23 October 2017
EMA/PRAC/707172/2017

Pharmacovigilance Risk Assessment Committee (PRAC)

Draft agenda for the meeting on 23-26 October 2017

Chair: June Raine – Vice-Chair: Almath Spooner

23 October 2017, 13:00 – 19:30, room 3/A

24 October 2017, 08:30 – 19:30, room 3/A

25 October 2017, 08:30 – 19:30, room 3/A

26 October 2017, 08:30 – 16:00, room 3/A

Organisational, regulatory and methodological matters (ORGAM)

9 November 2017, 09.00-12.00, room 7/B, via teleconference

Health and safety information

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

Disclaimers

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

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

Note on access to documents

Some documents mentioned in the agenda cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006, Rev. 1).

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

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1. Introduction

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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the PRAC plenary session to be held on 23-26 October 2017. See November 2017 PRAC minutes (to be published post December 2017 PRAC meeting).

1.2. Agenda of the meeting on 23-26 October 2017

Action: For adoption

1.3. Minutes of the previous meeting on 25-29 September 2017

Action: For adoption

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

2.1. Newly triggered procedures

2.1.1. Hydroxyethyl starch (HES)[1] (NAP)

Applicants: Fresenius Kabi Deutschland GmbH (Volulyte, Voluven), B. Braun Melsungen AG (Tetraspan, Venofundin), Seruwerk Bernburg AG (Hesra); various

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

Scope: Review of the benefit-risk balance following notification by Sweden of a referral under Article 107i of Directive 2001/83/EC, based on pharmacovigilance data

Action: For adoption of a list of questions

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

[1] Solution for infusion

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

3.1. Newly triggered procedures

3.1.1. Flupirtine (NAP)

Applicants: various

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

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

Action: For adoption of a list of questions

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 discussion

3.3. Procedures for finalisation

3.3.1. Daclizumab - ZINBRYTA (CAP) – EMEA/H/A-20/1456

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia; PRAC Co-rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

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 recommendation to CHMP

3.4. Re-examination procedures[2]

3.4.1. Paracetamol[3] (NAP); paracetamol, tramadol[2] (NAP) - EMEA/H/A-31/1445

Applicant(s): GlaxoSmithKline Consumer Healthcare AB (Alvedon 665 mg modified-release tablet), various

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Adam Przybylkowski

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

Action: For discussion

3.5. Others

None

4. Signals assessment and prioritisation[4]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Efavirenz – SUSTIVA (CAP), STOCRIN (CAP); tenofovir disoproxil - VIREAD (CAP); emtricitabine – EMTRIVA (CAP); efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG (Sustiva), Merck Sharp & Dohme Limited (Stocrin), Gilead Sciences International Limited (Viread, Emtriva, Atripla)

PRAC Rapporteur: To be appointed

Scope: Signal of autoimmune hepatitis

Action: For adoption of PRAC recommendation

EPITT 18956 – New signal

Lead Member State: PT, FR, UK, DE

4.1.2. Eltrombopag – REVOLADE (CAP)

Applicant(s): Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Signal of laboratory test interference, interference with bilirubin assay

[2] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[3] Modified release formulations
[4] 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

Action: For adoption of PRAC recommendation

EPITT 18955 – New signal

Lead Member State: ES

4.1.3. Rivaroxaban – XARELTO (CAP)

Applicant(s): Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of oesophagitis

Action: For adoption of PRAC recommendation

EPITT 18954 – New signal

Lead Member State: SE

4.2. New signals detected from other sources

4.2.1. Levonorgestrel[5] (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of arthralgia

Action: For adoption of PRAC recommendation

EPITT 19109 – New signal

Lead Member State: DE

4.3. Signals follow-up and prioritisation

4.3.1. Amitriptyline (NAP)

Applicant(s): various

PRAC Rapporteur: Agni Kapou

Scope: Signal of drug induced liver injury (DILI) and hepatocellular injury

Action: For adoption of PRAC recommendation

EPITT 18890 – Follow-up to June 2017

4.3.2. Levonorgestrel[6] (NAP)

Applicant(s): various

[5] Intrauterine device (IUD)
[6] Intrauterine device (IUD)

PRAC Rapporteur: Martin Huber

Scope: Signal of anxiety, panic attacks, mood changes, sleep disorders and restlessness

Action: For adoption of PRAC recommendation

EPITT 18849 – Follow-up to June 2017

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Andexanet alfa - EMEA/H/C/004108

Scope: Treatment of direct or indirect factor Xa (FXa) inhibitor when reversal of anticoagulation is needed

