (CAP); NAP - PSUSA/00010637/201803

Applicants: GMP-Orphan SA (Cuprior), various

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.6. Voriconazole - VFEND (CAP); NAP - PSUSA/00003127/201802

Applicant: Pfizer Limited, various

PRAC Rapporteur: Liana Gross-Martirosyan

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. Amitriptyline hydrochloride, chlordiazepoxide (NAP) - PSUSA/00000171/201802

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.2. Argatroban (NAP) - PSUSA/00009057/201801

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.3. Bilastine (NAP) - PSUSA/00003163/201803

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.4. Cilazapril (NAP); cilazapril, hydrochlorothiazide (NAP) - PSUSA/00000749/201802

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.5. Cilostazol (NAP) - PSUSA/00010209/201802

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.6. Ciprofloxacin[21] (NAP) - PSUSA/00000775/201801

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.7. Ciprofloxacin[22] (NAP) - PSUSA/00000776/201801

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.8. Dacarbazine (NAP) - PSUSA/00000919/201802

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

[21] Systemic use only
[22] Topical use only

6.3.9. Ethinylestradiol, gestodene[23] (NAP) - PSUSA/00010145/201802

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.10. Fenoterol, ipratropium (NAP) - PSUSA/00001367/201802

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.11. Human coagulation factor VIII[24] (NAP) - PSUSA/00009174/201802

Applicant(s): various

PRAC Lead: Daniela Philadelphy

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.12. Hydrochlorothiazide, losartan (NAP) - PSUSA/00001655/201802

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.13. Hydroxyethyl starch (NAP) - PSUSA/00001694/201803

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.14. Iloprost[25] (NAP) - PSUSA/00009190/201801

Applicant(s): various

PRAC Lead: Adrien Inoubli

[23] Transdermal application only
[24] Inhibitor bypassing fraction
[25] Intravenous (I.V) solution only

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.15. Lisdexamfetamine (NAP) - PSUSA/00010289/201802

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.16. Lomustine (NAP) - PSUSA/00001902/201801

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.17. Lorazepam (NAP) - PSUSA/00001909/201801

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.18. Mivacurium (NAP) - PSUSA/00002077/201801

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.19. Nafarelin (NAP) - PSUSA/00002105/201802

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.20. Nomegestrol (NAP) - PSUSA/00002181/201801

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.21. Olodaterol (NAP) - PSUSA/00010245/201803

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.22. Tauroselcholic [^{75}Se] acid (NAP) - PSUSA/00010486/201801

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Iloprost - VENTAVIS (CAP) - EMEA/H/C/000474/LEG 038

Applicant: Bayer AG

PRAC Rapporteur: Adrien Inoubli

Scope: Review of non-clinical and clinical data on pregnancy, including all cases reported from clinical trials, post-marketing experience and literature, as requested in the conclusions of PSUSA/00001724/201709 adopted in May 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)[26]

7.1.1. Chlormadinone acetate, ethinylestradiol (NAP) - EMEA/H/N/PSA/J/0030.1

Applicant: Gedeon Richter Plc (multiple product names)

PRAC Rapporteur: Martin Huber

Scope: MAH's response to S/0060 [amendment to a protocol previously agreed by PRAC in

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

January 2016 for a case control study comparing levonorgestrel and chlormadinone acetate in order to evaluate the role of oral contraceptives and the RIsk of VEnous Thromboembolism (VTE) (RIVET CC study), to include additional countries, update the study milestones and the statistical analysis plan (SAP) as per the advice by PRAC adopted in January 2018 on the assessment of the first PASS progress report] as per the request for supplementary information (RSI) adopted in June 2018

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

7.1.2. Tolvaptan – JINARC (CAP) - EMEA/H/C/PSA/S/0031

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Amendment to a protocol initially endorsed by PRAC in March 2016 (EMEA/H/C/PSP/0028.2) for a 4-year, multicentre, non-interventional PASS to measure the effectiveness of the risk minimisation measures in reducing the severity of liver injury in patients who experience an elevation of transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) > 3× upper limit of normal (ULN), or an adverse event (AE) consistent with hepatotoxicity in real life

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

7.1.3. Umeclidinium bromide – INCRUSE ELLIPTA (CAP), ROLUFTA ELLIPTA (CAP); umeclidinium bromide, vilanterol – ANORO ELLIPTA (CAP), LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/PSA/S/0032

