09 January 2017
EMA/PRAC/816784/2016
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 9 - 12 January 2017

Chair: June Raine – Vice-Chair: Almath Spooner

09 January 2017, 13:00 – 19:30, room 3/A

10 January 2017, 08:30 – 19:30, room 3/A

11 January 2017, 08:30 – 19:30, room 3/A

12 January 2017, 08:30 – 16:00, room 3/A

Organisational, regulatory and methodological matters (ORGAM)

26 January 2017, 09:00 – 12:00, room 7/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 scope 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).

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1. Introduction

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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the PRAC plenary session to be held 9 - 12 January 2017. See January 2017 PRAC minutes (to be published post February 2017 PRAC meeting).

1.2. Adoption of agenda of the meeting of 9 - 12 January 2017

Action: For adoption

1.3. Adoption of the minutes of the previous meeting of 28 November - 1 December 2016

Action: For adoption

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Human coagulation (plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP) Recombinant factor VIII: antihemophilic factor (recombinant) (NAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY (CAP) - EMEA/H/A-31/1448

Applicant: Baxter AG (Advate), Bayer Pharma AG (Helixate Nexgen, Iblias, Kogenate, Kovaltry), CSL Behring GmbH (Voncento), Pfizer Limited (Refacto AF), various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Brigitte Keller-Stanislawski

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

Action: For adoption of a list of experts for the ad hoc expert group meeting

3.2.2. Retinoids: acitretin (NAP); adapalene (NAP); alitretinoin - PANRETIN (CAP); bexarotene – TARGRETIN (CAP); isotretinoin (NAP); tazarotene (NAP); tretinoin (NAP) - EMEA/H/A-31/1446

Applicant: Eisai Ltd (Panretin, Targretin), various

PRAC Rapporteur: Ana Sofia Diniz Martins; PRAC Co-rapporteur: Julie Williams

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

Action: For adoption of a list of questions for the targeted meeting with patients and healthcare professionals (HCP)

3.3. Procedures for finalisation

None

3.4. Article 5(3) of Regulation (EC) No 726/2004 as amended: PRAC advice on CHMP request

None

3.5. Others

None

4. Signals assessment and prioritisation[1]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Amoxicillin (NAP)

Applicant: various

PRAC Rapporteur: To be appointed

Scope: Signal of drug rash eosinophilia systemic symptoms (DRESS) syndrome

Action: For adoption of PRAC recommendation

EPITT 18802 – New signal

Lead Member State: AT

4.1.2. Sodium iodide [^{131}I] (NAP)

Applicant: various

PRAC Rapporteur: To be appointed

Scope: Signal of hyperparathyroidism and parathyroid adenomas

Action: For adoption of PRAC recommendation

EPITT 18820 – New signal

Lead Member State: PT

4.2. New signals detected from other sources

4.2.1. Gabapentin (NAP)

Applicant: various

PRAC Rapporteur: To be appointed

Scope: Signal of respiratory depression without concomitant opioid use

Action: For adoption of PRAC recommendation

EPITT 18814 - New signal

Lead Member State: DE

[1] 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. Pembrolizumab – KEYTRUDA (CAP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of sarcoidosis

Action: For adoption of PRAC recommendation

EPITT 18806 – New signal

Lead Member State: NL

4.3. Signals follow-up and prioritisation

4.3.1. Azacitidine – VIDAZA (CAP) - EMEA/H/C/000978/SDA/031

Applicant: Celgene Europe Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of pericarditis and pericardial effusion

Action: For adoption of PRAC recommendation

EPITT 18733 – Follow-up to September 2016

4.3.2. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/SDA/090

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of incorrect use of device associated with adverse reactions including underdose, drug dose omission, accidental exposure to product and injection site reactions

Action: For adoption of PRAC recommendation

EPITT 18718 – Follow-up to September 2016

4.3.3. Fluconazole (NAP)

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of spontaneous abortion and stillbirth

Action: For adoption of PRAC recommendation

EPITT 18666 – Follow-up to May 2016

4.3.4. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/000717/SDA/048

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Signal of hemophagocytic lymphohistiocytosis (HLH)

Action: For adoption of PRAC recommendation

EPITT 18689 – Follow-up to September 2016

4.3.5. Paracetamol (NAP)

Applicant: various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of paracetamol use in pregnancy and child neurodevelopment

Action: For adoption of PRAC recommendation

EPITT 17796 – Follow-up to October 2016

4.3.6. Propofol (NAP); valproate (NAP)

Applicant: various

PRAC Rapporteur: Helga Haugom Olsen

Scope: Signal of pharmacokinetic drug interaction leading to an increased propofol exposure

Action: For adoption of PRAC recommendation

EPITT 18696 – Follow-up to September 2016

4.3.7. Proton pump inhibitors (PPIs): dexlansoprazole (NAP); esomeprazole – NEXIUM CONTROL (CAP) NAP; lansoprazole (NAP); omeprazole (NAP); pantoprazole – CONTROLOC CONTROL (CAP) - EMEA/H/C/001097/SDA/016, PANTECTA CONTROL (CAP) - EMEA/H/C/001099/SDA/016, PANTOLOC CONTROL (CAP) - EMEA/H/C/001100/SDA/015, PANTOZOL CONTROL (CAP) - EMEA/H/C/001013/SDA/016, SOMAC CONTROL (CAP) - EMEA/H/C/001098/SDA/021, NAP; rabeprazole (NAP)

Applicants: Pfizer Consumer Healthcare Ltd (Nexium Control), Takeda GmbH (Controloc Control, Pantecta Control, Pantoloc Control, Pantozol Control, Somac Control), various

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of incident chronic kidney disease (CKD) and progression to end stage renal disease (ESRD)

Action: For adoption of PRAC recommendation

EPITT 18698 – Follow-up to September 2016

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Glibenclamide - EMEA/H/C/004379, Orphan

Applicant: Pharma Services

Scope accelerated assessment: Treatment of neonatal diabetes

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

5.1.2. Meningococcal group B vaccine (recombinant, component, adsorbed) - EMEA/H/C/004051

Scope: Active immunisation of individuals of 10 to 40 years of age to prevents invasive meningococcal disease caused by Neisseria meningitides serogroup B