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

5.1.2. Binimetinib - EMEA/H/C/004052

Scope: Treatment of adult patients with unresectable or metastatic melanoma and treatment of unresectable melanoma with NRAS Q61 mutation

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

5.1.3. Ertugliflozin - EMEA/H/C/004315

Scope: Treatment of type 2 diabetes mellitus (T2DM)

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

5.1.4. Ertugliflozin, metformin hydrochloride - EMEA/H/C/004314

Scope: Treatment of type 2 diabetes mellitus (T2DM)

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

5.1.5. Ertugliflozin, sitagliptin - EMEA/H/C/004313

Scope: Treatment of type 2 diabetes mellitus (T2DM)

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

5.1.6. Trastuzumab - EMEA/H/C/002575

Scope: Treatment of metastatic breast cancer, early breast cancer and metastatic gastric cancer (MGC)

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

5.1.7. Trastuzumab - EMEA/H/C/004361

Scope: Treatment of metastatic breast cancer, early breast cancer and metastatic gastric cancer (MGC)

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. Aclidinium, formoterol - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/WS1221/0017; DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/WS1221/0017

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Updated RMP (version 3) to re-categorise 'hypersensitivity (anaphylactic responses, angioedema, and urticaria)' from important potential risk to important identified risk, remove 'use in non-Caucasian patients' as missing information (with the completion of clinical studies in Asian patients), and include milestones and due dates for PASS D6560R00004: an aclidinium bromide PASS to evaluate the risk of cardiovascular endpointsl and a drug utilisation study (DUS) (D6560R00002): common for aclidinium (DUS1) and aclidinium/formoterol fixed-dose combination (DUS2) to describe the characteristics and patterns of use of new users of aclidinium bromide (monotherapy or in combination) and new users of other medications for chronic obstructive pulmonary disease (COPD), to evaluate the potential for off-label use and to describe users of aclidinium (monotherapy or in combination) in patient subgroups for which there is missing information

Action: For adoption of PRAC Assessment Report

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

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

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

Action: For adoption of PRAC Assessment Report

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

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Updated 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. Annex II of the product information is updated accordingly

Action: For adoption of PRAC Assessment Report

5.2.4. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/II/0024, Orphan

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: Updated RMP (version 3.1) in order to submit protocol amendments of SHP617-400 (EU-AIR) study: a European multicentre, multi-country, post-authorisation, observation study (registry) of patients with chronic adrenal insufficiency (category 3). In addition, the MAH took the opportunity to implement a change agreed by the PRAC/CHMP as part of the assessment of MEA 005.3 dated July 2016 to remove from the RMP reference to study SHP617-404 (SWE-DUS): a category 3 study to monitor off-label use of Plenadren to evaluate physician prescribing patterns

Action: For adoption of PRAC Assessment Report

5.2.5. Insulin human - ACTRAPHANE (CAP) - EMEA/H/C/000427/WS1197/0072; ACTRAPID (CAP) - EMEA/H/C/000424/WS1197/0066; INSULATARD (CAP) - EMEA/H/C/000441/WS1197/0069; MIXTARD (CAP) - EMEA/H/C/000428/WS1197/0073; PROTAPHANE (CAP) - EMEA/H/C/000442/WS1197/0068

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Updated RMP (version 2.1) in line with the Guidance on format of the RMP in the EU (revision 2). Moreover, significant changes to the safety specification are proposed with this RMP update as some risks are now considered fully characterised and appropriately managed: 1) removal of the following important identified risks: hypoglycaemia, anaphylactic reactions, peripheral neuropathy, refraction disorders, lipodystrophy, urticaria, rash, oedema and diabetic retinopathy; 2) removal of the following important potential risks: immunogenicity, allergic reactions and lack of efficacy related to the new manufacturing process; and 3) removal of the following missing information: special patient groups

Action: For adoption of PRAC Assessment Report

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

5.3.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0056

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include a new indication for Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe for the treatment of active Still's disease, including systemic juvenile idiopathic arthritis and adult-onset Still's disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly. In addition, the MAH took the opportunity to make some 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. Atazanavir, cobicistat - EVOTAZ (CAP) - EMEA/H/C/003904/WS1193/0018; REYATAZ (CAP) - EMEA/H/C/000494/WS1193/0113

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: Update of sections 4.3 and 4.5 of the SmPC to include information on the contraindicated co-administration with grazoprevir-containing products, including elbasvir/grazoprevir fixed dose combination used for the treatment of chronic hepatitis C infection following the results of interaction studies. The Package Leaflets and the RMPs (Evotaz (version 5.0), Reyataz (version 13.0)) are updated accordingly. In addition, the MAH took the opportunity to make some editorial changes and typographical corrections in the Reyataz and Evotaz Product Information

