06 June 2016
EMA/PRAC/231459/2016
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 6-9 June 2016

Chair: June Raine – Vice-Chair: Almath Spooner

06 June 2016, 13:00 – 19:00, room 3/A

07 June 2016, 08:30 – 19:00, room 3/A

08 June 2016, 08:30 – 19:00, room 3/A

09 June 2016, 08:30 – 16:00, room 3/A

Organisational, regulatory and methodological matters (ORGAM)

23 June 2016, 09:00 – 12:00, room 7/B, via Adobe Connect

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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the PRAC plenary session to be held 06-09 June 2016. See June 2016 PRAC minutes (to be published post July 2016 PRAC meeting).

1.2. Agenda of the meeting of 06-09 June 2016

Action: For adoption

1.3. Minutes of the previous meeting on 10-13 May 2016

Action: For adoption

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Gadolinium-containing contrast agents (GdCA): gadobenic acid (NAP); gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid (NAP); gadoteric acid (NAP); gadoteridol (NAP); gadoxetic acid (NAP); gadoversetamide – OPTIMARK (CAP) - EMEA/H/A-31/1437

Applicant: Mallinckrodt Deutschland GmbH (Optimark); various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Doris Stenver

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data
Action: For adoption of a list of outstanding issues

3.2.2. Idelalisib – ZYDELIG (CAP) - EMEA/H/A-20/1439

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Ulla Wändel Liminga

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

3.3. Procedures for finalisation

None

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

None

3.5. Others

None

4. Signals assessment and prioritisation[1]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Dasabuvir - EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP)

Applicant: AbbVie Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of depression and suicidal ideation
Action: For adoption of PRAC recommendation

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

EPITT 18670 – New signal
Lead Member State: ES

4.1.2. Olanzapine – ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of restless leg syndrome (RLS)
Action: For adoption of PRAC recommendation
EPITT 18659 – New signal
Lead Member State: FI

4.1.3. Pazopanib – VOTRIENT (CAP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Signal of polycythaemia
Action: For adoption of PRAC recommendation
EPITT 18660 – New signal
Lead Member State: DK

4.2. New signals detected from other sources

4.2.1. Dasabuvir – EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP)

Applicant: AbbVie Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of risk of drug interaction with fluindione leading to a reduced international normalized ratio (INR)
Action: For adoption of PRAC recommendation
EPITT 18654 – New signal
Lead Member State: ES

4.2.2. Riociguat - ADEMPAS (CAP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Signal of increased mortality and serious adverse events (SAEs) in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) in a single clinical trial
Action: For adoption of PRAC recommendation
EPITT 18681 – New signal
Lead Member State: UK

4.3. Signals follow-up and prioritisation

4.3.1. Cisplatin (NAP)

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of peripheral arterial thromboembolic events (ATEs) and arterial occlusion
Action: For adoption of PRAC recommendation
EPITT 18560 – Follow-up to January 2016

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Allogeneic T cells genetically modified to express suicide gene - EMEA/H/C/002801, Orphan

Applicant: MolMed SpA, ATMP[1]

Scope: Treatment in haploidentical haematopoietic stem cell transplantation
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.2. Docetaxel - EMEA/H/C/004086

Scope: Treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.3. Empagliflozin, linagliptin - EMEA/H/C/003833

Scope: Treatment of type 2 diabetes mellitus
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.4. Emtricitabine, tenofovir disoproxil - EMEA/H/C/004137

Scope: Treatment of human immunodeficiency virus (HIV)-1 infection
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.5. Etelcalcetide - EMEA/H/C/003995

Scope: Treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.6. Miglustat - EMEA/H/C/004016

Scope: Treatment of Gaucher disease
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.7. Olaratumab - EMEA/H/C/004216, Orphan

Applicant: Eli Lilly Nederland B.V.

Scope (accelerated assessment): Treatment of soft tissue sarcoma
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.8. Palbociclib - EMEA/H/C/003853

Scope: Treatment of breast cancer

[1] Advanced-therapy medicinal product

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. Belimumab – BENLYSTA (CAP) - EMEA/H/C/002015/II/0041/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a revised RMP in order to change the scope of the pregnancy registry BEL114256 (category 3 study), to amend the due dates for studies HGS1006-C1074 and BEL116559. In addition, the MAH took the opportunity to correctly reflect the status of study BEL116027 (treatment Holiday) from planned to ongoing
Action: For adoption of PRAC AR

