11 June 2018
EMA/PRAC/395628/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 11-14 June 2018

Chair: June Raine – Vice-Chair: Almath Spooner

11 June 2018, 09:30 – 19:30, room 3/A

12 June 2018, 08:30 – 19:30, room 3/A

13 June 2018, 08:30 – 19:30, room 3/A

14 June 2018, 08:30 – 16:00, room 3/A

Organisational, regulatory and methodological matters (ORGAM)

28 June 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).

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1. Introduction

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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the PRAC plenary session to be held 11-14 June 2018. See June 2018 PRAC minutes (to be published post July 2018 PRAC meeting).

1.2. Agenda of the meeting on 11-14 June 2018

Action: For adoption

1.3. Minutes of the previous meeting on 14-17 May 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. 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 holding a public hearing

3.2.2. Radium (^{223}Ra) dichloride - XOFIGO (CAP) - EMEA/H/A-20/1459

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Valerie Strassmann

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

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

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[1]

None

3.5. Others

None

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

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); liraglutide – VICTOZA (CAP)

Applicant(s): AstraZeneca AB (Bydureon, Byetta), Eli Lilly Nederland B.V. (Trulicity), Novo Nordisk A/S (Victoza)

PRAC Rapporteur: To be appointed

Scope: Signal of diabetic ketoacidosis

Action: For adoption of PRAC recommendation

EPITT 19237 – New signal

Lead Member State(s): IT, NL, SE

4.1.2. Nivolumab – OPDIVO (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of keratoacanthoma

Action: For adoption of PRAC recommendation

EPITT 19250 – New signal

Lead Member State: DE

4.1.3. Rivaroxaban – XARELTO (CAP)

Applicant(s): Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of acquired haemophilia

Action: For adoption of PRAC recommendation

EPITT 19240 – New signal

Lead Member State: SE

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

4.1.4. Tacrolimus[3] – ADVAGRAF (CAP), ENVARSUS (CAP), MODIGRAF (CAP), TACFORIUS (CAP), NAP

Applicant(s): Astellas Pharma Europe B.V. (Advagraf, Modigraf), Chiesi Farmaceutici S.p.A. (Envarsus), Teva B.V. (Tacforius); various

PRAC Rapporteur: To be appointed

Scope: Signal of hepatitis E infection

Action: For adoption of PRAC recommendation

EPITT 19246 – New signal

Lead Member State: IE

4.1.5. Xylometazoline (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of serious ventricular arrhythmia in patients with long QT syndrome

Action: For adoption of PRAC recommendation

EPITT 19242 – New signal

Lead Member State: LV

4.2. New signals detected from other sources

4.2.1. Carbimazole (NAP); thiamazole (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: New information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy

Action: For adoption of PRAC recommendation

EPITT 19238 – New signal

Lead Member State: DE

4.2.2. Nabumetone (NAP)

Applicant(s): various

PRAC Rapporteur: Sabine Straus

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

Action: For adoption of PRAC recommendation

EPITT 19241 – New signal

[3] Systemic formulations only

Lead Member State: NL

4.3. Signals follow-up and prioritisation

4.3.1. Hydrochlorothiazide (NAP); Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP)

Applicant(s): Actavis Group PTC ehf (Actelsar HCT), Bayer Pharma AG (Kinzalkomb, PritorPlus), Boehringer Ingelheim International (MicardisPlus), Krka, d.d. (Ifirmacombi, Tolucombi), Noden Pharma DAC (Rasilez HCT), Novartis Europharm Limited (Copalia HCT, Dafiro HCT), Sanofi-aventis groupe (Irbesartan Hydrochlorothiazide Zentiva, Karvezide), Sanofi Clir SNC (CoAprovel), Teva B.V. (Irbesartan/Hydrochlorothiazide Teva); various

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of skin cancer

Action: For adoption of PRAC recommendation

EPITT 19138 – Follow-up to January 2018

4.3.2. Biotin (NAP)

Applicant(s): various

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of interference with clinical laboratory tests

Action: For adoption of PRAC recommendation

EPITT 19156 – Follow-up to February 2018

4.3.3. Varenicline – CHAMPIX (CAP) – EMEA/H/C/000699/SDA/048

Applicant(s): Pfizer Limited

PRAC Rapporteur: Anette Stark

Scope: Signal of loss of consciousness

Action: For adoption of PRAC recommendation

EPITT 19146 – Follow-up to February 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 UK Limited

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 May 2018

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Damoctocog alfa pegol - EMEA/H/C/004054, Orphan

Applicant: Bayer AG

Scope: Treatment and prophylaxis of haemophilia A

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

5.1.2. Doravirine - EMEA/H/C/004747

Scope: Treatment of adults infected with human immunodeficiency virus 1 (HIV-1) without past or present evidence of viral resistance to treatment of adults to doravirine

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

5.1.3. Doravirine, lamivudine, tenofovir disoproxil - EMEA/H/C/004746

Scope: Treatment of adults infected with human immunodeficiency virus 1 (HIV-1) without past or present evidence of viral resistance to doravirine, lamivudine, or tenofovir

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

5.1.4. Lanadelumab - EMEA/H/C/004806, Orphan

Applicant: Shire Pharmaceuticals Ireland Limited

Scope (accelerated assessment): Routine prevention of angioedema attacks and control of symptoms of hereditary angioedema (HAE) in patients aged 12 years and older

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

5.1.5. Neratinib - EMEA/H/C/004030

Scope (re-examination procedure): Extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER2)-overexpressed, amplified breast cancer who are less than one year from the completion of prior adjuvant trastuzumab based therapy

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

5.1.6. Pegfilgrastim - EMEA/H/C/004700

Scope: Treatment of neutropenia

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

5.1.7. Silodosin - EMEA/H/C/004964

Scope: Treatment of prostatic hyperplasia (BPH)

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

5.1.8. Ulipristal acetate - EMEA/H/C/005017

Scope: Treatment of uterine fibroids

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. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/II/0023

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Caroline Laborde

Scope: Update of Annex II.D following the submission of the thirteenth and final study report for the DUO registry (listed as a category 3 study in the RMP): a non-interventional post-approval safety study and additional risk minimisation measure in the bosentan EU RMP. The RMP (version 9.1) is updated accordingly

Action: For adoption of PRAC Assessment Report

5.2.2. Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/II/0086

Applicant: Actelion Registration Limited

PRAC Rapporteur: Caroline Laborde

Scope: Update of Annex II.D following the submission of the thirteenth and final study report for the DUO registry (listed as a category 3 study in the RMP): a non-interventional PASS and additional risk minimisation measure in the bosentan EU RMP. The RMP (version 9.1) is updated accordingly