Applicants: Glaxo Group Ltd (Anoro Ellipta, Incruse Ellipta, Laventair Ellipta), GlaxoSmithKline Trading Services Limited (Rolufta Ellipta)

PRAC Rapporteur: Amelia Cupelli

Scope: 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

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

7.1.4. Velmanase alfa – LAMZEDE (CAP) - EMEA/H/C/PSP/S/0060.1

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to S/0060 [protocol for the alfa-mannosidosis registry: a multicentre, multi-country, non-interventional, prospective cohort, in alfa-mannosidosis patients to evaluate the long-term effectiveness and safety profile of treatment with Lamzede (velmanase alfa) under conditions of routine clinical care and to characterize the entire alfa-mannosidosis population, including variability of clinical manifestation, progression and natural history] as per the request for supplementary information (RSI) adopted in June 2018

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[27]

7.2.1. Agalsidase beta - FABRAZYME (CAP) - EMEA/H/C/000370/MEA 060.4

Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 060.3 [protocol for a survey to assess the effectiveness of the patient home infusion educational materials in EU countries where the material is implemented [report submission due date: March 2019]] as per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

7.2.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 003.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 003.1 [protocol for an observational safety study using an existing database, study I4V-MC-B004: a retrospective cohort study to assess the long-term safety of baricitinib compared with other therapies used in the treatment of adults with moderate-to-severe rheumatoid arthritis in the course of routine clinical care [final report due date: 31/03/2031]] as per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

7.2.3. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 004.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 004.1 [protocol for assessing the effectiveness of the patient alert card and healthcare professional educational material, study I4V-MC-B010: a rheumatologist survey to assess the effectiveness of the risk minimisation measures (RMM) for Olumiant (baricitinib); and objective 3 of study I4V-MC-B011: a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries [final report anticipated within 4 months following the end of data]] as per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

[27] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

7.2.4. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 005.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 005.1 [protocol for an observational post marketing disease registry in EU patients, study I4V-MC-B011: a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries] as per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

7.2.5. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 20180204: a registry study to evaluate the risk of hypocalcaemia in paediatric patients treated with cinacalcet

Action: For adoption of advice to CHMP

7.2.6. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 012.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of a PASS protocol including the MAH's response to MEA 012 [statistical analysis plan (SAP) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes mellitus (T2DM); 2) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) study D1690C00019: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg Once daily in patients with T2DM and cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)] as per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

7.2.7. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 024.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of a PASS protocol including the MAH's response to MEA 024 [statistical analysis plan (SAP) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes mellitus (T2DM); 2) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) study D1690C00019: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg Once daily in patients with T2DM and cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)] as per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

7.2.8. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 011.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Submission of a PASS protocol including the MAH's response to MEA 011 [statistical analysis plan (SAP) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes mellitus (T2DM); 2) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) study D1690C00019: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg Once daily in patients with T2DM and cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)] as per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

7.2.9. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 014.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Submission of a PASS protocol including the MAH's response to MEA 014 [statistical analysis plan (SAP) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes mellitus (T2DM); 2) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) study D1690C00019: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg Once daily in patients with T2DM and cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)] as per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

7.2.10. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.6

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to previously agreed protocol for study 1245.96 protocol (version 5.0): an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors as requested in the outcome of the assessment of the second annual interim report adopted in September 2017

Action: For adoption of advice to CHMP

7.2.11. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 011.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 011.1 [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 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in April 2018

Action: For adoption of advice to CHMP

7.2.12. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 003.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 011.1 [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 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in April 2018

Action: For adoption of advice to CHMP

7.2.13. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 004.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Amendment to previously agreed protocol for study 1245.96 protocol (version 5.0): an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors as requested in the outcome of the assessment of the second annual interim report adopted in September 2017

Action: For adoption of advice to CHMP

7.2.14. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to previously agreed protocol for study 1245.96 protocol (version 5.0): an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors as requested in the outcome of the assessment of the second annual interim report adopted in September 2017

Action: For adoption of advice to CHMP

7.2.15. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 007.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 011.1 [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 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in April 2018