5.2.2. Colistimethate sodium – COLOBREATHE (CAP) - EMEA/H/C/001225/II/0021

Applicant: Forest Laboratories UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of the RMP (version.6.0) in order to add information on the first interim report for study CLB-MD-05 (an open-label observational safety study of Colobreathe compared with other inhaled antipseudomonal antibiotics in cystic fibrosis patients using cystic fibrosis registries, MEA 009) and the protocol for study CLB-MD-08 (a post-authorisation registry based safety study to evaluate the effectiveness of the risk minimisation educational materials, including DVD and patient and healthcare professional guide, implemented in the EU for Colobreathe)
Action: For adoption of PRAC AR

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

5.3.1. 5-aminolevulinic acid – AMELUZ (CAP) - EMEA/H/C/002204/II/0020

Applicant: Biofrontera Bioscience GmbH

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2) and of field cancerisation based on the phase III clinical study ALA-AK-CT007. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.2. Arsenic trioxide – TRISENOX (CAP) - EMEA/H/C/000388/II/0058

Applicant: Teva B.V.

PRAC Rapporteur: Claire Ferard

Scope: Extension of indication to include the induction of remission, and the consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 103/µl) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene for Trisenox. As a consequence, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated regarding the posology, efficacy and safety information and

warnings. In addition, a Risk Management Plan is introduced. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.3. Atazanavir, cobicistat – EVOTAZ (CAP) - EMEA/H/C/003904/II/0007/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Claire Ferard

Scope: Submission of the final study reports for two category 3 studies: study GS-US-216-114 (a phase III randomised, double-blind study to evaluate the safety and efficacy of GS-9350-boosted atazanavir versus ritonavir-boosted atazanavir each administered with emtricitabine/tenofovir disoproxil fumarate in human immunodeficiency virus (HIV)-1 infected, antiretroviral treatment-naïve adults) and study GS-US-216-105 (a phase II randomized, double-blinded study of the safety and efficacy of GS-9350-boosted atazanavir (ATV/GS-9350) compared to ritonavir boosted atazanavir (ATV/r) in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in HIV-1 infected, antiretroviral treatment-naive adults). The RMP (version 2.0) is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.4. Belimumab – BENLYSTA (CAP) - EMEA/H/C/002015/II/0040

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to add information on the effect of Benlysta on vaccine responses in subjects with systemic lupus erythematosus (SLE) based on the results from study BEL115470 (HGS1006-C1117) to fulfil MEA 004.3. The RMP is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.5. Canakinumab – ILARIS (CAP) - EMEA/H/C/001109/II/0043

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to amend the systemic juvenile idiopathic arthritis (SJIA) indication to include treatment of active Still's disease including adult-onset Still's disease (AOSD) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the annexes in line with the latest QRD template. An updated RMP (version 10) was provided as part of the application
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.6. Daclatasvir – DAKLINZA (CAP) - EMEA/H/C/003768/II/0018/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Submission of two final study reports for non-clincial studies NCPK 278 and NCPK 293 to evaluate the potential pharmacodynamic and pharmacokinetic interactions between amiodarone and hepatitis C virus (HCV) direct acting antivirals (DAAs) including daclatasvir, in order to fulfil MEAs 015 and 016 . As a consequence the RMP is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.7. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/II/0014

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include the prevention of cardiovascular events, based on the final data of the cardiovascular safety phase III clinical trial EMPA-REG OUTCOME. As a consequence, section 4.1 of the SmPC is updated in order to add safety information on this study. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.8. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - EMEA/H/C/000721/II/0067

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include the prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP (version 11.0) is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.9. Insulin degludec, insulin aspart – RYZODEG (CAP) - EMEA/H/C/002499/II/0017

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include the paediatric population from 1 to 18 years of age for Ryzodeg. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.10. Lumacaftor, ivacaftor – ORKAMBI (CAP) - EMEA/H/C/003954/II/0005/G

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final study reports for the following studies in order to address MEA 006: 1. Report L240: In vitro evaluation of the substrate and inhibitor potential of lumacaftor (VX-809) for breast cancer resistance protein and multidrug resistance protein 2. 2. Report L242: evaluation of the inhibition potential of VX-809 for uptakes transporters OAT1, OAT3, OCT1 and OCT2. 3. Report L239: In vitro drug-drug interaction studies of the sponsor's test article, VX-770. 4. Report L241: evaluation of the inhibition potential of VX-770 for uptake transporters OAT1, OAT3, OCT1 and OCT2. The RMP (version 2.1) is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.11. Methylthioninium chloride – METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP) - EMEA/H/C/002108/II/0030/G

Applicant: Provepharm SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.8 of the SmPC in order to include paresthesia, dysgeusia, syncope, presyncope, feeling of change in body temperature, chest discomfort, shoulder pain and limb discomfort based on data from two clinical studies. In addition, frequencies were added in the tabulated list of adverse reactions. The Package Leaflet is updated accordingly. The RMP (version 2.0) is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.12. Natalizumab – TYSABRI (CAP) - EMEA/H/C/000603/II/0095