Action: For adoption of PRAC Assessment Report

5.2.3. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0027, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 4.0) in order to re-classify an imposed non-interventional PASS listed as a category 2 study in the RMP (specific obligation) to a study listed as a category 3 in the RMP (required additional pharmacovigilance activities). This study is an observational registry (DF-VOD2013-03-REG) aiming at recording safety and outcome data in patients diagnosed with severe veno-occlusive disease (VOD) following haematopoietic stem cell transplantation (HSCT) treated or not with Defitelio (defibrotide). Annex II of the product information is updated accordingly

Action: For adoption of PRAC Assessment Report

5.2.4. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/II/0030, Orphan

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 2.10) in order to revise the risk re-categorisation justifications and lay language wording, as well as to add clarifications to the described additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures and set up date of EU network of laboratories, as requested by PRAC following the assessment of the annual renewal procedure completed in February 2018

Action: For adoption of PRAC Assessment Report

5.2.5. Follitropin alfa, lutropin alfa - PERGOVERIS (CAP) - EMEA/H/C/000714/II/0055

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 5.1) in order to revise the epidemiology section based on the recent literature data, to revise the non-clinical part of the safety specification section with the data available from recombinant human follicle stimulating hormone (r-hFSH), recombinant human luteinizing hormone (r-hLH) and Pergoveris (follitropin alfa/lutropin alfa) as well as to revise the clinical trial section for clinical studies for r-hFSH/r-hLH for ovulation induction (OI) and assisted reproductive technologies (ART). In addition, the patient exposure data is updated and a reference is added to the recently approved pharmaceutical forms (solution for injection in pre-filled pen (300 IU/150 IU, 450 IU/225 IU and 900 IU/450 IU)). Finally, the RMP is aligned with GVP module V on 'Risk management systems', revision 1

Action: For adoption of PRAC Assessment Report

5.2.6. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0022

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of the RMP (version 9) in order to remove PASS D5165C00001 (listed as a category 3 study in the RMP): 'a phase 3, multicentre, open label, randomized study to assess the efficacy and safety of osimertinib (AZD9291) in combination with durvalumab (MEDI4736) versus osimertinib monotherapy in patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have received prior EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy (CAURAL)' from the pharmacovigilance plan

Action: For adoption of PRAC Assessment Report

5.2.7. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0023

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of the RMP (version 9) in order to remove PASS D5160C00022 (listed as a category 3 study in the RMP): 'an open label, multinational, multicentre, real world treatment study of single agent osimertinib for patients with advanced/metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have received prior therapy with an EGFR tyrosine kinase inhibitor (EGFR-TKI) (ASTRIS)' from the pharmacovigilance plan

Action: For adoption of PRAC Assessment Report

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

5.3.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0045

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to add information related to earlier treatment extension and related increment intervals based on the final study results of study ALTAIR: an interventional, randomized, open-label phase 4 study evaluating the efficacy and safety of repeated doses of intravitreal (IVT) aflibercept with variable treatment intervals in Japanese subjects with neovascular age-related macular degeneration (AMD). The package leaflet and the RMP (version 24.1) are updated accordingly

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

5.3.2. Ambrisentan - VOLIBRIS (CAP) - EMEA/H/C/000839/II/0054, Orphan

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.2 and 5.2 of the SmPC based on results of GSK1325760 study: a juvenile nonclinical toxicology study to further investigative the respiratory function following oral dosing from postnatal days 7 through 36, including an assessment of recovery. The RMP (version 7.5) is updated accordingly. In addition, the MAH took the opportunity to correct typographical errors including the frequency of the adverse drug reaction 'rash' in section 4.8 of the SmPC as well as the date of renewal. The MAH also proposed to introduce a minor update in the Braille section. Moreover, the MAH took the opportunity to propose a combined version of the SmPCs for the different authorised strengths

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

5.3.3. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0004

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of section 4.8 of the SmPC in order to update the safety information based on the primary results from study IMvigor211: a phase 3, open-label, multicentre, randomized study to investigate the efficacy and safety of atezolizumab (anti-programme death-ligand 1 (PD-L1) antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy. The package leaflet and the RMP (version 3.0) are updated accordingly. This fulfils ANX 002 (submission of the final clinical study report (CSR) listed as an imposed post-authorisation efficacy study (PAES) in Annex II.D). In addition, the MAH took the opportunity to implement some editorial changes throughout the product information

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

5.3.4. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0006

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of section 4.8 of the SmPC in order to include pneumonia as an adverse drug reaction with a frequency 'common' as requested in the final PRAC recommendation dated February 2018 for the signal on pneumonia (EPITT - 18950). The package leaflet and the RMP (version 6.0) are updated accordingly

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

5.3.5. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRIMBOW (CAP) - EMEA/H/C/004257/II/0002

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Extension of indication to include all adult patients with moderate or severe chronic obstructive pulmonary disease (COPD). As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated in order to add the results of two phase 3 studies, namely: 1) study Triple 7 (CCD-05993AA1-07): a multinational, multicentre, randomised, open-label, active-

controlled, 26-week, 2-arm, parallel group study to evaluate the non-inferiority of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pressurised metered dose inhaler (pMDI) (CHF 5993) *vs* fixed combination of fluticasone furoate plus vilanterol administered via dry powder inhaler (DPI) (Relvar) plus tiotropium bromide (Spiriva) for the treatment of patients with COPD; 2) study Triple 8 (CCD-05993AA1-08): a 52-week, double blind, double dummy, randomized, multinational, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pMDI (CHF 5993) versus indacaterol/glycopyrronium (Ultibro) via DPI in patients with COPD (TRIBUTE). 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

5.3.6. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0018, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include children aged one month and older to the authorised population for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to include the new population, update the posology and the safety information. The package leaflet and the RMP (version 6.0) are updated accordingly

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

5.3.7. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0005

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of advanced hepatocellular carcinoma in adults following prior systemic therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated with safety and efficacy information. The package leaflet and the RMP (version 4.0) are updated accordingly

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

5.3.8. Choriogonadotropin alfa - OVITRELLE (CAP) - EMEA/H/C/000320/II/0073/G

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC in order to indicate that thromboembolism can also occur without the presence of ovarian hyperstimulation syndrome (OHSS). The package leaflet and risk management plan (RMP) (version 5.1) are updated accordingly; 2) update of the RMP to extend the important potential risk of 'misuse' to 'weight loss and anabolic growth promoting effect'. In addition, the MAH took the opportunity to update the list of local representatives in the package

leaflet, to make editorial changes in the product information and in the Annex A (list of authorised presentations). The MAH also took the opportunity to make some minor revisions in the RMP

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

5.3.9. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/II/0026

Applicant: Orion Corporation

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include the 'sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation'. As a consequence, section 4.1, 4.2, 4.4, 4.6, 4.7, 4.8 and 5.1 of the SmPC are updated. In addition, the package leaflet and the RMP (version 7.0) are updated accordingly