Action: For adoption of advice to CHMP

7.2.16. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002.1

Applicant: Tesaro UK Limited

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 002 [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 as

per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

7.2.17. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/MEA 021.2

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Amendment to the previously agreed protocol in July 2016 for study CLDE225A2404: a non-interventional, multi-national, multicentre PASS to assess the long-term safety and tolerability of Odomzo (sonidegib) administered in patients with locally advanced basal cell carcinoma (laBCC), in order to execute and update the milestones, sample size and execution methods

Action: For adoption of advice to CHMP

7.3. Results of PASS imposed in the marketing authorisation(s)[28]

7.3.1. Amino acid combinations, glucose, triglyceride combinations, with or without electrolytes, mineral compounds[29] (NAP) - EMEA/H/N/PSR/S/0017

Applicant: Baxter Healthcare Limited (Numeta)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to PSR/S/0017 [PASS results for a multicentre, non-interventional, uncontrolled, open-label, observational study in children (up to age 24 months) to generate descriptive data for serum magnesium (Mg) levels in full-term, new born infants and children up to 24 months of age following dosing with Numeta G16%E; to observe the following parameters in subjects who receive parenteral nutrition (PN) with Numeta G16%E: 1) actual infused Numeta G16%E intake (mL/kg/day); 2) actual nutritional intake (total calories from oral, enteral, and parenteral sources other than Numeta); 3) adverse events (AEs) and serious adverse events (SAEs), including clinically significant (CS) abnormal laboratory results and CS abnormal vital signs] as per the request for supplementary information (RSI) adopted in June 2018

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

7.3.2. Ivabradine – CORLENTOR (CAP), IVABRADINE ANPHARM (CAP), PROCORALAN (CAP); NAP - EMEA/H/C-N/PSR/S/0019

Applicants: Anpharm Przedsiebiorstwo Farmaceutyczne (Ivabradine Anpharm), Les Laboratoires Servier (Corlentor, Procolaran), various

PRAC Rapporteur: Menno van der Elst

[28] In accordance with Article 107p-q of Directive 2001/83/EC
[29] Alanine, arginine, aspartic acid, cysteine, glucose anhydrous, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, olive oil refined, ornithine, phenylalanine, proline, serine, sodium chloride, sodium glycerophosphate hydrated, soya bean oil refined, taurine, threonine, tryptophan, tyrosine, valine, potassium acetate, calcium chloride dihydrate, magnesium acetate tetrahydrate

Scope: Results for a drug utilisation study (DUS) conducted in several European Economic Area (EEA) countries aimed at describing the characteristics of ivabradine users, as well as describing the patterns of use of ivabradine and adherence to the existing risk minimisation measures

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

7.4. Results of PASS non-imposed in the marketing authorisation(s)[30]

7.4.1. Atazanavir, atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/II/0117

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final reports for studies AI424397 (PRINCE I) and AI424451 (PRINCE II) listed as a category 3 studies in the RMP. These studies were phase 3b, prospective, single arm, open-label, international, multicentre studies to evaluate the safety, efficacy and pharmacokinetics of atazanavir powder boosted with ritonavir and administered with an optimised nucleoside reverse transcriptase inhibitor (NRTI) background therapy, in human immunodeficiency virus (HIV) infected paediatric patients. The RMP is updated accordingly (version 15.0). 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

7.4.2. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 006.4

Applicant: Hexal AG

PRAC Rapporteur: Patrick Batty

Scope: 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)

Action: For adoption of PRAC Assessment Report

7.4.3. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 006.4

Applicant: Sandoz GmbH

PRAC Rapporteur: Patrick Batty

Scope: 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

[30] 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

annually. Patients were followed-up for a total of five years (one year in the SCN study and four years within the registry)

Action: For adoption of PRAC Assessment Report

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

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

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

Action: For adoption of PRAC Assessment Report

7.4.5. Moroctocog alfa - REFACTO AF (CAP) - EMEA/H/C/000232/II/0147

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report for study B1831007 (previously referred to as study 3082B2-4435-WW) (listed as a category 3 study in the RMP): a post authorisation safety surveillance registry in previously untreated patients with severe haemophilia A in usual care settings (in fulfilment of post-approval commitment MEA 115)

Action: For adoption of PRAC Assessment Report

7.4.6. Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/II/0049

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report for study PZP034AKR02 listed as a category 3 study in the RMP): a non-interventional PASS to monitor the safety and effectiveness of Votrient (pazopanib) in Korea