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section sections 4.2, 4.3, 4.8, 5.1 and 5.2 of the SmPC based on the results of paediatric studies 101MS028 and 101MS328, in accordance with the paediatric investigation plan (EMEA-001095-PIP-12). The RMP (version 21) is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.13. Nepafenac – NEVANAC (CAP) - EMEA/H/C/000818/II/0032

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include the 'reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients' for the 3 mg/ml strength based on data from the phase III studies C-12-067 and C-12-071. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to update the annexes in line with the latest QRD template. The RMP (version 7) is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.14. Nintedanib – VARGATEF (CAP) - EMEA/H/C/002569/II/0009

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Leonidas Klironomos

Scope: Submission of the final clinical study report for study 1199.120: an open label, dose escalation phase I study to evaluate the safety and tolerability of continuous twice-daily oral treatment of nintedanib in Japanese patients with hepatocellular carcinoma, to fulfil MEA 003. The RMP is updated accordingly. In addition, the MAH took the opportunity to update the RMP with the required updates requested in the outcome of EMEA/H/C/WS0766 variation
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.15. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0012

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the monotherapy treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL): - after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, or - after at least two prior therapies in patients who are not candidates for ASCT. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the proposed new indication, add a warning that patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL, and update the safety and pharmacodynamic information. The Package Leaflet is updated accordingly. Furthermore,

the product information is brought in line with the latest QRD template version 10.0. Moreover, the RMP (version 5.0) is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.16. Ofatumumab – ARZERRA (CAP) - EMEA/H/C/001131/II/0045/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the combination of Arzerra with fludarabine and cyclophosphamide or in combination with bendamustine for the treatment of adult patients with relapsed chronic lymphocytic leukaemia (CLL). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 and 9 of the SmPC are updated .The Package Leaflet and the RMP (version 13) are updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.17. Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/II/0008/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.2 and 5.2 of the SmPC with recommendations for patients with renal impairment based on the results of study D0816C00006 (MEA 006), that evaluated the influence of mild and moderate renal impairment on the pharmacokinetics of Olaparib. The Package Leaflet and RMP are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the product information in line with the latest QRD template version and to introduce minor corrections in the product information. Furthermore, a grouping of two type IB variations is submitted to revise the study milestones dates for the category 3 study D0816C00005 and category 1 study D0816C00002 in the RMP. The annex II has been amended accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.18. Pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/II/0007

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the second line treatment of non-small cell lung cancer (NSCLC). As a consequence, sections 4.1, 4.2 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.19. Posaconazole – NOXAFIL (CAP) - EMEA/H/C/000610/II/0044

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.2 of the SmPC in order to strengthen the information about non-interchangeability of the oral formulations based on new reports of medication errors related to confusion between posaconazole tablets and oral suspension in prescribing. The Package Leaflet and the RMP are updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.20. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/II/0057

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX) in the SmPC for the subcutaneous formulation. As a consequence, section 4.1 of the SmPC is updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. Moreover, the RMP (version 18) is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.21. Vandetanib – CAPRELSA (CAP) - EMEA/H/C/002315/II/0016

Applicant: AstraZeneca AB

PRAC Rapporteur: Claire Ferard

Scope: Extension of indication to include the treatment of paediatric population. As a consequence, sections 4.1, 4.2, 4.6, 4.8, 5.1 and 5.2 of the SmPC are. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.22. Vismodegib – ERIVEDGE (CAP) - EMEA/H/C/002602/II/0025/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4, 4.6, 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information in the product information after finalisation of study MO25616 (specific obligation (SOB) 013). Considering the fulfilment of the SOB, the MAH is also proposing the switch of the conditional marketing authorisation (MA) to a full MA not subject to specific obligations. Data from the same study also fulfilled the analysis required in MEA 005 regarding evaluation of the time for washout of vismodegib after treatment discontinuation and in MEA 008 regarding reporting of adverse events. The Package Leaflet and the RMP are updated accordingly. Furthermore, the MAH took the opportunity to update the RMP with regard to the results from non-clinical studies subject to variation EMEA/H/C/002602/II/21 and to propose the deletion of hyponatremia as an important potential risk in the RMP and as an adverse drug reatcion in the product information as discussed in the previous PSUR (PSUSA/00010140/201407)
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.3.23. Vorapaxar – ZONTIVITY (CAP) - EMEA/H/C/002814/II/0005