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

5.3.10. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0102, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Submission of the clinical study report (CSR) of study C11-003 (listed as a category 3 study in the RMP): an observational, multicentre, multinational long term follow up study of atypical haemolytic uremic syndrome (aHUS) patients treated with eculizumab in a prior clinical study. The RMP (version 18) is updated accordingly, in line with the new RMP template and include proposals to remove the missing information 'long term safety in aHUS patients', to align the frequency of the submission of the reports on the healthcare professionals (HCP) survey as well as the controlled distribution and the aHUS registry to PSUR submission every 2 years

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

5.3.11. Enoxaparin sodium - INHIXA (CAP) - EMEA/H/C/004264/X/0026

Applicant: Techdow Europe AB

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add two new strengths of 30,000 IU (300 mg)/3 mL and 50,000 IU (500 mg)/5 mL for enoxaparin sodium solution for injection in vial, for subcutaneous, extracorporeal and intravenous administration. The RMP (version 3) is updated accordingly

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

5.3.12. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0050

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC based on the final clinical study report (CSR) of study EXSCEL (EXenatide Study of Cardiovascular Event Lowering): 'a randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus' in fulfilment of PAM (LEG 009). The package leaflet and the RMP (version 31) are updated accordingly

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

5.3.13. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS1343/0036; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS1343/0032

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the results of a PASS, the Salford lung study (SLS)-asthma (HZA115150) (listed as a category 1 study in the RMP): a 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate/vilanterol inhalation powder delivered once daily via a novel dry powder inhaler compared with usual maintenance therapy in subjects with asthma to further investigate the risk of pneumonia (ANX005). The RMP (version 9.2) is updated accordingly. In particular, the RMP is updated to amend the important identified risk of pneumonia in line with findings from the study, to provide a justification for the removal of the important potential risk of asthma related intubations and deaths as well as to provide a justification for the removal of missing information related to long term use in asthma (>1 year). Consequently, Annex II is updated

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

5.3.14. Human normal immunoglobulin - PRIVIGEN (CAP) - EMEA/H/C/000831/II/0129

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.3 of the SmPC to remove the contraindication on hyperprolineamia based on a comprehensive data survey of data from all available sources. The package leaflet and RMP (version 6.0) are updated accordingly

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

5.3.15. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0054

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.1 of the SmPC to update the overall survival data of ipilimumab 3mg/kg monotherapy pooled across studies based on the final results of study CA184332 and CA184338 (listed as category 3 studies in the RMP), in order to fulfil MEA 035 and MEA 030.1 respectively. Study CA184332 is a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab as first line therapy in a community practice setting and study CA184438 is a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving

ipilimumab as first line therapy. The RMP (version 18.4) is updated accordingly

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

5.3.16. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0069, Orphan

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include treatment of cystic fibrosis in children age 12 to less than 24 months who have one of the currently approved gating mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene for Kalydeco (ivacaftor) 50 mg and 75 mg granules. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Relevant consequential changes are made to Kalydeco (ivacaftor) 150 mg film-coated tablet product information. 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

5.3.17. Lapatinib - TYVERB (CAP) - EMEA/H/C/000795/II/0051

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.1 and 5.1 of the SmPC based on results from study EGF114299/LAP016A2307 (listed as a condition (ANX027.4) in Annex II): a phase 3 trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI versus lapatinib plus an AI as first- or second-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received prior trastuzumab and endocrine therapies. Annex II is updated accordingly. In addition, the RMP (version 34.0) is updated accordingly

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

5.3.18. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/X/0034/G

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Grouped variations consisting of: 1) extension application to introduce a new pharmaceutical form (granules) in 2 strengths (100/125 mg and 150/188 mg) for paediatric use from 2 to 5 years. The RMP (version 4.0) is updated accordingly; 2) update of sections 4.1, 4.2, 4.5, 4.8 and 5.3 of the SmPC of the tablet formulations to bring it in line with the proposed paediatric 2-5 year old extension application

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

5.3.19. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0039

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer after two or more prior systemic therapies, based on data from study ONO-4538-12: a Phase 3 study, multicentre, double-blind, randomized study in patients with unresectable advanced or recurrent gastric cancer. As a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. Annex II, package leaflet and the RMP (version 11.0) are updated accordingly

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

5.3.20. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0041

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include adjuvant treatment of adults and adolescents of 12 years of age and older with completely resected stage III and IV melanoma. 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 efficacy and safety information from pivotal study CA209238: a phase 3, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab after complete resection of stage IIIb/c or stage IV melanoma in subjects who are at high risk for recurrence. The package leaflet and the RMP (version 12.0) are updated accordingly. The MAH also took the opportunity to revise the due dates for two category 4 studies, namely study CA209172: a single-arm, open-label, multicentre clinical trial with nivolumab for subjects with histologically confirmed stage III (unresectable) or stage IV melanoma progressing post prior treatment containing an anti-cytototoxic T lymphocyte-associated antigen (CTLA-4) monoclonal antibody; and study CA209171: an open-label, multicentre clinical trial with nivolumab monotherapy in subjects with advanced or metastatic squamous cell (Sq) non-small cell lung cancer (NSCLC) who have received at least one prior systemic regimen for the treatment of stage IIIb/IV SqNSCLC. In addition, the MAH took the opportunity to make minor editorial changes to the product information

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

5.3.21. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0004, Orphan

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.8 of the SmPC to include new safety information related to hydrocephalus. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to correct some typographical errors in section 5.1 of the SmPC

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

5.3.22. Octocog alfa - ADVATE (CAP) - EMEA/H/C/000520/II/0091

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.2 of the SmPC in order to remove a statement mentioning that 'the use of the 2 mL presentation has not been documented for paediatric subjects below 2 years of age'. This update follows the final results from study 061101 (listed as a category 3 study in the RMP): a prospective, non-interventional, post-marketing surveillance study that assessed the safety and efficacy of Advate (octocog alfa) reconstituted in 2 mL of sterile water for injection during routine clinical practice in the EU. The package leaflet and the RMP (version 15.1) are updated accordingly

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

5.3.23. Octocog alfa - ADVATE (CAP) - EMEA/H/C/000520/II/0092

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to add new data on immune tolerance induction (ITI) following the final results from study PASS-INT-004: a prospective, multicentre, uncontrolled, open-label, non-interventional post-authorisation safety surveillance study conducted to evaluate Advate (octocog alfa) in ITI therapy in subjects with moderate or severe haemophilia A (baseline factor VIII ≤ 2%) and a high titre (> 5 Bethesda units (BU)) inhibitor to FVIII. The RMP (version 16.0) is updated accordingly

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

5.3.24. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0020

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include the use of Lynparza (olaparib) tablets as monotherapy for the treatment of adult patients with BRCA-1/2-mutated human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting. 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 16) are updated accordingly