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

5.1.3. Methotrexate - EMEA/H/C/003756

Scope: Treatment of rheumatological and dermatological diseases

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

5.1.4. Nusinersen - EMEA/H/C/004312, Orphan

Applicant: Biogen Idec Ltd

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

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

5.1.5. Tadalafil - EMEA/H/C/004666

Scope: Treatment of erectile dysfunction in adult males

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

5.1.6. Tivozanib hydrochloride monohydrate - EMEA/H/C/004131, Orphan

Applicant: EUSA Pharma

Scope: Treatment of adult patients with advanced renal cell carcinoma (RCC)

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

5.1.7. Umeclidinium - EMEA/H/C/004654

Scope: Treatment of chronic obstructive pulmonary disease (COPD)

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. Albiglutide - EPERZAN (CAP) - EMEA/H/C/002735/II/0029/G

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Grouped variation to: 1) update the RMP to amend the category 3 study 201805: an observational study of the risk of common malignant neoplasms and malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide compared to those prescribed other antidiabetic agents, in order to use a different database to study the risk of neoplasms in association with albiglutide exposure; 2) update the RMP to add a new category 3 study as an additional pharmacovigilance activity study 207351: an observational study to assess maternal and foetal outcomes following exposure to albiglutide during pregnancy

Action: For adoption of PRAC Assessment Report

5.2.2. Darunavir - PREZISTA (CAP) - EMEA/H/C/000707/WS1059/0084; Darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/WS1059/0015

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 3.1) in order to delete the category 3 study TMC114HIV3015: a single arm, open label trial to assess the pharmacokinetics of darunavir/ritonavir, darunavir/cobistat, etravirine and rilpivirine in human immunodeficiency virus (HIV)-1 infected pregnant women, and replace it by pharmacokinetics data in HIV-1 pregnant women

Action: For adoption of PRAC Assessment Report

5.2.3. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0065

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 18) to update the 'important potential risk: hypercalcemia following treatment discontinuation in patients with growing skeletons' to 'important potential risk: hypercalcemia following treatment discontinuation in patients with growing skeletons and the adult population'. The RMP is updated based on Amgen's updated safety assessment conducted in 2016. The MAH also took the opportunity to request the removal of the important potential risk of fracture healing complications as recommended in April 2016 by PRAC in procedure EMEA/H/C/PSUSA/00000954/201509. Furthermore, addition of study 20090601: a post-marketing active safety surveillance programme for soliciting adverse events of special interest in the United States as a category 4 study pharmacovigilance activity

Action: For adoption of PRAC Assessment Report

5.2.4. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0051

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 23) to update the 'important potential risk: hypercalcemia following treatment discontinuation in patients with growing skeletons' with the new important potential risk: hypercalcemia following treatment discontinuation in patients other than those with growing skeletons'. The MAH also took the opportunity to include minor changes for correction and/or to add clarification

Action: For adoption of PRAC Assessment Report

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

5.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0105

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Extension of indication to include the treatment of psoriatic arthritis in adults. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 21) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

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

5.3.2. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/II/0043

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 5.3 of the SmPC in order to delete the statement that amifampridine has not been fully tested in carcinogenicity models and to include the findings from the carcinogenicity reports as required in completed SOB 004 (carcinogenicity testing in an appropriate model). Annex II and the RMP (version 9) are updated accordingly

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

5.3.3. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0027

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.8 of the SmPC to add that the safety profile of ataluren in non-ambulatory patients is similar to the safety profile in ambulatory patients following the results of a 48-week open label extension study in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD). The RMP (version 6.3) is updated accordingly

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

5.3.4. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/II/0024

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.3 of the SmPC to reflect the results of the non-clinical study (XL184-NC-036) assessing the carcinogenicity potential in rat. The RMP is updated accordingly

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

5.3.5. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0010

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC to reflect the safety and efficacy findings of study A2303 (a phase III, multicentre, randomized, open label, study of oral *vs* standard chemotherapy in adult patients with anaplastic lymphoma kinase (ALK)-rearranged (ALK-positive) advanced non-small cell lung cancer (NSCLC) who have been treated previously with chemotherapy (platinum doublet) and crizotinib) to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib. Annex II, the Package Leaflet, Labelling and the RMP (version 5) are updated accordingly

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

5.3.6. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/II/0015

Applicant: Boehringer Ingelheim GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include the treatment with Synjardy as adjunct to standard care therapy in adult patients with type 2 diabetes mellitus (T2DM) and high cardiovascular risk when the treatment with empagliflozin and metformin is appropriate and empagliflozin is needed to reduce the risk of all-cause mortality by reducing cardiovascular death and cardiovascular death or hospitalization for heart failure. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated based on the final clinical study report of study EMPA-REG OUTCOME: 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 T2DM patients with increased cardiovascular risk. The Package Leaflet and the RMP (version 5.0) are updated accordingly

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

5.3.7. Fampridine - FAMPYRA (CAP) - EMEA/H/C/002097/II/0036/G

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Sabine Straus

Scope: Grouped variation to 1) update sections 4.2 and 5.1 of the SmPC, Annex II and the Package Leaflet based on the results of the clinical study ENHANCE: a multicentre, randomized, double blind, placebo controlled study to assess the long-term efficacy and safety of prolonged release fampridine 10 mg, administered twice daily in subjects with multiple sclerosis; 2) update of section 4.6 of the SmPC based on the data from pregnancy registry; 3) update of section 4.2 and 5.2 of the SmPC based on the core data sheet (CDS) and PRAC review of the Fampyra PSUR 03. The RMP (version 11) is updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10.0). Finally, a switch from a conditional to a standard marketing authorisation (MA) is assessed as part of this procedure

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

5.3.8. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/II/0040

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Update of section 4.6 of the SmPC to add information on the use of fingolimod in pregnancy. In addition, update of section 5.3 of the SmPC to include information about the dose correspondence between human and the species used for the preclinical tests of teratogenicity. The RMP (version 12.0) is updated accordingly. The MAH took the opportunity to introduce minor editorial changes in sections 4.4, 4.5, 4.6 and 5.2 of the SmPC and in Annex II.D