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include the treatment of patients with peripheral arterial disease (PAD) and as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the contact details of local representative in Luxembourg in the Package Leaflet. Furthermore, the product pnformation is brought in line with the latest QRD template (version 9.1). Moreover, the RMP (version 2.0) is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

6. Periodic safety update reports (PSURs)

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

6.1.1. Aclidinium bromide, formoterol fumarate dihydrate – BRIMICA GENUAIR (CAP), DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201511

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.2. Aflibercept – EYLEA (CAP) - PSUSA/00010020/201511

Applicant: Bayer Pharma AG

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.3. Boceprevir – VICTRELIS (CAP) - PSUSA/00009081/201511

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.4. Cobicistat, darunavir – REZOLSTA (CAP) - PSUSA/00010315/201511

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.5. Dalbavancin – XYDALBA (CAP) - PSUSA/00010350/201511

Applicant: Durata Therapeutics International B.V.

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.6. Darifenacin – EMSELEX (CAP) - PSUSA/00000933/201510

Applicant: Merus Labs Luxco S.A.R.L.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.7. Eribulin – HALAVEN (CAP) - PSUSA/00001254/201511

Applicant: Eisai Europe Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.8. Erlotinib – TARCEVA (CAP) - PSUSA/00001255/201511

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.9. Fluticasone furoate, vilanterol – RELVAR ELLIPTA (CAP), REVINTY ELLIPTA (CAP) - PSUSA/00010099/201511

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.10. Follitropin alfa – BEMFOLA (CAP), GONAL-F (CAP), OVALEAP (CAP) - PSUSA/00001463/201510

Applicant: Finox Biotech AG (Bemfola), Merck Serono Europe Limited (Gonal-F), Teva B.V. (Ovaleap)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.11. Follitropin alfa, lutropin alfa – PERGOVERIS (CAP) - PSUSA/00001464/201510

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.12. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - PSUSA/00009175/201511 (with RMP)

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.13. Ibrutinib – IMBRUVICA (CAP) - PSUSA/00010301/201511

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.14. Ketoconazole – KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201511

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.15. Lidocaine, prilocaine – FORTACIN (CAP) - PSUSA/00010110/201511

Applicant: Plethora Solutions Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.16. Mercaptamine – CYSTAGON (CAP), PROCYSBI (CAP) - PSUSA/00001987/201510

Applicant: Orphan Europe S.A.R.L. (Cystagon), Raptor Pharmaceuticals Europe BV (Procysbi)

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.17. Metformin, saxagliptin – KOMBOGLYZE (CAP) - PSUSA/00002686/201511

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.18. Mixture of polynuclear iron(iii)-oxyhydroxide, sucrose and starches – VELPHORO (CAP) - PSUSA/00010296/201511 (with RMP)

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

6.1.19. Nintedanib – VARGATEF (CAP) - PSUSA/00010318/201511

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Leonidas Klironomos

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.20. Pixantrone – PIXUVRI (CAP) - PSUSA/00009261/201511

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.21. Radium Ra^{223} dichloride – XOFIGO (CAP) - PSUSA/00010132/201511

Applicant: Bayer Pharma AG

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.22. Rituximab – MABTHERA (CAP) - PSUSA/00002652/201511

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.23. Rotavirus vaccine, live, oral, pentavalent – ROTATEQ (CAP) - PSUSA/00002666/201511 (with RMP)

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.24. Sapropterin – KUVAN (CAP) - PSUSA/00002683/201512 (with RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.25. Simeprevir – OLYSIO (CAP) - PSUSA/00010255/201511

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.26. Stiripentol – DIACOMIT (CAP) - PSUSA/00002789/201511

Applicant: Biocodex

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.27. Tilmanocept – LYMPHOSEEK (CAP) - PSUSA/00010313/201511

Applicant: Navidea Biopharmaceuticals Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.28. Tolvaptan – JINARC (CAP) - PSUSA/00010395/201511

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.29. Trametinib – MEKINIST (CAP) - PSUSA/00010262/201511

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

6.1.30. Vedolizumab – ENTYVIO (CAP) - PSUSA/00010186/201511

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

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

6.2.1. Sevelamer – RENAGEL (CAP), RENVELA (CAP), SEVELAMER CARBONATE ZENTIVA (CAP), TASERMITY (CAP), NAP - PSUSA/00002697/201510

Applicant: Genzyme Europe BV (Renagel, Renvela, Sevelamer Carbonate Zentiva, Tasermity), various

PRAC Rapporteur: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

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

6.3.1. Acetylsalicylic acid, bisoprolol (NAP) - PSUSA/00010287/201511

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.2. Acitretin (NAP) - PSUSA/00000051/201510