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

5.3.25. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0021

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of SmPC sections 4.5, 4.6 and 5.2 to reflect the results of study D5160C00036 assessing the effect of single and multiple oral doses of osimertinib on the pharmacokinetics of a P-glycoprotein (P-gp) probe drug (fexofenadine) in patients with advanced epidermal growth factor receptor mutated (EGFRm) non-small-cell lung carcinoma (NSCLC) that have progressed on a prior epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) regimen. The package leaflet and the RMP (version 9) are updated accordingly. In addition, the MAH took the opportunity to make a minor correction in Annex

II and to implement minor editorial and/or QRD template related changes in the SmPC and package leaflet

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

5.3.26. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0024

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2 and 5.2 of the SmPC based on the results from study D5160C00008 to determine the pharmacokinetics, safety and tolerability of osimertinib following a single oral dose to patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment. The RMP (version 9) is updated accordingly

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

5.3.27. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0043

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include first line treatment of non-squamous non-small cell lung cancer (NSCLC) in combination with pemetrexed and platinum chemotherapy based on the efficacy and safety data from pivotal study KEYNOTE-189, supported by data from KEYNOTE-021 cohorts C and G. KEYNOTE-189 is a phase 3, randomized, placebo-controlled study undertaken to evaluate the efficacy and safety of pembrolizumab +pemetrexed + carboplatin or cisplatin (pembrolizumab combo) versus saline placebo + pemetrexed + carboplatin or cisplatin (control) in previously untreated subjects with advanced/metastatic non-squamous NSCLC with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations. KEYNOTE-021 is a phase 1/2 study of pembrolizumab in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 16.2) are updated accordingly

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

5.3.28. 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

5.3.29. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0149

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the maintenance of remission of granulomatosis with polyangiitis (GPA) (Wegener's) and microscopic polyangiitis (MPA). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 17.0) are updated accordingly. In addition, the MAH took the opportunity to implement a terminology change in Annex II

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

5.3.30. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0150

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the treatment of patients with moderate to severe pemphigus vulgaris (PV). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 17.0) are updated accordingly

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

5.3.31. Sirolimus - RAPAMUNE (CAP) - EMEA/H/C/000273/II/0164

Applicant: Pfizer Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of patients with lymphangioleiomyomatosis. As a consequence, section 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 6.0) are updated accordingly. In addition, the MAH took the opportunity to reflect minor formatting changes in the labelling

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

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

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

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 the RMP template, revision 2

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

5.3.33. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0076

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include as a paediatric indication 'treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids' to RoActemra (tocilizumab) 162 mg solution for injection in pre-filled syringe formulation, based on data from phase Ib pharmacokinetic/pharmacodynamic bridging study WA28118 (JIGSAW 118), designed to confirm the RoActemra subcutaneous dosing regimens in patients aged 1 to 17 years old with sJIA, as well as assess the safety of the RoActemra subcutaneous formulation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 24.0) are updated accordingly. In addition, sections 4.2, 4.8 and 5.2 of the SmPC of RoActemra (tocilizumab) 20 mg/mL concentrate for solution for infusion formulation are updated to reflect data from the pivotal intravenous study WA18221 (TENDER), a randomised, placebo-controlled study to evaluate the effect of tocilizumab on disease response in patients with active sJIA

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

5.3.34. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/II/0009

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include slowing the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 4 at initiation of treatment with evidence of rapidly progressing disease based on the results of a completed post-authorisation efficacy study (PAES), study 156-13-210: a phase 3b, multicentre, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the efficacy and safety of tolvaptan (45 to 120 mg/day, split-dose) in subjects with CKD between late stage 2 to early stage 4 due to autosomal dominant polycystic kidney disease. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC and Annex II are updated. The package leaflet and the RMP (version 13.2) are updated accordingly. The MAH took the opportunity to introduce minor editorial changes to the product information

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

5.3.35. Vardenafil - LEVITRA (CAP) - EMEA/H/C/000475/WS1390/0062; VIVANZA (CAP) - EMEA/H/C/000488/WS1390/0058

Applicant: Bayer AG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.4 and 4.8 of the SmPC to reflect data from two post-marketing

observational studies namely 1) study NCT00759174: a study to assess whether phosphodiesterase type 5 inhibitor (PDE5) inhibitors increase the chance of triggering the onset of acute non-arteritic anterior ischaemic optic neuropathy (NAION)', 2) study NCT01131104: 'a study to determine if there is a possible association between NAION and PDE5 inhibitors'; indicating an increased risk of NAION when using phosphodiesterase 5 (PDE5) inhibitors. The MAH also proposed to terminate the NAION study 12912: a prospective case crossover study to assess whether PDE5 inhibitor exposure in men with erectile dysfunction increases the risk for the development of NAION. The RMP (version 5.0) is updated accordingly. In addition, the product information is brought in line with the QRD template (version 10.0) and the contact details of the Bulgarian local representative are updated in the package leaflet. The package leaflets for the 5 mg, 10 mg and 20 mg film-coated tablet strengths are combined into a single package leaflet and the product information for the 10 mg orodispersible tablet is updated for aspartame and sorbitol, according to the annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, the MAH took the opportunity to introduce some editorial amendments to the product information

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. Tolvaptan[4] - JINARC (CAP) - PSUSA/00010395/201711

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.2. Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP), DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201711

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.3. Aflibercept[5] - EYLEA (CAP) - PSUSA/00010020/201711

Applicant: Bayer AG

[4] Indicated for adults with autosomal dominant polycystic kidney disease (ADPKD)
[5] Ophthalmological indication(s) only

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.4. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/201711

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.5. Autologous CD34^{+} enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - PSUSA/00010505/201711

Applicant: GlaxoSmithKline Trading Services Limited, ATMP[6]

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CAT and CHMP

6.1.6. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201712

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.7. Cabozantinib - CABOMETYX (CAP), COMETRIQ (CAP) - PSUSA/00010180/201711

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.8. Daclizumab - ZINBRYTA[7] - PSUSA/00010518/201711 (with RMP)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

[6] Advanced therapy medicinal product
[7] European Commission (EC) decision on the MA withdrawal of Zinbryta dated 27 March 2018

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.9. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/201711

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.10. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/201711

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.11. Darbepoetin alfa - ARANESP (CAP) - PSUSA/00000932/201710

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.12. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin) (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) - INFANRIX HEXA (CAP) - PSUSA/00001122/201710

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.13. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/201712

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.14. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/201711

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.15. Empagliflozin, linagliptin - GLYXAMBI (CAP) - PSUSA/00010539/201711

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.16. Eribulin - HALAVEN (CAP) - PSUSA/00001254/201711

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.17. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/201711

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.18. Fentanyl[8] - IONSYS (CAP) - PSUSA/00010453/201711