Action: For adoption of PRAC Assessment Report

7.4.7. Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/II/0050

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report for study PZP034A2401 (listed as a category 3 study in the RMP): 'a prospective observational study of real world treatment patterns and treatment outcomes in patients with advanced or metastatic renal cell carcinoma receiving pazopanib'

Action: For adoption of PRAC Assessment Report

7.4.8. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/II/0069

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final 5-year report for study ZOL446H2422 (listed as a category 3 study in the RMP): a non-interventional post-authorisation safety study using health registries to compare safety of Aclasta (zoledronic acid) against oral bisphosphonates and untreated population controls

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. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.5

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third annual interim report for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitors [final report expected in July 2020]

Action: For adoption of advice to CHMP

7.5.2. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 004.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Third annual interim report for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitors [final report expected in July 2020]

Action: For adoption of advice to CHMP

7.5.3. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third annual interim report for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitors [final report

expected in July 2020]

Action: For adoption of advice to CHMP

7.5.4. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.4

Applicant: Hexal AG

PRAC Rapporteur: Patrick Batty

Scope: Seventh annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal and Zarzio (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) due date: 31/12/2019]

Action: For adoption of advice to CHMP

7.5.5. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.4

Applicant: Sandoz GmbH

PRAC Rapporteur: Patrick Batty

Scope: Seventh annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal and Zarzio (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) due date: 31/12/2019]

Action: For adoption of advice to CHMP

7.5.6. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 012.7

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Seventh annual interim pooled report for studies D2403 (a long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started on fingolimod once daily or treated with another approved disease-modifying therapy), D2404 (multinational Gilenya pregnancy exposure registry in multiple sclerosis (MS)), D2406 (a long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS newly initiated on fingolimod once daily or treated with another approved disease-modifying therapy) and study D2409 (a long-term, open-label, multicentre study assessing long-term cardiovascular risks in patients treated with fingolimod). This procedure also includes an annual report for the pregnancy intensive monitoring (PRIM) study

Action: For adoption of advice to CHMP

7.5.7. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.5

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third progress report for study MK-8259-013, the ulcerative colitis (UC) Nordic registry: a non-interventional observational longitudinal PASS of Simponi (golimumab) in the treatment of UC using Nordic national health registries

Action: For adoption of advice to CHMP

7.5.8. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/MEA 045.9

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: MAH's response to MEA 045.8 [fourth annual progress report for diabetes pregnancy registry (NN304-4016): an international non-interventional prospective cohort study to evaluate the safety of treatment with insulin detemir in pregnancy women with diabetes mellitus] as per the request for supplementary information (RSI) adopted in April 2018

Action: For adoption of advice to CHMP

7.5.9. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 001.6

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

7.5.10. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/ANX 011.4

Applicant: Teva B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Fourth interim report for the prospective observational study to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the VTE risk in users of combined oral contraceptives containing levonorgestrel (as imposed in accordance with Article 10(a) of Regulation (EC) No 726/2004

Action: For adoption of advice to CHMP

7.5.11. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.3

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH’s response to MEA 005.2 [results of a feasibility assessment conducted in US healthcare databases as per the agreed protocol (final version dated 25 May 2017) for

study C38072-AS-50027: a long-term non-interventional cohort study comparing the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using secondary administrative healthcare data (listed as category 3 study in the RMP)] as per the request for supplementary information (RSI) adopted in May 2018

Action: For adoption of advice to CHMP

7.5.12. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/MEA 003.8

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Seventh interim report for the Kuvan adult maternal paediatric European registry (KAMPER) registry, study EMR700773-001: a non-imposed, non-interventional exploring the long-term safety of Kuvan (sapropterin) use in patients with hyperphenylalaninaemia (HPA) as well as information regarding Kuvan use during pregnancy in women with HPA and data regarding childhood growth and neurocognitive outcomes

Action: For adoption of advice to CHMP

7.6. Others

7.6.1. Albutrepenonacog alfa - IDELVION (CAP) - EMEA/H/C/003955/MEA 001

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Progress study report for clinical study CSL654-3003 (listed as a category 3 study in the RMP): a phase 3b open-label, multicentre, safety and efficacy extension study of a recombinant coagulation factor IX albumin fusion protein (rIX-FP) in subjects with haemophilia B, including previously untreated patients (PUP)