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.3. Artemether, lumefantrin (dispersible tablet) (NAP) - PSUSA/00009060/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.4. Azelastine, fluticasone (NAP) - PSUSA/00010067/201510

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.5. Bromocriptine (NAP) - PSUSA/00000438/201510

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.6. Ceftazidime (NAP) - PSUSA/00000608/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.7. Clindamycin (NAP) - PSUSA/00000795/201510

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.8. Didanosine (NAP) - PSUSA/00001054/201510

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.9. Human coagulation factor VIII, human von Willebrand factor (NAP) - PSUSA/00001621/201510

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.10. Ivermectin (topical use) (NAP) - PSUSA/00010376/201510

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.11. Letrozole (NAP) - PSUSA/00001842/201510

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.12. Meningococcal group c polysaccharide conjugate vaccine (NAP) - PSUSA/00001971/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.13. Methylphenidate (NAP) - PSUSA/00002024/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.14. Metoclopramide (NAP) - PSUSA/00002036/201510

Applicant: various

PRAC Lead: Ingebjørg Buajordet

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.15. Milrinone (NAP) - PSUSA/00002064/201510

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.16. Paraffin liquid (NAP) - PSUSA/00009251/201510

Applicant: various

PRAC Lead: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.17. Perindopril (NAP) - PSUSA/00002354/201510

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.18. Piretanide (NAP) - PSUSA/00002433/201510

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.19. Rabeprazole (NAP) - PSUSA/00002601/201510

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.3.20. Tetrabenazine (NAP) - PSUSA/00002911/201510

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Trametinib – MEKINIST (CAP) - EMEA/H/C/002643/MEA 002

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Follow-up from PSUSA/00010262/201511: submission of the second annual report for cardiomyopathy-related adverse reactions
Action: For adoption of advice to CHMP

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[2]

7.1.1. Alipogene tiparvovec – GLYBERA (CAP) - EMEA/H/C/PSP/0046

Applicant: UniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for study REG-uQ-Glyb-001: a lipoprotein lipase deficiency (LPLD) registry: observational longitudinal pharmacoepidemiologic study in LPLD patients, either treated or not treated with alipogene tiparvovec
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

7.1.2. Cholic acid– KOLBAM (CAP) - EMEA/H/C/PSP/0017.1

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Revised PASS protocol for a patient registry to monitor the long term safety and efficacy in patients treated with cholic acid
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

7.1.3. Dexamfetamine (NAP) - EMEA/H/N/PSP/0018.2

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG.

PRAC Rapporteur: Julie Williams

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

Scope: Revised PASS protocol to evaluate the long-term safety profile of dexamfetamine in children with attention deficit hyperactivity disorder (ADHD), specifically targeting key issues such as cardiovascular events, growth and psychiatric related adverse events
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

7.1.4. Domperidone (NAP) - EMEA/H/N/PSP/j/0031.1

Applicant: Janssen (Motilium), various

PRAC Rapporteur: Claire Ferard

Scope: Revised PASS protocol for a drug utilisation study on domperidone use in Europe using databases to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the changes in the product information and the distribution of a DHPC. The secondary objective of the study is to characterise the extent to which domperidone is prescribed for conditions that are not labelled
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

7.1.5. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSP/044

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Protocol for a prospective non-interventional post-authorisation safety study (study CC-5013-MDS-010), designed as myelodysplastic syndromes (MDS) disease registry of patients with transfusion dependent international prognostic scoring system (IPSS) low or intermediate-1-MDS and isolated deletion (5q)
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

7.1.6. Levonorgestrel (NAP) - EMEA/H/N/PSP/J/0045

Applicant: Bayer Pharma AG, various
PRAC Rapporteur: Ulla Wändel Liminga

Scope: Revised PASS protocol for study EURAS-LCS12: a European active surveillance study of LCS-12, an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to assess among new users the risks of certain events associated with the use of LCS-12 compared with established IUDs (e.g. Mirena, copper IUDs) during standard clinical practice and to describe drug utilisation patterns
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

7.1.7. Susoctocog alfa – OBIZUR (CAP) - EMEA/H/C/PSP/0043

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: PASS protocol for a prospective, non-interventional study to collect and analyse immediate and long-term data on clinical efficacy and safety of all patients with acquired haemophilia and who are treated with Obizur (study 241501)
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[3]

7.2.1. Insulin detemir – LEVEMIR (CAP) - EMEA/H/C/000528/MEA/045.5

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Revised PASS protocol for diabetes pregnancy registry (NN304-4016)
Action: For adoption of advice to CHMP