Applicant: Incline Therapeutics Europe Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.19. Fluciclovine (^{18}F) - AXUMIN (CAP) - PSUSA/00010594/201711

Applicant: Blue Earth Diagnostics Ltd

PRAC Rapporteur: Patrick Batty

[8] Transdermal system - centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.20. Follitropin delta - REKOVELLE (CAP) - PSUSA/00010554/201711

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.21. Fondaparinux - ARIXTRA (CAP) - PSUSA/00001467/201712

Applicant: Aspen Pharma Trading Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.22. Fosamprenavir - TELZIR (CAP) - PSUSA/00001470/201710

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.23. Glycerol phenylbutyrate - RAVICTI (CAP) - PSUSA/00010454/201711

Applicant: Horizon Pharma Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.24. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - PSUSA/00009175/201711

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.25. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/201711

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.26. Insulin detemir - LEVEMIR (CAP) - PSUSA/00001750/201710

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.27. Ixazomib - NINLARO (CAP) - PSUSA/00010535/201711

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.28. Ketoconazole[9] - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201711

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.29. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/201711 (with RMP)

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.30. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - PSUSA/00010607/201711

Applicant: Pfizer Limited

PRAC Rapporteur: Jean-Michel Dogné

[9] Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.31. Metformin, saxagliptin - KOMBOGLYZE (CAP) - PSUSA/00002686/201711

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.32. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/201711

Applicant: Amicus Therapeutics UK Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.33. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - PSUSA/00010296/201711

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

6.1.34. Necitumumab - PORTRAZZA (CAP) - PSUSA/00010471/201711

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.35. Nelarabine - ATRIANCE (CAP) - PSUSA/00002132/201710

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.36. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/201712

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.37. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/201711

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.38. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/201711

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.39. Pentosan polysulfate sodium[10] - ELMIRON (CAP) - PSUSA/00010614/201712

Applicant: bene-Arzneimittel GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.40. Pixantrone - PIXUVRI (CAP) - PSUSA/00009261/201711

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.41. Rituximab - BLITZIMA (CAP), MABTHERA (CAP), RITEMVIA (CAP), RITUZENA (CAP), RIXATHON (CAP), RIXIMYO (CAP), TRUXIMA (CAP) - PSUSA/00002652/201711

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

[10] Centrally authorised product(s) only

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.42. Rotavirus vaccine pentavalent (live, oral) - ROTATEQ (CAP) - PSUSA/00002666/201711

Applicant: MSD Vaccins

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.43. Sapropterin - KUVAN (CAP) - PSUSA/00002683/201712

Applicant: BioMarin International Limited

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.44. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/201712

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.45. Simeprevir - OLYSIO[11] - PSUSA/00010255/201711

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.46. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201712

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

[11] European Commission (EC) decision on the MA withdrawal of Olysio dated 5 March 2018

6.1.47. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/201711

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.48. Tenofovir alafenamide - VEMLIDY (CAP) - PSUSA/00010575/201711

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.49. Tilmanocept - LYMPHOSEEK (CAP) - PSUSA/00010313/201711

Applicant: Norgine B.V.

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.50. Turoctocog alfa - NOVOEIGHT (CAP) - PSUSA/00010138/201710

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.51. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/201711

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.52. Venetoclax - VENCLYXTO (CAP) - PSUSA/00010556/201712

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

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

6.2.1. Bosentan - STAYVEER (CAP), TRACLEER (CAP); NAP - PSUSA/00000425/201711

Applicants: Marklas Nederlands BV (Stayveer), Actelion Registration Limited (Tracleer), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.2. Erlotinib - TARCEVA (CAP); NAP - PSUSA/00001255/201711

Applicants: Roche Registration GmbH (Tarceva), various

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.3. Insulin human - ACTRAPID (CAP), INSUMAN (CAP); insulin human, insulin isophane[12] - ACTRAPHANE (CAP), INSULATARD (CAP), MIXTARD (CAP), PROTAPHANE (CAP); NAP - PSUSA/00001753/201710

Applicants: Novo Nordisk A/S (Actraphane, Actrapid, Insulatard, Mixtard, Protaphane), Sanofi-Aventis Deutschland GmbH (Insuman), various

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.4. Sevelamer - RENAGEL (CAP), RENVELA (CAP), SEVELAMER CARBONATE ZENTIVA (CAP), TASERMITY (CAP); NAP - PSUSA/00002697/201710

Applicants: Genzyme Europe BV (Renagel, Renvela, Sevelamer carbonate Zentiva, Tasermity), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

[12] Subcutaneous and intravenous routes of administration only

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

6.3.1. Acitretin (NAP) - PSUSA/00000051/201710

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.2. Atorvastatin (NAP) - PSUSA/00010347/201710

Applicant(s): various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.3. Atovaquone, proguanil (NAP) - PSUSA/00000266/201710

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.4. Carvedilol, ivabradine (NAP) - PSUSA/00010586/201711

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.5. Deoxycholic acid (NAP) - PSUSA/00010525/201710

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.6. Diphtheria, tetanus, pertussis (acellular, component), haemophilus type b conjugate vaccine (adsorbed) (NAP) - PSUSA/00001121/201710

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.7. Epinastine (NAP) - PSUSA/00001231/201710

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.8. Etifoxine (NAP) - PSUSA/00001321/201710

Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.9. Ezetimibe (NAP) - PSUSA/00001346/201710

Applicant(s): various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.10. Flupirtine (NAP) - PSUSA/00010225/201710

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.11. Hydroxyzine (NAP); hydroxyzine chloride, hydroxyzine pamoate[13] (NAP) - PSUSA/00001696/201711

Applicant(s): various

[13] Including all fixed combinations

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.12. Ketotifen[14] (NAP) - PSUSA/00001813/201710

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.13. Methoxyflurane (NAP) - PSUSA/00010484/201711

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.14. Methylphenidate (NAP) - PSUSA/00002024/201710

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.15. Minoxidil[15] (NAP) - PSUSA/00002067/201710

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.16. Morphine (NAP); morphine, cyclizine (NAP) - PSUSA/00010549/201710

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

[14] Oral formulations only
[15] Topical formulations only

6.3.17. Prulifloxacin (NAP) - PSUSA/00002569/201710

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.18. Treprostinil (NAP) - PSUSA/00003013/201711

Applicant(s): 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. Anakinra - KINERET (CAP) - EMEA/H/C/000363/LEG 028.2

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to LEG 028.1 [review on the feasibility of conducting a PASS in order to evaluate the risk of adverse cardiovascular events associated with long-term use of anakinra in patients with rheumatoid arthritis (RA) as requested in the conclusions of EMEA/H/C/PSUSA/00000209/201605 adopted by PRAC in December 2016] as per the request for supplementary information (RSI) adopted at the December 2017 meeting

Action: For adoption of advice to CHMP

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[16]