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

5.3.9. Insulin degludec - TRESIBA (CAP) - EMEA/H/C/002498/II/0024/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variation to update sections 4.2 and 5.1 of the SmPC in order to include updated information on the use of Tresiba in terms of transfer from other basal insulin regimens and the effects of Tresiba on hypoglycaemia following the completion of studies NN1250-3995 (SWITCH 1: a randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, both with insulin aspart as mealtime insulin in subjects with type 1 diabetes) and NN1250-3998 (SWITCH 2:a randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, with or without oral antidiabetic drugs in subjects with type 2 diabetes), comparing the safety and efficacy of Tresiba (insulin degludec) and insulin glargine U-100. The Package Leaflet, Labelling and RMP (version 7.0) are updated accordingly. The MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10.0). Finally, minor changes have been made to the SmPC section 4.2 and the corresponding section of the Package Leaflet to clarify the correct use of Tresiba (insulin degludec)

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

5.3.10. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0089/G

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Grouped variation including: 1) extension of indication to add the treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who have undergone autologous stem cell transplantation (ASCT). Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC, the Package Leaflet and RMP are updated accordingly; 2) Introduction of a 7-day pack sizes for the 10 mg and 15 mg strengths with subsequent changes to the Product Information. The RMP (version 31.1) is updated accordingly

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

5.3.11. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/II/0161/G

Applicant: AbbVie Ltd.

PRAC Rapporteur: Claire Ferard

Scope: Grouped variation including: 1) extension of indication to include children aged 14 days and older in the treatment of human immunodeficiency virus (HIV)-1. As a consequence, sections 4.1, 4.2, 4.3, 4.8, 5.1 and 5.2 of the SmPC are updated. The studies provided in support of the paediatric indication are part of the agreed PIP decision P/0144/2012. In addition, the MAH further updated section 4.4 to add information regarding the use of Kaletra oral solution with feeding tubes. The Package Leaflet, Labelling and RMP (version 8) are updated accordingly; 2) addition of a new pack size of 120 mL in (2 x 60ml bottles) for Kaletra 80mg/ml and 20 mg/ml oral solution (EU/1/01/172/003); 3) addition of a new 2 ml oral dose syringe for the 120 mL presentation

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

5.3.12. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0017

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) after platinum-based therapy in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated in order to add the proposed new indication, add a warning that patients with a baseline performance score ≥ 2, untreated brain metastasis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the SCCHN clinical trial and update the undesirable effect and safety information. The Labelling and RMP (version 6.0) are updated accordingly

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

5.3.13. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0024

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to reflect the final overall survival and response data, including duration of response with longer follow-up, following completion of PAES CA209037: a randomized, open-label, phase 3 trial of nivolumab versus investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 therapy) and its addendum on predictability of efficacy with biomarkers. This fulfils ANX 001 (submission of CA209037 final study report) and 003.1 (submission of results relating to the exploration of the optimal cut-off for death-ligand 1 (PD-L1) positivity based on current assay method used to further elucidate its value as predictive of nivolumab efficacy as part of CA209037 results submission). Annex II and the RMP (version 5.5) are updated accordingly

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

5.3.14. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0016

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include a new indication for Gazyvaro (obinutuzumab) in combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response for the treatment of patients with previously untreated advanced follicular lymphoma. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC, Package Leaflet and the RMP (version 3.0) are updated accordingly. In addition, the due date for provision of the final clinical study report for study BO21223/GALLIUM (multicentre, phase III, open label, randomized study in previously untreated patients with advanced indolent non-Hodgkin's lymphoma evaluating the benefit of obinutuzumab + chemotherapy compared to rituximab + chemotherapy followed by obinutuzumab or rituximab maintenance therapy in responders) listed in the RMP as a category 3 has been updated. Furthermore, the Product Information is brought in line with the missing information of QRD template version 9.1 regarding annex II C. In addition, clarification or editorial changes to the SmPC are proposed for accuracy and clarity

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

5.3.15. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0014

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of classical Hodgkin lymphoma (cHL) in adults who have refractory disease, or who have relapsed after greater than 3 prior lines of therapy, based on the results from study KEYNOTE-087, an open-label phase II trial of pembrolizumab in subjects with relapsed or refractory cHL and study KEYNOTE-013, a phase Ib multi-cohort trial of pembrolizumab in subjects with hematologic malignancies. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 5.0) are updated accordingly

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/0018/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Grouped variation to update section 5.1 of the SmPC to reflect the data from the post-authorisation efficacy studies (PAES) in melanoma study P001 (phase I study of pembrolizumab alone in patients with progressive locally advanced or metastatic carcinoma, melanoma, and non-small cell lung carcinoma), study P002 (randomized, phase II study of pembrolizumab versus chemotherapy in patients with advanced melanoma) and study P006 (a multicentre, randomized, controlled, three-arm, phase III study to evaluate the safety and efficacy of two dosing schedules of pembrolizumab compared to ipilimumab in patients with advanced melanoma). Annex II and the RMP (version 6.0) are updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.17. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/II/0005/G

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variation to 1) update section 4.2 of the SmPC in order to include a revised dosing regimen as a result of the new 25 mg vial presentation; 2) change of the pack size of the finished product and update of sections 6.5 and 6.6 of the SmPC. Annex II, Package Leaflet, Labelling and RMP (version 2.0) are updated accordingly

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

5.3.18. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/II/0014

Applicant: Zambon SpA

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final study report for the study VDD4193 (safinamide: in vitro metabolic stability in human cryopreserved hepatocytes, by fatty acid amide hydrolase enzyme (FAAH), recombinant human n-acylethanolamine acid amidase (NAAA) and recombinant human acid ceramidase (ASAHl)) conducted in order to identify specific substances blocking the amidases (inhibitors of amidases) involved in the metabolism of safinamide (MEA 001.2). The RMP is updated accordingly

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

5.3.19. Sevelamer - RENVELA (CAP) - EMEA/H/C/000993/WS0965/0035; SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/WS0965/0007