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

5.3.3. Avanafil - SPEDRA (CAP) - EMEA/H/C/002581/II/0027/G

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variation consisting of: 1) update of section 4.4 to reflect the results of clinical study TA-402: a double-blind, randomized, placebo-controlled, single-dose, parallel study to assess the effects of avanafil on multiple parameters of vision, including, but not limited to visual acuity, intraocular pressure, pupillometry, and colour vision discrimination, in healthy male subjects; 2) update of section 4.6 of the SmPC in order to reflect the results of clinical study TA-401: a randomized, double-blind, placebo-controlled, parallel group, multicentre clinical trial of the effect of avanafil on spermatogenesis in healthy adult males and adult males with mild erectile dysfunction. The Package Leaflet and the RMP (version 5.1) are updated accordingly. In addition, the MAH took the opportunity to make an editorial correction on the approved SmPC by adding the missing adverse reaction epistaxis from the tabulated list of adverse reactions reported in section 4.8. Additionally, the MAH took the opportunity to align the information of Package Leaflet section 3 to SmPC section 4.2

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/0002

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.5 and 5.2 of the SmPC, based on the final study report of an in vitro study investigating the inhibitory effect of baricitinib on the organic anion transporter 2 (OAT2) in fulfilment of MEA 001. The RMP (version 3.0) is updated accordingly

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

5.3.5. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/II/0025/G, Orphan

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic phase (CP) chronic myelogenous leukaemia (CML) for Bosulif based on study AV001: a multicentre phase 3 randomized, open-label study of bosutinib versus imatinib in adult patients with newly diagnosed CP CML. In addition, the MAH updated the SmPC with safety and efficacy data from study B1871006: a phase 1/2 study of bosutinib in Ph+ leukaemias, and study B1871008: a phase 3 randomized, open-label study of bosutinib versus imatinib in subjects with newly diagnosed CP Ph+ CML. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly. Furthermore, Annex IIIA is brought in line with the latest QRD template (version 10)

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

5.3.6. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0048, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of adult patients with $CD30^+$ cutaneous T-cell lymphoma (CTCL) who require systemic therapy, based on data from study C25001 ('ALCANZA' study): a phase 3 trial of brentuximab vedotin (SGN-35) versus physician's choice (methotrexate or bexarotene) in patients with cd30-positive cutaneous t-cell lymphoma. 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) 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/0002/G

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.1 of the SmPC to reflect the final study results from clinical

study XL184-308: a phase 3, randomized, controlled study of cabozantinib (XL184) *vs* everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior vascular endothelial growth factor (VEGFR) tyrosine kinase inhibitor therapy, to fulfil the condition to the marketing authorisation listed as a post-authorisation efficacy study (PAES) in Annex II. The RMP (version 2.0) is updated accordingly

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

5.3.8. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0060

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to update the information on pregnancy and lactation based on two pharmacokinetic (PK) studies evaluating the transfer of Cimzia into breastmilk (UP0016 study: a multicentre, post-marketing study to evaluate the concentration of certolizumab pegol in the breast milk of mothers receiving treatment with Cimzia phase 1B (clinical pharmacology) study) and via the placenta (UP0017 study: a multicentre post-marketing study to evaluate the placental transfer of certolizumab pegol in pregnant women receiving treatment with Cimzia). The Package Leaflet and the RMP (version 12) are updated accordingly

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

5.3.9. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0065

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of plaque of psoriasis in adult patients. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 13) are updated accordingly

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

5.3.10. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0068

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture as well as the prevention of osteoporosis in women and men at increased risk of fracture who are starting or have recently started long-term glucocorticoid therapy. As a consequence, sections 4.1 and 5.1 of the SmPC are updated to reflect the new indications based on the analysis of the data from the pivotal study glucocorticoid-induced osteoporosis (GIOP): study 20101217: a randomized, double-blind, active controlled study evaluating the efficacy and safety of denosumab compared with risedronate in glucocorticoid-treated individuals. The Package Leaflet and the RMP (version 19.0) are updated accordingly

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

5.3.11. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0055

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with multiple myeloma and in adults with bone metastases from solid tumours for Xgeva. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 24.0) are updated accordingly