7.1.1. Cerliponase alfa – BRINEURA (CAP) - EMEA/H/C/PSP/S/0063

Applicant: BioMarin International Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol for study 190-504 (previously known as study 190-501): a non-interventional PASS in order to evaluate the long term safety of cerliponase alfa, including the occurrence of serious hypersensitivity reactions and anaphylaxis in patients with neuronal ceroid lipfuscinosis type 2 (CLN2)

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

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

7.1.2. Chlormadinone acetate, ethinyl estradiol (NAP) - EMEA/H/N/PSA/J/0030

Applicant: Gedeon Richter Plc (multiple product names)

PRAC Rapporteur: Valerie Strassmann

Scope: Amendment to a protocol previously agreed by PRAC in 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

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

7.1.3. Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Daclatasvir – DAKLINZA (CAP); dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir – ZEPATIER (CAP); glecaprevir, pibrentasvir – MAVIRET (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, peritepreviir, ritonavir – VIEKIRAX (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatasvir – EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir - VOSEVI - EMEA/H/C/PSA/J/0028.1

Applicants: AbbVie Limited (Exviera, Maviret, Viekirax), Bristol-Myers Squibb Pharma EEIG (Daklinza), Gilead Sciences International Ltd (Epclusa, Harvoni, Sovaldi, Vosevi), Merck Sharp & Dohme Limited (Zepatier)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to PSA/J/0028 [substantial amendment to the previously agreed joint protocol in January 2018 for a non-interventional imposed PASS on early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAAV) therapy in order to estimate the risk of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAAV therapy exposure relative to no DAAV therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in April 2018

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

7.1.4. Dexketoprofen, tramadol (NAP) - EMEA/H/N/PSP/S/0062

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

PRAC Rapporteur: Eva Segovia

Scope: PASS protocol for a drug utilisation study (DUS) on tramadol-dexketoprofen (DKP-TRAM) fixed combination to evaluate the pattern of prescriptions of DKP-TRAM and assess the risk of adverse events (AE) (e.g. nausea, vomiting, diarrhoea, vertigo) in DKP-TRAM *vs.* tramadol monotherapy (including tramadol-paracetamol combinations) users, with a special

focus on patients 75 years old and over

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

7.1.5. Nonacog beta pegol– REFIXIA (CAP) - EMEA/H/C/PSP/S/0059

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a non-interventional PASS in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate safety of N9-GP during long term routine use

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

7.1.6. Prasterone – INTRAROSA (CAP) - EMEA/H/C/PSP/S/0061

Applicant: Endoceutics Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a non-interventional PASS: a drug utilisation study (DUS) to describe the baseline characteristics, utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa (prasterone) and to assess whether EU prescribers abide by the contraindications stated in the EU SmPC

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

7.1.7. Velmanase alfa – LAMZEDE (CAP) - EMEA/H/C/PSP/S/0060

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: 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

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[17]

7.2.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 005.3

Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA005.2 [PASS protocol in order to collect long-term data using

[17] 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

the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR) psoriatic arthritis (PsA) registry 'BSRBR PsA registry': a disease registry in the EU for PsA and psoriasis] as per the request for supplementary information (RSI) adopted in January 2018

Action: For adoption of advice to CHMP

7.2.2. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 003

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: PASS protocol for study D3250R00026 'the benralizumab pregnancy exposure study': a post-marketing surveillance study on vaccines and medications in pregnancy surveillance system (VAMPSS) (from initial opinion/MA)

Action: For adoption of advice to CHMP

7.2.3. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.1

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002 [Protocol (version 1.0) for study NIS-KYNTHEUM-1345: an observational PASS of suicidal behaviour, serious infections, major adverse cardiovascular events (MACE) and malignancy in psoriasis patients treated with brodalumab. The brodalumab assessment of hazards: a multinational safety (BRAHMS) study in electronic healthcare databases [final report expected in Q3 2030] (from initial opinion/MA)] as per the request for supplementary information (RSI) adopted in January 2018

Action: For adoption of advice to CHMP

7.2.4. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/MEA 004

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a non-interventional prospective cohort study in the treatment of children with X-linked hypophosphataemia (XLH) to assess the long term safety of Crysvita (burosumab) during routine clinical care using data collected in a European disease registry for XLH [final report expected in December 2028] (from initial opinion/MA)

Action: For adoption of advice to CHMP

7.2.5. Conestat alfa - RUCONEST (CAP) - EMEA/H/C/001223/MEA 019.2

Applicant: Pharming Group N.V

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 019.1 [revised protocol for a survey to measure the

effectiveness of risk minimisation materials distributed to treatment centres/prescribing physicians] as per the request for supplementary information (RSI) adopted in January 2018

Action: For adoption of advice to CHMP

7.2.6. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/MEA 020.2

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 020.1 [protocol for a survey to evaluate the physician education component of the simplified Ozurdex (dexamethasone) educational materials in order to assess the effectiveness of the educational material provided to physicians treating patients with Ozurdex by evaluating the physicians' knowledge and understanding of the key information in the Ozurdex injector's guide] as per the request for supplementary information (RSI) adopted in January 2018

Action: For adoption of advice to CHMP

7.2.7. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 047

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: Protocol for study No GS EU 276 4487: a prospective, longitudinal, observational registry of emtricitabine/tenofovir disoproxil fumarate for human immunodeficiency virus 1 (HIV-1) pre-exposure prophylaxis (PrEP) in the European Union (as requested in the conclusions of variation II/135)

Action: For adoption of advice to CHMP

7.2.8. Florbetaben (^{18}F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.6

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Patrick Batty

Scope: Amended protocol to previously agreed protocol in September 2016 for PASS study FBB-01_03_13 (PASS 2): a non-interventional, prospective observational multicentre, multi-country registry to observe usage pattern, safety and tolerability of the diagnostic agent NeuraCeq (florbetaben (^{18}F)) in clinical practice [final clinical study report (CSR) expected in Q2/2020]

Action: For adoption of advice to CHMP

7.2.9. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/MEA 002

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for PsoBEST registry: a registry on the treatment of psoriasis with biologics

and systemic therapeutics exploring the long-term safety and effectiveness of conventional systemic and biological treatment of psoriasis and psoriatic arthritis in clinical routine in Germany

Action: For adoption of advice to CHMP

7.2.10. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/MEA 003

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study PSOLAR: a multicentre, open long-term safety registry study of guselkumab in adult patients with psoriasis, specifically in serious infections, major adverse cardiovascular events (MACE), serious hypersensitivity reactions and malignancies

Action: For adoption of advice to CHMP

7.2.11. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Draft protocol synopsis for the extension of the Dutch melanoma treatment registry (DMTR) to include paediatric subjects and collect safety data to obtain additional safety information in paediatric patients [final clinical study report (CSR) expected in December 2028] (from variation II/44)