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Extension of indication to include the control of hyperphosphataemia in paediatric patients (>6 years of age and a body surface area (BSA) of >0.75 m^2) with chronic kidney disease. As a consequence, section 4.2 of the SmPC is updated to detail the posology in the paediatric patients. The Package Leaflet is updated accordingly. The RMP is updated

accordingly

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

5.3.20. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS1075/0006; HARVONI (CAP) - EMEA/H/C/003850/WS1075/0043; Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS1075/0037

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final non-clinical study report PC-334-2035 assessing the potential for a pharmacokinetic interaction via transporter or enzyme based inhibition when sofosbuvir and other Direct Acting Antivirals (DAAs) are used concomitantly with amiodarone. The RMPs (version 1.0 (Epclusa), version 2.0 (Harvoni), version 5.0 (Sovaldi)) are updated accordingly

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

5.3.21. Sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/II/0039

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to add treatment of chronic hepatitis C in adolescents aged 12 to <18 years. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics. The Package Leaflet and RMP (version 2) are updated accordingly

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

5.3.22. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0007

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report from the category 3 nonclinical study 1070056 to perform an evaluation of a subset of tissues from the 6-month rat study using Ki-67 immunohistochemistry and to quantify cell proliferation

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

5.3.23. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0008/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report from the category 3 clinical pharmacology study CLDE225A2120, a relative bioavailability study to evaluate timing of meal relative to dose and fast conditions and effect of light meal (low fat meal). The clinical study report (CSR) submission date for category 3 study X2116 is changed from Q1 2017 to Q4 2018. The

clinical study report (CSR) due date for the category 3 CLDE225A2404 study (non-interventional PASS to further characterise long term efficacy) is changed from Q4 2024 to Q1 2025. The RMP (version 5.0) is updated accordingly

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

5.3.24. Sulphur hexafluoride - SONOVUE (CAP) - EMEA/H/C/000303/X/0034/G

Applicant: Bracco International B.V.

PRAC Rapporteur: Claire Ferard

Scope: Grouped variation including 1) extension application to introduce intravesical use as a new route of administration; 2) addition of a new indication to include use in ultrasonography of the excretory urinary tract in paediatric patients to detect or exclude vesicoureteral reflux. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6 of the SmPC are updated. The Package Leaflet and the RMP (version 9.1) are updated accordingly. In addition, the MAH took the opportunity to bring Annex IIIA in line with the latest QRD template (version 10)

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

5.3.25. Trifluridine, tipiracil - LONSURF (CAP) - EMEA/H/C/003897/II/0002/G

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations to: 1) update of sections 4.2, 4.4 and 5.2 of the SmPC following availability of the final clinical study report for study TO-TAS-102-106: a phase I, open-label study evaluating the safety, tolerability, and pharmacokinetics of TAS-102 in patients with advanced solid tumours and varying degrees of hepatic impairment (requested in MEA 002). The RMP (version 5.0) is updated accordingly to remove the missing information 'use in patients with moderate to severe hepatic impairment' and to add 'hyperbilirubinaemia in patients with baseline moderate to severe hepatic impairment' as important potential risk; 2) update of sections 4.5 and 5.2 of the SmPC following availability of the results in vitro CYP induction study of tipiracil hydrochloride (TPI) using the appropriate concentration of TPI (requested in a recommendation). The RMP is updated accordingly; 3) update of section 4.2 of the SmPC in order to correct inconsistencies in the dose calculation according to body surface area. The package leaflet is updated to add 'interstitial lung disease'. Finally, the MAH took the opportunity to update Annex IIIA in accordance with the latest QRD template

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

5.3.26. Umeclidinium bromide, vilanterol - ANORO (CAP) - EMEA/H/C/002751/WS1031/0013; Umeclidinium, vilanterol - LAVENTAIR (CAP) - EMEA/H/C/003754/WS1031/0014

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of section 4.8 of the SmPC in order to add the adverse reactions 'vision blurred', 'intraocular pressure increased' and 'paradoxical bronchospasm' and to change the

frequency of the adverse reaction 'glaucoma' from not known to rare. The Package Leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to 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

6. Periodic safety update reports (PSURs)

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

6.1.1. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201606

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.2. Ambrisentan - VOLIBRIS (CAP) - PSUSA/00000129/201606

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.3. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201607

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.4. Avanafil - SPEDRA (CAP) - PSUSA/00010066/201606 (with RMP)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.5. Belatacept - NULOJIX (CAP) - PSUSA/00000311/201606 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.6. Brinzolamide, brimonidine tartrate - SIMBRINZA (CAP) - PSUSA/00010273/201606

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.7. Bromfenac - YELLOX (CAP) - PSUSA/00000436/201605

Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.8. Cabazitaxel - JEVTANA (CAP) - PSUSA/00000476/201606

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.9. Canakinumab - ILARIS (CAP) - PSUSA/00000526/201606

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.10. Daclatasvir - DAKLINZA (CAP) - PSUSA/00010295/201607

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.11. Dasatinib - SPRYCEL (CAP) - PSUSA/00000935/201606

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.12. Edoxaban - LIXIANA (CAP) - PSUSA/00010387/201606

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.13. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/201605

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.14. Fidaxomicin - DIFICLIR (CAP) - PSUSA/00001390/201605

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.15. Galsulfase - NAGLAZYME (CAP) - PSUSA/00001515/201605

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.16. Glycerol phenylbutyrate - RAVICTI (CAP) - PSUSA/00010454/201605

Applicant: Horizon Pharma Ireland Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.17. Human fibrinogen, human thrombin - EVARREST (CAP); EVICEL (CAP); RAPLIXA (CAP); TACHOSIL (CAP) - PSUSA/00010297/201606

Applicant: Takeda Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.18. Human papillomavirus vaccine (rDNA) (4-valent) - GARDASIL (CAP); SILGARD (CAP) - PSUSA/00001634/201605

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.19. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201606

Applicant: Sanofi Pasteur MSD

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.20. Human plasma protease C1 inhibitor - CINRYZE (CAP) - PSUSA/00010104/201606