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

5.3.12. Idarucizumab - PRAXBIND (CAP) - EMEA/H/C/003986/II/0007

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to reflect the final results from study 1321.3, the RE-VERSE-AD study (reversal effects of idarucizumab on active dabigatran): a phase 3 case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0 g idarucizumab (BI 655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures - RMP category 3 study (MEA 001). The RMP (version 3.0) is updated accordingly. In addition, the MAH took the opportunity to update the immunogenicity section in 5.1 of SmPC and to bring the product information (PI) in line with the latest QRD template (version 10)

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

5.3.13. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0032/G

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of: 1) extension of indication of the approved chronic lymphocytic leukaemia (CLL) indication for Zydelig to include its use in combination with bendamustine and rituximab based on the results of the primary analysis of pivotal study GS-US-312-0115: a phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia. As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (version 2.2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet; 2) submission of the final clinical study report (CSR) for study 101-08: a phase 2, single-arm study evaluated idelalisib monotherapy and in combination with rituximab in elderly subjects with previously untreated CLL or small lymphocytic lymphoma. Inclusion of this report provides additional safety data to support the evaluation of the use of idelalisib in patients with CLL, and fulfilment of PAM008; 3) submission of the final clinical study report (CSR) for study GS-US-312-0123: a phase 3 randomized study evaluated idelalisib in combination with bendamustine and rituximab in subjects with previously untreated CLL

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

5.3.14. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0204

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final registry report from C0168T71 study: a review and analysis of birth outcomes from Swedish, Danish and Finish medical birth registers and an evaluation of pregnancy data from multiple sources. Section 4.6 of the SmPC, the Package Leaflet and the RMP (version 13.2) are updated accordingly. The MAH also took the opportunity to bring the product information in line with the QRD template and update the local representatives of the Package Leaflet

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

5.3.15. Ivabradine - CORLENTOR (CAP) - EMEA/H/C/000598/WS1180/0047; IVABRADINE ANPHARM (CAP) - EMEA/H/C/004187/WS1180/0006; PROCORALAN (CAP) - EMEA/H/C/000597/WS1180/0046

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC with new adverse drug reactions (ADRs): ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. The Package Leaflet and the RMP (version 6) are updated accordingly. In addition, the MAH took the opportunity to align the Product Information in line with the latest QRD template (version 10.0)

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

5.3.16. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0011/G, Orphan

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of hepatocellular carcinoma (HCC) based on pivotal study 304: a multicentre, randomized, open-label, phase 3 trial to compare the efficacy and safety of lenvatinib versus sorafenib in first-line treatment of subjects with unresectable HCC. 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) are updated accordingly; 2) section 4.2 of the SmPC is updated to add that the medicinal product can be administered as a suspension in water or apple juice. In addition, the labelling is updated to include an unique identifier

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

5.3.17. Lumacaftor, ivacaftor – ORKAMBI (CAP) – EMEA/H/C/003954/X/0020

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Extension application (line extension) to add a new strength of film-coated tablets (100 mg lumacaftor/125 mg ivacaftor) for paediatric use from 6 to 11 years of age. The RMP (version 3.1) is updated accordingly

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

5.3.18. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0128

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.6 of the SmPC in order to reflect the final study results from a non-interventional safety study BV29684, which assessed the safety of oseltamivir exposure in pregnant women (RMP category 3 study (MEA099)). The RMP (version 15.0) is updated accordingly

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

5.3.19. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0064/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Grouped variation consisting of: 1) extension of indication for Isentress 100 mg granules for oral suspension to include the treatment of human immunodeficiency virus type 1 (HIV-1) in exposed full-term neonates under the age of 4 weeks based on safety and pharmacokinetic (PK) data from a pivotal phase 1 study IMPAACT P1110 (protocol 080) conducted in a total of 42 HIV-1 exposed full-term infants (defined as ≥37 weeks gestational age and ≥2,000 g), who received either 2 single doses of oral suspension within 48 hours of birth and day 7-10 of age (cohort I), or a multiple-dose regimen of raltegravir over the first 6 weeks of age (cohort II). 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. The provision of the results of IMPAACT P1110 study addresses the final paediatric investigation plan (PIP) measure, i.e. study 4, conducted to generate PK, safety, and tolerability data in HIV exposed neonates and infants <6 weeks of age born to HIV infected mothers; 2) update of the suspension volume from 5 mL to 10 mL for a final suspension concentration of 10 mg/mL to facilitate accurate measurements of the smaller doses required for neonates. As a consequence, the 5 mL syringe supplied in the current commercial kit is replaced with 3 new oral dosing syringes, and sizes (1 mL, 3 mL, and 10 mL) from a different (new) supplier. As a consequence, sections 6.5 and 6.6 of the SmPC are updated. The labelling, the instructions for use in the Package Leaflet and the RMP (version 12.0) are updated accordingly