7.2.2. Insulin human – INSUMAN (CAP) - EMEA/H/C/000201/MEA/047.2

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's responses to MEA 047.1 [PASS protocol for study HUBIN-C-06380, a prospective cohort study organised as exposure registry] as per request for supplementary information adopted in September 2015
Action: For adoption of advice to CHMP

7.2.3. Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA/006.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: MAH's responses to MEA 006.1 [revised protocol for naloxegol observational safety study in patients taking opioids for non-cancer pain (study D2288R00084)] as per request for supplementary information adopted in November 2015
Action: For adoption of advice to CHMP

7.2.4. Necitumumab – PORTRAZZA (CAP) - EMEA/H/C/003886/MEA/001

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for a physician/oncologist knowledge survey to assess physicians'/oncologists' understanding of the key conditions for the safe use of necitumumab
Action: For adoption of advice to CHMP

7.2.5. Necitumumab – PORTRAZZA (CAP) - EMEA/H/C/003886/MEA/002

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for an observational prospective study to assess the incidence, severity, and sequelae of all serious life-threatening identified and potential risks for necitumumab treatment in the approved indication

Action: For adoption of advice to CHMP

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

7.2.6. Sofosbuvir – SOVALDI (CAP) - EMEA/H/C/002798/MEA/021.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's responses to MEA 021 [protocol for study GS-EU-337-2030: an observational, cross-sectional post-authorisation safety study to assess healthcare providers awareness of risks related to sofosbuvir and ledipasvir/sofosbuvir (LDV/SOF)] as per request for supplementary information adopted in January 2016
Action: For adoption of advice to CHMP

7.2.7. Sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/MEA/013.2

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: MAH's responses to MEA 013.1 [revised protocol for study GS-EU-337-1820: a prospective observational drug utilisation study (DUS) of ledipasvir/sofosbuvir (LDV/SOF) in adults with hepatitis C (HCV)/human immunodeficiency virus (HIV) co-infection] asper request for supplementary information adopted in January 2016
Action: For adoption of advice to CHMP

7.2.8. Sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/MEA/014.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: MAH's responses to MEA 014 [protocol for study GS-EU-337-2030: an observational, cross-sectional PASS to assess healthcare providers awareness of risks related to sofosbuvir and ledipasvir/sofosbuvir (LDV/SOF)] as per request for supplementary information as adopted in January 2016
Action: For adoption of advice to CHMP

7.3. Results of PASS imposed in the marketing authorisation(s)[4]

7.3.1. Cyproterone, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0003

Applicant: Bayer Pharma AG, various

PRAC Rapporteur: Menno van der Elst

Scope: Results of a drug utilisation study (DUS) (database) for cyproterone/ethinylstradiol to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription
Action: For adoption of a recommendation to CMDh

7.4. Results of PASS non-imposed in the marketing authorisation(s)[5]

7.4.1. Bivalirudin – ANGIOX (CAP) - EMEA/H/C/000562/II/0068

Applicant: The Medicines Company UK Ltd.

PRAC Rapporteur: Julie Williams

[4] In accordance with Article 107p-q of Directive 2001/83/EC
[5] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

Scope: Submission of the final results for the drug utilisation study Eurovision 2. The RMP has been amended to refine the additional risk minimisation measures in line with the findings of the study
Action: For adoption of PRAC Assessment Report

7.4.2. Fluticasone furoate – AVAMYS (CAP) - EMEA/H/C/000770/II/0030/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final clinical study report for post authorisation safety study (PASS) 201077: a retrospective case-control studyof rare adverse events associated with intranasal steroids. In addition, submission of a revised RMP (version 11) to include cataracts and glaucoma as identified risks, following the recommendation of PSUSA/00009154/201504 adopted in December 2015
Action: For adoption of PRAC Assessment Report

7.4.3. Indacaterol – HIROBRIZ BREEZHALER (CAP) - EMEA/H/C/001211/WS/0944; ONBREZ BREEZHALER (CAP) - EMEA/H/C/001114/WS/0944; OSLIF BREEZHALER (CAP) - EMEA/H/C/001210/WS/0944

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final study report for study US PASS QAB149B2432 (CQAB149BS232861) to fulfil MEA 017/MEA 015/MEA 015 for Onbrez Breezhaler, Hirobriz Breezhaler and Oslif Breezhaler respectively. In addition, the RMPs (version 9.0) are also updated to reflect results from this completed study and to remove it from the ongoing pharmacovigilance activities
Action: For adoption of PRAC Assessment Report

7.4.4. Insulin glargine – LANTUS (CAP) - EMEA/H/C/000284/II/0105

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report for a PASS: UK SoloStar differentiation study, a study in patients with type 1 ortype 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin with the current and new labels. This submission addresses MEA 037
Action: For adoption of PRAC Assessment Report