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.21. Hydroxycarbamide[2] - SIKLOS (CAP) - PSUSA/00001692/201606

Applicant: Addmedica

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

[2] Indication in sickle cell syndrome

Action: For adoption of recommendation to CHMP

6.1.22. Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/201606

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.23. Lesinurad - ZURAMPIC (CAP) - PSUSA/00010470/201606

Applicant: Gruenenthal GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.24. Levofloxacin[3] - QUINSAIR (CAP) - PSUSA/00010429/201605

Applicant: Raptor Pharmaceuticals Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.25. Lutetium (^{177}Lu) chloride - LUMARK (CAP) - PSUSA/00010391/201606

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

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.26. Matrix-applied characterised autologous cultured chondrocytes - MACI (CAP) - PSUSA/00010116/201606

Applicant: Vericel Denmark ApS

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CAT and CHMP

[3] Centrally authorised product only

6.1.27. Mirabegron - BETMIGA (CAP) - PSUSA/00010031/201606

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.28. Mixture of polynuclear iron(III) oxyhydroxide, sucrose, starches - VELPHORO (CAP) - PSUSA/00010296/201605

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.29. Nepafenac - NEVANAC (CAP) - PSUSA/00002143/201605

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.30. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201607

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.31. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201606

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.32. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201606

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.33. Pertuzumab - PERJETA (CAP) - PSUSA/00010125/201606

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.34. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201606

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.35. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/201607

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.36. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201606

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.37. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201606

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.38. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201606

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.39. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201606

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.40. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201607

Applicant: Vanda Pharmaceuticals Ltd.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.41. Tedizolid phosphate - SIVEXTRO (CAP) - PSUSA/00010369/201606

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.42. Tolvaptan[4] - JINARC (CAP) - PSUSA/00010395/201605

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.43. Trametinib - MEKINIST (CAP) - PSUSA/00010262/201605

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

[4] Indications for autosomal dominant polycystic kidney disease (ADPKD) only

6.1.44. Umeclidinium bromide, vilanterol - ANORO (CAP); LAVENTAIR (CAP) - PSUSA/00010264/201606

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

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

6.2.1. Capsaicin - QUTENZA (CAP); NAP - PSUSA/00000533/201605

Applicant: Astellas Pharma Europe B.V. (Qutenza), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.2. Human normal immunoglobulin - FLEBOGAMMA DIF (CAP); HIZENTRA (CAP); HYQVIA (CAP); KIOVIG (CAP); PRIVIGEN (CAP); NAP - PSUSA/00001633/201605

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.3. PSUR procedures including nationally authorised products (NAPs) only

6.3.1. Bemiparin (NAP) - PSUSA/00000312/201604

Applicant: various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.2. Benazepril, hydrochlorothiazide (NAP) - PSUSA/00000314/201605

Applicant: various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.3. Bismuth subcitrate potassium, metronidazole, tetracycline (NAP) - PSUSA/00010199/201605

Applicant: various

PRAC Lead: Nikica Mirosevic Skvrce

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.4. Budesonide (NAP) - PSUSA/00000449/201604

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.5. Clevidipine (NAP) - PSUSA/00010288/201605

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.6. Docosanol (NAP) - PSUSA/00010092/201604

Applicant: various

PRAC Lead: Nikica Mirosevic Skvrce

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.7. F(Ab')2 fragments of equine antirabies immunoglobulin (NAP) - PSUSA/00001348/201605

Applicant: various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.8. Fusidic acid (NAP) - PSUSA/00010226/201605

Applicant: various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.9. Goserelin (NAP) - PSUSA/00001562/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.10. Human hemin (NAP) - PSUSA/00001629/201605

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.11. Human prothrombin complex (NAP) - PSUSA/00001638/201604

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.12. Hydroxyzine chloride, hydroxyzine pamoate and all fixed combination, hydroxyzine (NAP) - PSUSA/00001696/201605

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.13. Isoniazide, rifampicin (NAP) - PSUSA/00001792/201605

Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.14. Lactulose (NAP) - PSUSA/00001821/201605

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.15. Latanoprost[5] (NAP) - PSUSA/00001832/201604

Applicant: various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.16. Loperamide (NAP) - PSUSA/00001903/201605

Applicant: various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.17. Macrogol 3350 (NAP) - PSUSA/00001924/201605

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.18. Macrogol 4000 and combinations[6] (NAP) - PSUSA/00010392/201605

Applicant: various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

[5] Except products with paediatric indication
[6] For systemic use

6.3.19. Misoprostol[7] (NAP) - PSUSA/00010353/201605

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.20. Moxifloxacin[8] (NAP) - PSUSA/00009231/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.21. Moxifloxacin[9] (NAP) - PSUSA/00002094/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.22. Nadifloxacin (NAP) - PSUSA/00002102/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.23. Nefopam (NAP) - PSUSA/00002131/201603

Applicant: various

PRAC Lead: Nikica Mirosevic Skvrce

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.24. Nicardipine (NAP) - PSUSA/00002149/201605

Applicant: various

[7] For gynaecological indication, labour induction
[8] For systemic use
[9] For topical ophthalmic use

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.25. Sulprostone (NAP) - PSUSA/00002828/201604

Applicant: various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.26. Tirofiban (NAP) - PSUSA/00002974/201605

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.27. Treprostinil (NAP) - PSUSA/00003013/201605

Applicant: various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/LEG 029

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a safety assessment of all haemorrhagic events for cinacalcet events in all controlled clinical studies with cinacalcet, irrespective of indication as requested in the conclusions of EMEA/H/C/PSUSA/00000756/201602 adopted by the PRAC on 29 September 2016

Action: For adoption of advice to CHMP

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[10]

7.1.1. Hydroxyethyl starch (NAP) - EMEA/H/N/PSA/S/0011

Applicant: B. Braun Melsungen AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a revised PASS protocol for the retrospective drug utilisation study (ENCEPP/SDDP/12540) to investigate the routine use of hydroxyethyl starch (HES)-containing infusion solutions of B.Braun Melsungen AG in hospitals