Action: For adoption of advice to CHMP

7.6.2. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/MEA 003

Applicant: Clovis Oncology UK Limited

PRAC Rapporteur: Annika Folin

Scope: Protocol for study CO-338-095 (listed as a category 3 study in the RMP): an in vivo drug-drug interaction (DDI) study with breast cancer resistance protein (BCRP) substrate, a phase 1, open label, DDI study to determine the effect of rucaparib on the pharmacokinetics of rosuvastatin in patients with advanced solid tumours (from initial opinion/MAA)

Action: For adoption of advice to CHMP

7.6.3. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/MEA 004

Applicant: Clovis Oncology UK Limited

PRAC Rapporteur: Annika Folin

Scope: Protocol for study CO-338-095 (listed as a category 3 study in the RMP): an in vivo drug-drug interaction (DDI) study with contraceptives: a phase 1, open label, DDI study to determine the effect of rucaparib on the pharmacokinetics of oral contraceptives in female patients with advanced solid tumours

Action: For adoption of advice to CHMP

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0059 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.2. Conditional renewals of the marketing authorisation

8.2.1. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0021 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A., ATMP[31]

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CAT and CHMP

[31] Advanced therapy medicinal product

8.2.2. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0009 (without RMP)

Applicant: Intercept Pharma Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.2.3. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0032 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3. Renewals of the marketing authorisation

8.3.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/R/0040 (with RMP)

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Karen Pernille Harg

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/R/0042 (with RMP)

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Karen Pernille Harg

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/R/0039 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.4. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/R/0024 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.5. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/R/0040 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.6. Indacaterol, glycopyrronium - ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/R/0028 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.7. Mifamurtide - MEPACT (CAP) - EMEA/H/C/000802/R/0047 (without RMP)

Applicant: Takeda France SAS

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.8. Para-aminosalicylic acid - GRANUPAS (CAP) - EMEA/H/C/002709/R/0026 (without RMP)

Applicant: Eurocept International B.V.

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.9. Pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/R/0025 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.10. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/R/0032 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

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

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Julie Williams

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

Action: For adoption of advice to CHMP

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

None

10.3. Other requests

None

10.4. Scientific Advice

None

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. Dienogest, ethinylestradiol[32] (NAP) - DE/H/xxxx/WS/534

Applicant(s): Bayer Vital GmbH (Celimona, Celimone, Maxim, Valette)

PRAC Lead: Martin Huber

Scope: PRAC follow-up consultation on a worksharing procedure to assess the risk of venous thromboembolism compared to levonorgestrel/ethinylestradiol-containing combined hormonal contraceptives (CHCs)

Action: For adoption of advice to Member States

11.2.2. Finasteride (NAP) - SE/H/xxxx/WS/243

Applicant(s): Merck Sharp & Dohme BV (Chibro-Proscar, Pilus, Propecia, Proscar, Prostide), various

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on a worksharing procedure assessing the results of a Nordic register-based nested case-control study examining male breast cancer incidence in finasteride users compared to non-users

Action: For adoption of advice to Member States

[32] Combined hormonal contraceptive (CHC)

11.2.3. Minocycline (NAP) - ES/H/PSUFU/00002065/201708

Applicant(s): Almirall, Biogaran, Meda, Mylan, Teofarma, Tillomed, various

PRAC Lead: Maria del Pilar Rayon

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on foetal exposure and utilisation of minocycline during pregnancy as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on minocycline (PSUSA/00002065/201708) concluded in May 2018

Action: For adoption of advice to Member States

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Brexit: preparedness of the regulatory network and capacity increase

Action: For discussion

12.4.2. Regulatory science engagement plan to 2025

Action: For discussion

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) expected for 2018 – planning update dated Q3 2018

Action: For information

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 the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management plan (RMP) template for industry - revision

Action: For adoption

12.14.2. Risk management systems

None

12.14.3. Risk minimisation measures: Patient alert cards and patient reminder cards - clarification

Action: For discussion

12.14.4. 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

12.20.1. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific considerations III: risk management in pregnant and breastfeeding women - Update

Action: For discussion

13. Any other business

Next meeting on: 29-31 October 2018

14. Explanatory notes

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

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures
(Items 2 and 3 of the PRAC agenda)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

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/