7.4.5. Insulin glulisine – APIDRA (CAP) - EMEA/H/C/000557/II/0066

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Julie Williams

Scope: Submission of the final clinical study report for a PASS: UK SoloStar differentiation study, a study in patients with type 1 ortype 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin with the current and new labels. This submission addresses MEA 037
Action: For adoption of PRAC Assessment Report

7.4.6. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/II/0038

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study report for study CA184242: a risk minimisation tool effectiveness evaluation survey. The RMP (version 12) is updated accordingly
Action: For adoption of PRAC Assessment Report

7.4.7. Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP) - EMEA/H/C/001095/II/0062

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report for study V59_54OB, a post-licensure observational safety surveillance study of Menveo vaccination in children 2 through 10 years of age, in order to update the safety information of Menveo in subjects aged 2-10 years of age to fulfil MEA 024
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[6]

7.5.1. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA/005.6

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 005.5 [six-monthly status report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information adopted in February 2016
Action: For adoption of advice to CHMP

7.5.2. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA/006.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 006.1 [first status report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information adopted in February 2016
Action: For adoption of advice to CHMP

7.5.3. Canagliflozin, metformin – VOKANAMET (CAP) - EMEA/H/C/002656/MEA/004.6

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 004.5 [six-monthly status report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study as

[6] In line with the revised variations regulation for any submission before 4 August 2013

requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information adopted in February 2016
Action: For adoption of advice to CHMP

7.5.4. Canagliflozin, metformin – VOKANAMET (CAP) - EMEA/H/C/002656/MEA/005.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 005.1 [first status report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information adopted in February 2016
Action: For adoption of advice to CHMP

7.5.5. Estrogens conjugated, bazedoxifene – DUAVIVE (CAP) - EMEA/H/C/002314/MEA/002.3

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: First interim analysis report for an US PASS: active surveillance of conjugated estrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data (study B2311060, category 3 study)
Action: For adoption of advice to CHMP

7.5.6. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA/004.5

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Interim results of the enhanced safety surveillance study D2560C00008: a postmarketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age
Action: For adoption of advice to CHMP

7.5.7. Micafungin – MYCAMINE (CAP) - EMEA/H/C/000734/MEA/013.2

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 013.1 [annual interim report from an observational database-assisted comparative cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma (protocol number: ISN 9463-CL-140): a multicentre cohort study of the short and long-term safety of micafungin and Other parenteral antifungal agents (MYCOS)] as per request for supplementary information adopted in December 2015
Action: For adoption of advice to CHMP

7.5.8. Temsirolimus – TORISEL (CAP) - EMEA/H/C/000799/LEG/031.4

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to LEG 031.3 [interim results from Japanese non-interventional studies 3066K5-4406 (Torisel 25 mg for intravenous drip infusion special investigation - all patients survey) and B1771016 (Torisel 25 mg for intravenous drip infusion special investigation - survey on long term use)] as per request for supplementary information adopted in January 2016
Action: For adoption of advice to CHMP

7.6. Others

7.6.1. Gadoversetamide – OPTIMARK (CAP) - EMEA/H/C/000745/ANX 014.7

Applicant: Mallinckrodt Deutschland GmbH

PRAC Rapporteur: Almath Spooner

Scope: From R/012: revised protocol for study ALS-Gd64/001 as per request for supplementary information adopted in December 2015
Action: For adoption of advice to CHMP

7.6.2. Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) – PANDEMRIX[7] - EMEA/H/C/000832/MEA 122.1

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's responses to MEA 0122 [final study report for PASS study EPI-FLU H1N1-014 VS: an observational retrospective database analysis to estimate the risk of multiple sclerosis following vaccination with Arepanrix in Manitoba, Canada] as per request for supplementary information adopted in March 2016
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

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

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

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

[7] Marketing Authorisation expired on 13 August 2015

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/0040 (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. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/R/0022 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation
Action: For adoption of advice to CHMP

8.3. Renewals of the marketing authorisation

8.3.1. 5-aminolevulinic acid – AMELUZ (CAP) - EMEA/H/C/002204/R/0023 (without RMP)

Applicant: Biofrontera Bioscience GmbH

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of advice to CHMP

8.3.2. Desloratadine – DASSELTA (CAP) - EMEA/H/C/002310/R/0012 (without RMP)

Applicant: Krka, d.d., Novo mesto

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of advice to CHMP

8.3.3. Desloratadine – DESLORATADINE RATIOPHARM (CAP) - EMEA/H/C/002404/R/0015 (without RMP)

Applicant: Ratiopharm GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of advice to CHMP