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

7.1.2. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/PSP/0040.2

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Submission of a revised PASS protocol for the prospective, multinational, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole (using the existing European Registry on Cushing's syndrome (ERCUSYN)), to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

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

7.1.3. Lesinurad - ZURAMPIC (CAP) - EMEA/H/C/003932/PSP/S/0050.1

Applicant: Gruenenthal GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of a revised PASS protocol for an observational post-authorisation safety study of lesinurad patients (SATURATES) to further assess cardiovascular (CV) safety with a focus on major adverse cardiovascular events (MACE), and renal safety, in gout patients treated with Zurampic, lesinurad (LESU) in combination with xanthine oxidase inhibitors (XOI) (LESU+XOI cohort), compared to similar patients who are continuing treatment with XOI monotherapy (XOI mono cohort)

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

7.1.4. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/PSA/S/0012

Applicant: Celgene Europe Limited

PRAC Rapporteur: Rafe Suvarna

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

Scope: Submission of a revised PASS protocol in order to amend the study milestones for the study CC-4047-MM015 : a non-interventional post authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma to monitor incidence of adverse reactions and to monitor the implementation and compliance of Celgene pregnancy prevention programme and off label use and controlled distribution system on a country basis in agreement with relevant national competent authorities

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

7.1.5. Thiocolchicoside (NAP) - EMEA/H/N/PSA/J/0010

Applicant: Sanofi

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of a revised PASS protocol for the EUPAS1108, a drug utilisation study of thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical record databases study

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[11]

7.2.1. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/MEA 002

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of a PASS protocol for the category 3 Biogen multiple sclerosis (MS) pregnancy exposure registry 109MS402 to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product

Action: For adoption of advice to CHMP

7.2.2. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 045

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of a PASS protocol for a drug utilisation study (GS-EU-276-4027) to characterize: 1) prescribers' level of knowledge about the key risks of Truvada for a pre-exposure prophylaxis (PrEP) indication and assess the effectiveness of risk minimisation measures, 2) prescribing practices in routine clinical practice of Truvada for PrEP by describing the demographics of human immunodeficiency virus (HIV)-1 uninfected individuals who were prescribed Truvada for PrEP, and the prescribed dosing schedule for Truvada for PrEP as reported by the prescriber, as a result of variation II/0126 finalised at CHMP/PRAC in July 2016 to extend the indication to PrEP

[11] 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

Action: For adoption of advice to CHMP

7.2.3. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/MEA 167.1

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of a revised PASS protocol for study B1801396 : an observational cohort study to evaluate the risk of adverse pregnancy outcomes in patients treated with etanercept compared to those not treated with etanercept or other biologics using merged data from Sweden, Denmark and Finland, as per the conclusions of variation II/184 further to the RSI adopted in July 2016

Action: For adoption of advice to CHMP

7.2.4. Fentanyl - IONSYS (CAP) - EMEA/H/C/002715/MEA 002

Applicant: Incline Therapeutics Europe Ltd

PRAC Rapporteur: Almath Spooner

Scope: Submission of a PASS protocol for the study MDCO-ION-16-03, a IONSYS prescriber survey to evaluate the effectiveness of the IONSYS EU RMP Healthcare Provider Educational Programme.

Action: For adoption of advice to CHMP

7.2.5. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Submission of a PASS protocol to further investigate and characterise the associations of lenalidomide and TFR/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/ or refractory mantle cell lymphoma (RRMCL) (EMEA/H/C/000717/II/0079)

Action: For adoption of advice to CHMP

7.2.6. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/MEA 015

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of a PASS protocol for a post-marketing observational registry (AP24534-14-401) to evaluate the incidence of and risk factors for vascular occlusive events associated with Iclusig (ponatinib) in routine clinical practice in the US (OMNI)

Action: For adoption of advice to CHMP

7.3. Results of PASS imposed in the marketing authorisation(s)[12]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[13]

7.4.1. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0025

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for PASS 206207-025: a prospective observational study to evaluate long-term safety in real-world clinical practice

Action: For adoption of PRAC Assessment Report

7.4.2. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0039

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of final report of the drug utilisation study REVIEU (CETB115B2406): a multinational, retrospective, observational drug utilisation study in selected countries in the European Union in fulfilment of MEA 21.1.

Action: For adoption of PRAC Assessment Report

7.4.3. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0040

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final data from the nested eltrombopag HCV-TARGET cohort study: a prospective observational cohort study nested within the Hepatitis C Therapeutic Registry and Research Network (HCV- TARGET) to evaluate real world use of eltrombopag in adult patients with chronic hepatitis C virus infection who are unable to initiate or maintain optimal interferon based therapy due to thrombocytopenia. The RMP (version 44.0) is updated accordingly

Action: For adoption of PRAC Assessment Report

7.4.4. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0198

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of the final clinical study report for the BSPAR (British society for

[12] In accordance with Article 107p-q of Directive 2001/83/EC
[13] 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

paediatric and adolescent rheumatology) etanercept registry, a cohort study (category 3 in the RMP)

Action: For adoption of PRAC Assessment Report

7.4.5. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0054

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final clinical study report (CSR) for study VX12-770-112: a rollover study to evaluate the long-term safety and efficacy of ivacaftor treatment in subjects ≥6 years of age with cystic fibrosis (CF) and a non-G551D mutation in the CFTR gene. The RMP (version 5.4) is updated accordingly

Action: For adoption of PRAC Assessment Report

7.4.6. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/WS1047/0055; Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/WS1047/0016

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final clinical study report (CSR) for study VX12-770-115: an ocular safety study of ivacaftor-treated paediatric patients 11 years of age or younger with cystic fibrosis (CF) as a follow up of Kalydeco MEA 023 and Orkambi MEA 004. The RMPs (version 5.3 (Kalydeco) and version 2.6 (Orkambi)) are updated accordingly

Action: For adoption of PRAC Assessment Report

7.4.7. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/WS0943/0009; VICTOZA (CAP) - EMEA/H/C/001026/WS0943/0041

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final results from a category 3 study: liraglutide safety and surveillance programme using the Optum research database study, and its sub-study on breast cancer