Action: For adoption of advice to CHMP

7.2.12. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/MEA 014.4

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to a previously agreed protocol by PRAC in November 2015 for study NN8022-4241: a drug utilisation study (DUS) in Europe including retrospective chart review to evaluate whether Saxenda (liraglutide) is used according to the approved indication and posology, as requested in the conclusions of MEA 014.3 on the pilot study adopted in February 2018

Action: For adoption of advice to CHMP

7.2.13. Mercaptamine - CYSTADROPS (CAP) - EMEA/H/C/003769/MEA 001.1

Applicant: Orphan Europe SARL

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 001 [protocol for study CYT-DS-001 (listed as a category 3 study in the RMP): an open-label longitudinal PASS to assess the safety of Cystadrops (mercaptamine) in paediatric and adult cystinosis patients in long term use [final clinical study report (CSR) due date: by 2021] as per the request for supplementary information

(RSI) adopted in February 2018

Action: For adoption of advice to CHMP

7.2.14. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 045 [protocol for study RRA-20745: a PASS to investigate the long-term safety in adult patients with moderately to severely active Crohn's disease] as per the request for supplementary information adopted in January 2018

Action: For adoption of advice to CHMP

7.3. Results of PASS imposed in the marketing authorisation(s)[18]

7.3.1. Alanine, arginine, aspartic acid, calcium chloride dihydrate, cysteine, glucose anhydrous, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, magnesium acetate tetrahydrate, methionine, olive oil refined, ornithine, phenylalanine, potassium acetate, proline, serine, sodium chloride, sodium glycerophosphate hydrated, soya bean oil refined, taurine, threonine, tryptophan, tyrosine, valine (NAP) - EMEA/H/N/PSR/S/0017

Applicant: Baxter Healthcare Ltd. (Numeta)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 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 G 16% E; to observe the following parameters in subjects who receive parenteral nutrition (PN) with Numeta G 16% E: 1) actual infused Numeta G 16% 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

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

7.3.2. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/PSR/S/0014

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: PASS results for an observational study to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis

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

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

7.3.3. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0012

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: PASS results for an observational post-authorisation modified prescription-event monitoring safety study to monitor the safety and utilization of Xarelto (rivaroxaban) for the prevention of stroke in patients with acute fibrillation (AF), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England, extended to include acute coronary syndrome patients

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)[19]

7.4.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/II/0038

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Karen Pernille Harg

Scope: Submission of the final report from study CLE-20098-096 (listed as a category 3 study in the RMP): a non-interventional PASS, drug utilisation study (DUS) to assess the effectiveness of risk-minimisation measures of Thymanax/Valdoxan (agomelatine)

Action: For adoption of PRAC Assessment Report

7.4.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/II/0039

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Karen Pernille Harg

Scope: Submission of the final report from study CLE-20098-096 (listed as a category 3 study in the RMP): a non-interventional PASS, drug utilisation study (DUS) to assess effectiveness of risk-minimisation measures of Thymanax/Valdoxan (agomelatine)

Action: For adoption of PRAC Assessment Report

7.4.3. Azilsartan medoxomil - EDARBI (CAP) - EMEA/H/C/002293/II/0021

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from a drug utilisation study (DUS) (listed as a category 3 study in the RMP): a retrospective non-interventional cohort study using a patient level electronic medical records database in Germany aimed to describe the prescription of Edarbi (azilsartan medoxomil) in patients with essential hypertension and

[19] 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

those prescribed Edarbi (azilsartan medoxomil) for other reasons. The RMP (version 5.0) is updated accordingly

Action: For adoption of PRAC Assessment Report

7.4.4. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/II/0087

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for study GS-EU-236-0141 (listed as a category 3 study in the RMP, in fulfilment of a MEA 006): an observational drug utilisation study (DUS) of Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil) in adults with human immunodeficiency virus 1 (HIV-1) infection

Action: For adoption of PRAC Assessment Report

7.4.5. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/II/0035

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report for the online survey for EU PAS register number EUPAS13634 measuring the effectiveness of the Mycamine (micafungin) prescriber checklist in the EU. The RMP (version 18.0) is updated accordingly

Action: For adoption of PRAC Assessment Report

7.4.6. Prucalopride - RESOLOR (CAP) - EMEA/H/C/001012/II/0042

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final clinical study report (CSR) for the post-authorisation drug utilisation study (DUS) SHP555-804 (in fulfilment of MEA 006.11): a DUS to examine characteristics of patients prescribed Resolor (prucalopride) and a pharmacoepidemiological study of the occurrence of major cardiovascular events, pregnancy, and pregnancy outcomes in the UK clinical practice research datalink (CPRD) database. The RMP (version 14.0) is updated accordingly

Action: For adoption of PRAC Assessment Report

7.4.7. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0070/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report from the LUMINOUS study (CRFB002A2406): an observational, multicentre study to assess the long term safety and effectiveness of ranibizumab in routine clinical practice, in fulfilment of the

post-authorisation measures MEA 036, MEA 048 and MEA 054; The RMP is updated accordingly; 2) submission of an updated RMP (version 17.0) to include changes not consequential to LUMINOUS study. In addition, the MAH is proposing the removal of the use of educational materials and targeted follow-up checklists listed in Annex II-D of the product information

Action: For adoption of PRAC Assessment Report

7.4.8. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0186

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Caroline Laborde

Scope: Submission of the final report from study GS-EU-174-1846 (listed as a category 3 study in the RMP, in fulfilment of MEA 273): a multicentre, non-interventional, retrospective, matched cohort study of patients mono-infected with chronic hepatitis B and with moderate or severe renal impairment treated with Viread (tenofovir disoproxil) or entecavir

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. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.12

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Fifth annual report for PASS B1781044: a cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe [final clinical study report (CSR) expected in April 2020]

Action: For adoption of advice to CHMP

7.5.2. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/MEA 005.6

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 005.5 [annual reports from rheumatoid arthritis registries from the US National Databank of Rheumatic Diseases (RA0005), German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (RA0020), Register for Antirheumatic Therapies in Sweden (ARTIS) (RA0021), British Society for Rheumatology Biologicals Register (BSRBR) (RA0022)] as per the request for supplementary information (RSI) adopted in January 2018

Action: For adoption of advice to CHMP

7.5.3. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 002.3

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Third progress report and an interim report for study H9X-MC-B009, the dulaglutide European modified prescription-event monitoring and network database study: a multi-database collaborative research programme of observational studies to monitor the utilisation and safety of dulaglutide in the EU

Action: For adoption of advice to CHMP

7.5.4. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/MEA 005.5

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 005.3 [Interim study report for study DSE-EDO-01-14-EU (EUPAS17062): a drug utilisation study (DUS), multinational, multicentre involving a retrospective chart review of edoxaban users' medical records. Nested in the study, a cross-sectional survey of all participating prescribing physicians is performed, starting from the date of the first data abstraction and repeated over the course of the study to evaluate the effectiveness of the physician educational programme] as per the request for supplementary information (RSI) adopted in January 2018