8.3.4. Desloratadine – DESLORATADINE TEVA (CAP) - EMEA/H/C/002419/R/0014 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of advice to CHMP

8.3.5. Fidaxomycin – DIFICLIR (CAP) - EMEA/H/C/002087/R/0026 (with RMP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of advice to CHMP

8.3.6. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/R/0020 (without RMP)

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of advice to CHMP

8.3.7. Levetiracetam – LEVETIRACETAM ACTAVIS GROUP (CAP) - EMEA/H/C/002305/R/0012 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of advice to CHMP

8.3.8. Ranibizumab – LUCENTIS (CAP) - EMEA/H/C/000715/R/0062 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

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

9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders of centrally authorised products for human use

Action: For adoption of the confidential human-pharmacovigilance inspection programme 2016-2019 (first revision 2016)

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Posaconazole – NOXAFIL (CAP) - EMEA/H/C/000610/II/0044

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Rafe Suvarna

Scope: PRAC consultation on a variation to update section 4.2 of the SmPC in order to strengthen the information about non-interchangeability of the oral formulations based on new reports of medication errors related to confusion between posaconazole tablets and oral suspension in prescribing. The Package Leaflet and the RMP are updated accordingly
Action: For adoption of advice to CHMP

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

None

10.3. Other requests

10.3.1. Dapagliflozin – EDISTRIDE (CAP) - EMEA/H/C/004161/LEG 001; FORXIGA (CAP) - EMEA/H/C/002322/LEG 019 dapagliflozin, metformin – EBYMECT (CAP) - EMEA/H/C/004162/LEG 001; XIGDUO (CAP) - EMEA/H/C/002672/LEG 005

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: PRAC consultation on the assessment of the risk of toe amputation with dapagliflozin-containing medicinal products in the context of the ongoing article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing medicinal products
Action: For adoption of advice to CHMP

10.3.2. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/LEG 006 empagliflozin, metformin – SYNJARDY (CAP) - EMEA/H/C/003770/LEG 004

Applicant: Boehringer Ingelheim GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: PRAC consultation on the assessment of the risk of toe amputation with empagliflozin-containing medicinal products in the context of the ongoing article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing medicinal products

Action: For adoption of advice to CHMP

10.4. 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.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Gadolinium-containing contrast agents (GdCA): Gadobenate dimeglumine; gadobutrol; gadodiamide; gadopentetic acid dimeglumine, gadoteric acid (intra-articular formulation); gadoteric acid (intravenous and intravascular formulations); gadoteridol; gadoxetic acid disodium (NAP)

Applicant: various

Lead member: Rafe Suvarna

Scope: PRAC consultation on a post-authorisation measure to conduct further clinical studies to assess the retention of gadolinium in bone resulting from the 2010 referral procedures under Article 20 of Regulation (EC) 726/2004 and Article 31 of Directive 2001/83/EC for gadolinium-containing contrast agents
Action: For adoption of advice to Member States

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC working group - Recommendations on efficiency of plenary meetings – best practice guide

PRAC lead: Martin Huber, Rafe Suvarna, 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

12.3.1. Working Party with Healthcare Professionals' Organisations (HCPWP) and Working Party with Patients' and Consumers' Organisations (PCWP) - Nomination of PRAC representative(s)

Action: For discussion

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

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. Good Pharmacovigilance Practice (GVP) module IX on Signal management – revision 1 and addendum

PRAC lead: Sabine Straus
Action: For adoption

12.11.2. 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 auditable requirement project update

Action: For discussion

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – non-interventional imposed PASS final results - new procedure under 107q of Directive 2001/83/EC - consultation on main milestones

PRAC lead: Valerie Strassmann
Action: For discussion

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 hearings - preparation of PRAC public hearings dry-run

Action: For discussion

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) – revised PRAC process for GVP modules in 2016/2017 - update on GVP status overview

Action: For discussion

12.20.2. Good Pharmacovigilance Practices (GVP) – revised PRAC process for GVP modules in 2016/2017 - GVP Module V on Risk Management Plans and GVP module XVI on risk Communication: overlap and future scopes

Action: For discussion

12.20.3. Good Pharmacovigilance Practice (GVP) Chapter P.II. on biologicals

PRAC lead: Sabine Straus

Action: For discussion

12.20.1. EMA Procedure Management department – optimising operating model

Action: For discussion

13. Any other business

14. Explanatory notes

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

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures

(Items 2 and 3 of the PRAC agenda)

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

Signals assessment and prioritisation

(Item 4 of the PRAC agenda)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient.
The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC agenda)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects.
RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC agenda)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.
PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC agenda)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections

(Item 9 of the PRAC agenda)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/