Action: For adoption of PRAC Assessment Report

7.4.8. Pioglitazone - ACTOS (CAP) - EMEA/H/C/000285/WS0991/0075; GLUSTIN (CAP) - EMEA/H/C/000286/WS0991/0073; Pioglitazone, glimepiride - TANDEMACT (CAP) - EMEA/H/C/000680/WS0991/0051 Pioglitazone, metformin - COMPETACT (CAP) - EMEA/H/C/000655/WS0991/0062; GLUBRAVA (CAP) - EMEA/H/C/000893/WS0991/0047

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final study report for the clinical practice research datalink (CPRD)

GOLD linkage study (Pioglitazone_5018) conducted to investigate a possible association of the use of pioglitazone with prostate cancer and data on the incidence of adjudicated prostate cancer in patients receiving pioglitazone in the long-term insulin resistance intervention after stroke (IRIS) trial

Action: For adoption of PRAC Assessment Report

7.4.9. Saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/WS0960/0033/G; Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/WS0960/0040/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Group of variations consisting of final epidemiological study results for studies D1680R00011 (a cohort study comparing risk of major cardiovascular (CV) events between patients with type 2 diabetes mellitus (T2DM) who are new initiators of saxagliptin and those who are new initiators of oral antidiabetic drug (OAD) treatments in classes other than DPP-4 inhibitors), D1680R00012 (a cohort study comparing risk of hospitalization with acute liver failure between patients with T2DM exposed to saxagliptin and those exposed to other OAD treatments), D1680R00013 (a cohort study comparing risk of hospitalization with infections between patients with T2DM exposed to saxagliptin and those exposed to other OAD treatments), D1680R00014 (a cohort study comparing risk of hospitalization for severe hypersensitivity (including severe cutaneous reactions) between patients with T2DM exposed to saxagliptin and those exposed to other OAD treatments) and D1680R00015 (a cohort study comparing risk of hospitalization for acute kidney injury between patients with T2DM initiating saxagliptin and those initiating other OAD treatments), and consequent update of the RMP. As a consequence, the RMP (version 11) is updated accordingly. In addition, routine changes are made in parts III (pharmacovigilance plan, overview of planned pharmacovigilance actions) and IV. A safety review based on literature has also been included to investigate acute kidney injury associated with saxagliptin, saxagliptin and metformin at the PRAC request

Action: For adoption of PRAC Assessment Report

7.4.10. Voriconazole - VFEND (CAP) - EMEA/H/C/000387/II/0121

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of study A1501102 evaluating the effectiveness of additional risk minimisation measure that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving Voriconazole in the European Union (EU). The RMP (version 5) is updated accordingly

Action: For adoption of PRAC Assessment Report

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

7.5.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/MEA 023.2

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of interim results report of the nested case-control analysis in two Spanish Populations and Germany of the category 3 PASS Study No. CLE-20098-094, a post-authorisation safety study of agomelatine and the risk of hospitalisation for acute liver injury further to variation II/18

Action: For adoption of advice to CHMP

7.5.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/MEA 023.2

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of interim results report of the nested case-control analysis in two Spanish Populations and Germany of the category 3 PASS Study No. CLE-20098-094, a post-authorisation safety study of agomelatine and the risk of hospitalisation for acute liver injury further to variation II/18

Action: For adoption of advice to CHMP

7.5.3. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/MEA 010

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of an interim results report for a category 3 study TMC207TBC4002: a multinational prospective multidrug resistant tuberculosis patient registry to monitor bedaquiline safety, utilisation, and emergence of resistance

Action: For adoption of advice to CHMP

7.5.4. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.4

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.3: first interim analysis report for an US category 3, PASS (B2311060 study): active surveillance of conjugated estrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data as per the request for supplementary information (RSI) adopted in June 2016

Action: For adoption of advice to CHMP

7.5.5. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 013.3

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of MAH's responses to MEA 13.2 [second annual interim report from an observational database-assisted comparative cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma (protocol number: ISN 9463-CL-140) a multicentre cohort study of the short and long-term safety of micafungin and Other parenteral antifungal agents (MYCOS)] as per the request for supplementary information adopted in June 2016

Action: For adoption of advice to CHMP

7.5.6. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/PSP/001.2

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of the first annual interim report of the five year post authorisation safety study (PASS - ENCEPP/SDPP/8585) to assess the safety and incidence of side effects in a cohort of postmenopausal women prescribed ospemifene relative to patients diagnosed with but not treated for vulvar and vaginal atrophy (VVA) and patients on selective oestrogen receptor modulators (SERMs) for oestrogen-deficiency conditions or breast cancer prevention

Action: For adoption of advice to CHMP

7.5.7. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/MEA 012

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of the interim result report for the risk minimisation assessment survey and interim report for risk minimisation measures distribution to assess the effectiveness of two risk minimisation measures (DHPC and HCP brochure)

Action: For adoption of advice to CHMP

7.5.8. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/MEA 004.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an interim report for the post-authorisation safety study NN7008-3553, a multicentre non-interventional study of safety and efficacy of turoctocog alfa (recombinant factor VIII (rFVIII)) during long-term treatment of severe and moderately severe haemophilia A (FVIII ≤2%)

Action: For adoption of advice to CHMP

7.6. Others

7.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.9

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 005.7: provision of data to address additional pharmacovigilance activity in the RMP: canagliflozin Independent Data Monitoring Committee (IDMC) status reports for studies DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus) and DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on Renal endpoints in adult subjects with type 2 diabetes mellitus), as per the request for supplementary information (RSI) adopted in July 2016

Action: For adoption of advice to CHMP

7.6.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.10

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Provision of the fifth canagliflozin Independent Data Monitoring Committee (IDMC) status report for the DIA3008 (CANVAS) and DIA4003 (CANVAS-R) studies

Action: For adoption of advice to CHMP

7.6.3. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.6

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Bi-annual status reports for DNE3001/CREDENCE: a randomized, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (September 2016 status report)