Action: For adoption of advice to CHMP

7.5.5. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 010.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

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

Action: For adoption of advice to CHMP

7.5.6. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 002.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

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

Action: For adoption of advice to CHMP

7.5.7. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

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

Action: For adoption of advice to CHMP

7.5.8. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.8

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Third interim study report for a US (listed as category 3 study in the RMP) non-interventional PASS (B2311060 study): an active surveillance of conjugated oestrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data

Action: For adoption of advice to CHMP

7.5.9. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 003.4

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: First interim report for a drug utilisation study (DUS) on conjugated oestrogens/ bazedoxifene (CE/BZA) in the European Union (EU) to describe baseline characteristics and utilisation patterns of EU patients initiating Duavive (oestrogens conjugated/bazedoxifene) or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT)

Action: For adoption of advice to CHMP

7.5.10. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/MEA 004.5

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 004.4 [interim results for study XM22-ONC-50002: a multi-country, multicentre, retrospective observational drug utilisation study (DUS) to describe the pattern of lipegfilgrastim use and specifically to quantify the extent of lipegfilgrastim off-label use in routine clinical practice in several countries in the European Union (EU)] as per the request for supplementary information adopted in January 2018

Action: For adoption of advice to CHMP

7.5.11. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 023.1

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

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

Action: For adoption of advice to CHMP

7.5.12. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 013.5

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 013.4 [annual interim report from an observational database-assisted comparative cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma 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 (RSI) adopted at the September 2017 PRAC meeting

Action: For adoption of advice to CHMP

7.5.13. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/MEA 036.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Annual report (covering the period from 01 February 2017 to 31 January 2018) on the effectiveness of risk minimisation measures (RMM) for multiple patch use with copies of Council for International Organizations of Medical Sciences (CIOMS) reports of medication errors and misuse

Action: For adoption of advice to CHMP

7.5.14. Rivastigmine - PROMETAX (CAP) - EMEA/H/C/000255/MEA 037.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Annual report (covering the period from 01 February 2017 to 31 January 2018) on the effectiveness of risk minimisation measures (RMM) for multiple patch use with copies of Council for International Organizations of Medical Sciences (CIOMS) reports of medication errors and misuse

Action: For adoption of advice to CHMP

7.5.15. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.3

Applicant: Actelion Registration Limited

PRAC Rapporteur: Julie Williams

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

Action: For adoption of advice to CHMP

7.5.16. Somatropin - OMNITROPE (CAP) - EMEA/H/C/000607/MEA 010.2

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Third interim report for a phase 4 study in 200 small children born small for gestational age (SGA) to measure diabetogenic potential of recombinant human growth hormone (rhGH) therapy in short children born SGA and the occurrence and clinical implications of anti-rhGH antibodies

Action: For adoption of advice to CHMP

7.5.17. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/MEA 045.4

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final study report for SUMMACTA study (WA22479 and ML22928), UK British Society of Rheumatology Biologics Register (BSRBR) registry collecting further safety data, including data on hypersensitivity, in patients who switch route of tocilizumab administration from intravenous to subcutaneous pharmaceutical forms (from extension application X/30)

Action: For adoption of advice to CHMP

7.5.18. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/MEA 019

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Interim results for study BO39807: an observational study of cardiac events in patients with metastatic breast cancer who have low left ventricular ejection fraction (LVEF) prior to initiating treatment with Kadcyla (trastuzumab emtansine)

Action: For adoption of advice to CHMP

7.5.19. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second yearly progress report (28 January 2017-27 January 2018) for study PGL14-001: a prospective, multinational, multicentre, non-interventional study to evaluate the long-term safety of Esmya (ulipristal acetate) in particular the endometrial safety and the current prescription and management patterns of Esmya (ulipristal acetate) in a long-term treatment setting [final clinical study report (CSR) expected in 2023]

Action: For adoption of advice to CHMP

7.6. Others

7.6.1. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/MEA 013.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

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

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. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0053 (without RMP)

Applicant: BioMarin Europe Ltd

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. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/R/0003 (without RMP)

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3. Renewals of the marketing authorisation

8.3.1. Aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/R/0087 (without RMP)

Applicant: Noden Pharma DAC

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.2. Aripiprazole - ABILIFY MAINTENA (CAP) - EMEA/H/C/002755/R/0025 (with RMP)

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.3. Etravirine - INTELENCE (CAP) - EMEA/H/C/000900/R/0052 (with RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Caroline Laborde

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.4. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/R/0079 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.5. Macitentan - OPSUMIT (CAP) - EMEA/H/C/002697/R/0027 (with RMP)

Applicant: Actelion Registration Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.6. Memantine - MEMANTINE ACCORD (CAP) - EMEA/H/C/002766/R/0010 (without RMP)

Applicant: Accord Healthcare Limited

PRAC Rapporteur: Dolores Montero Corominas

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

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Dienogest, ethinylestradiol (NAP) - DE/H/xxxx/WS/534

Applicant: Bayer (Celimona, Celimone, Maxim, Valette)

PRAC Lead: Valerie Strassmann

Scope: PRAC consultation on a worksharing variation assessing the risk of venous thromboembolism with combined hormonal contraceptives (CHCs) containing dienogest/ethinylestradiol (DNG/EE) compared to levonorgestrel/ethinylestradiol-containing CHCs

Action: For adoption of advice to Member States

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – recommendations, implementation plan and goals

PRAC lead: Martin Huber, Menno van der Elst, Tatiana Magalova, Albert van der Zeijden, Ghania Chamouni, Jan Neuhauser, Ulla Wändel Liminga

Action: For discussion

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. European Network Training Centre (EU NTC) - operation of pharmacovigilance in the EU training needs and priorities - plan for training 2018 – 2020

Action: For discussion

12.4.2. Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Action: For discussion

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

Action: For discussion

12.10.3. PSURs repository

None

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

Action: For adoption

12.11. Signal management

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

PRAC lead: 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 - EudraVigilance stakeholder change management plan: integration with the identity and access management (IAM2) project deliverables

Action: For discussion

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

12.14.2. Risk management plan for centrally authorised biological products – Guideline on safety specification – prioritisation strategy

PRAC lead: Doris Stenver, Menno van der Elst, Patrick Batty, Sabine Straus, Ulla Wändel Liminga

Action: For adoption

12.14.3. 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. Good Pharmacovigilance Practices (GVP) – GVP revisions during 2018 revision cycle

Action: For discussion

12.20.2. Type II variations – PRAC and CHMP involvement

Action: For discussion

13. Any other business

Next meeting on: 09-12 July 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/