Action: For adoption of advice to CHMP

7.6.4. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.9

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 004.7: provision of data to address additional pharmacovigilance activity in the RMP: Canagliflozin Independent Data Monitoring Committee (IDMC) status reports for studies DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on

cardiovascular outcomes in adult subjects with type 2 diabetes mellitus) and DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on Renal endpoints in adult subjects with type 2 diabetes mellitus), as per the request for supplementary information (RSI) as adopted in July 2016

Action: For adoption of advice to CHMP

7.6.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.10

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Provision of a fifth Independent Data Monitoring Committee (IDMC) status report for the DIA 3008 (CANVAS) and DIA4003 (CANVAS-R) studies

Action: For adoption of advice to CHMP

7.6.6. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.6

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Bi-annual status reports for DNE3001/CREDENCE: a randomized, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (September 2016 status report)

Action: For adoption of advice to CHMP

7.6.7. Epoetin beta - NEORECORMON (CAP) - EMEA/H/C/000116/LEG 051.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Submission of a summary of the results achieved with the LungSys II project (systems biology of lung cancer – dynamic properties of early metastasis and therapeutic interventions) with focus on relevant results concerning the erythropoietin/erythropoietin receptor system and erythropoiesis stimulating agents (ESA)

Action: For adoption of advice to CHMP

7.6.8. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 008.3

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of MAH's responses to MEA 008.2 regarding the annual interim report on an i3 drug safety epidemiology study CNTO148ART4002: golimumab safety and surveillance programme using the Optum research database

Action: For adoption of advice to CHMP

7.6.9. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/LEG 035

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a summary report on data on the effectiveness of the patient reminder card (PRC) introduced as additional risk minimisation measure for the existing identified risk of osteonecrosis of the jaw (EMEA/H/C/000595/II/0056)

Action: For adoption of advice to CHMP

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

8.1.1. Alipogene tiparvovec - GLYBERA (CAP) - EMEA/H/C/002145/S/0057 (without RMP)

Applicant: uniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CAT and CHMP

8.1.2. Canakinumab - ILARIS (CAP) - EMEA/H/C/001109/S/0047 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.3. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0016 (without RMP)

Applicant: Laboratoires CTRS - Boulogne Billancourt

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.4. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0005 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.5. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0019 (without RMP)

Applicant: Orphan Europe S.A.R.L.

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.2. Conditional renewals of the marketing authorisation

8.2.1. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/R/0023 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.2.2. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/R/0009 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.2.3. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0017 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Rafe Suvarna

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.2.4. Pixantrone - PIXUVRI (CAP) - EMEA/H/C/002055/R/0034 (with RMP)

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3. Renewals of the marketing authorisation

8.3.1. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/R/0030 (with RMP)

Applicant: Addmedica

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.2. Imiquimod - ZYCLARA (CAP) - EMEA/H/C/002387/R/0012 (with RMP)

Applicant: Meda AB

PRAC Rapporteur: Rafe Suvarna

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.3. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/R/0052 (with RMP)

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.4. Linagliptin, metformin - JENTADUETO (CAP) - EMEA/H/C/002279/R/0036 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.5. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/R/0035 (without RMP)

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

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

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

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

10.3.1. Capecitabine - XELODA (CAP) - EMEA/H/C/000316/LEG 033

Applicant: Roche Registration Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of MAH's submission addressing the proposal by a group of authors (Prof. J. Schellens et al.) put forward to the CHMP and PRAC to review the SmPC of fluoropyrimidines (Xeloda (capecitabine) and 5-fluorouracil (5FU)) and suggesting that screening for dihydropyriminidine dehydrogenase (DPYD) variants and dose reductions in patients taking fluoropyrimidines could reduce the risk of toxicity in patients with dihydropyrimidine dehydrogenase deficiency

Action: For adoption of advice to CHMP

10.3.2. Human normal immunoglobulin – HYQVIA (CAP) - EMEA/H/C/002491/II/0032

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: PRAC consultation on a direct healthcare professional communication (DHPC) and proposed measures evaluated in the framework of a variation to update of section 4.2 and 4.8 of the SmPC in order to add information on infusion site leakage. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template (version 10)

Action: For adoption of advice to CHMP

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. Sulfamethoxazole, trimethoprim (co-trimoxazole) (NAP)

Applicant: various

PRAC Lead: Željana Margan Koletić

Scope: PRAC consultation on an assessment from Croatia on prolongation of QT interval and torsade de pointes (TdP) and proposed wording for inclusion in the product information

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

12.2.1. Conditional marketing authorisation for medicinal product for human use – report on 10 years of experience

Action: For discussion

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

12.3.1. Advisory group on classification of post-authorisation studies (CPAS) - metrics

Action: For discussion

12.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP) - work plan 2017

Action: For adoption

12.3.3. Working Party with Patients' and Consumers' Organisations (PCWP) – work plan 2017

Action: For adoption

12.4. Cooperation within the EU regulatory network

12.4.1. Pharmacovigilance operation - EU training curriculum design document

Action: For adoption

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. 2017 PRAC work plan – consolidation

Action: For discussion

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - PRAC work tracking including quarterly workload measures and performance indicators for the last three months - predictions

Action: For discussion

12.8.2. Marketing authorisation applications (MAA) - planned for 2017

Action: For discussion

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

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: Sabine Straus

Action: For discussion

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

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

12.13.2. Pharmacovigilance adverse drug reaction project – status update and audit preparation

Action: For discussion

12.13.3. Guide on the interpretation of spontaneous case reports of suspected adverse reactions to medicines – draft revision 1

Action: For adoption

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.14.3. Good Pharmacovigilance Practice (GVP) Module V on risk management systems- draft revision 2

Action: For adoption

12.14.4. Good Pharmacovigilance Practice (GVP) Module XVI on risk minimisation measures: selection of tools and effectiveness indicators – draft revision 2

Action: For adoption

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

Action: For adoption

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

12.18.3. Results of PASS imposed in the marketing authorisation(s)[14] – communication strategy

Action: For discussion

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Serious cutaneous adverse reactions (SCARs) - regulatory perspective

PRAC lead: Sabine Straus, Herve Le Louet, Zane Neikena

Action: For discussion

13. Any other business

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

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/