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

5.3.20. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0060/G, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variation consisting of: 1) extension of indication to include paediatric

population for the use in the paediatric chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients from 1 year of age and older. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 6.5, 6.6 and 8 of the SmPC are updated accordingly. The RMP (version 18) is updated accordingly. Furthermore, the Product information is brought in line with the latest QRD template (version 10); 2) addition of a low-dose romiplostim 125 microgram vial presentation for powder for solution for injection (4 vials pack); 3) addition of a 1 vial pack size of a low-dose romiplostim 125 microgram presentation

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

5.3.21. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/WS1211/0059; RISTABEN (CAP) - EMEA/H/C/001234/WS1211/0051; TESAVEL (CAP) - EMEA/H/C/000910/WS1211/0059; XELEVIA (CAP) - EMEA/H/C/000762/WS1211/0063

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to modify the information on dosing, an existing warning and administration instructions, respectively for use of sitagliptin in patients with type 2 diabetes mellitus (T2DM) and renal impairment. The RMP (version 8) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet for Tesavel and to bring the Product Information in line with the latest QRD template (version 10). Minor editorial changes are also introduced in the Product Information

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

5.3.22. Sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/WS1212/0085/G; JANUMET (CAP) - EMEA/H/C/000861/WS1212/0085/G; RISTFOR (CAP) - EMEA/H/C/001235/WS1212/0072/G; VELMETIA (CAP) - EMEA/H/C/000862/WS1212/0088/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2. and 5.2 of the SmPC in order to modify the information on dosing, and administration instructions respectively for use of sitagliptin/metformin in patients with type 2 diabetes mellitus (T2DM) and moderate renal impairment. The RMP (version 8) is updated accordingly. In addition, section 4.5 of the SmPC is updated to include information on the concomitant use of ranolazine, vandetanib, dolutegravir and cimetidine. Furthermore, the MAH took the opportunity to update the list of local representatives in the Package Leaflet for Efficib and to bring the product information (PI) in line with the latest QRD template (version 10). Minor editorial changes are also introduced in the Product Information

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

5.3.23. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/II/0065

Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on study A6181109: 'a randomized double-blind phase 3 study of adjuvant sunitinib *vs*. placebo in subjects at high risk of recurrent RCC'. The Package Leaflet and the RMP (version 16) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC and Package Leaflet. This procedure fulfils PAM (FU2 22.5). Furthermore, the product information (PI) is brought in line with the latest QRD template (version 10)

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

5.3.24. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0004

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to provide 96 week data from studies GS-US-320-0108 and GS-US-320-0110, listed as category 3 studies in the RMP. GS-US-320-0108 is an ongoing phase 3, randomized, double-blind, non-inferiority study evaluating the safety and efficacy of Vemlidy 25 mg compared with tenofovir disoproxil fumarate 300 mg in hepatitis B e-antigen (HBeAg)-negative subjects with chronic hepatitis B. GS-US-320-0110 is a an ongoing phase 3, randomized, double-blind, non-inferiority study evaluating the safety and efficacy of Vemlidy versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive subjects with chronic hepatitis B. The Package Leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

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

5.3.25. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0072

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of juvenile idiopathic polyarthritis (pJIA) rheumatoid factor positive or negative and extended oligoarthritis in patients of 2 years of age and older, who have responded inadequately to previous therapy with methotrexate. 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 23.0) are updated accordingly

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

6. Periodic safety update reports (PSURs)

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

6.1.1. Alirocumab - PRALUENT (CAP) - PSUSA/00010423/201703

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.2. Alogliptin - VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone - INCRESYNC (CAP) - PSUSA/00010061/201704

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.3. Canagliflozin - INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/201703

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.4. Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/201703

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.5. Certolizumab pegol - CIMZIA (CAP) - PSUSA/00000624/201703

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.6. Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins - CHONDROCELECT[7] - PSUSA/00000273/201604

Applicant: TiGenix NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For information

6.1.7. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/201704

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.8. Dimethyl fumarate - TECFIDERA (CAP) - PSUSA/00010143/201703

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.9. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin) (acellular, component), hepatitis b (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) - HEXACIMA (CAP); HEXAXIM (Art 58[8]); HEXYON (CAP) - PSUSA/00010091/201704

Applicants: Sanofi Pasteur SA (Hexacima, Hexaxim), Sanofi Pasteur Europe (Hexyon)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.10. Empagliflozin - JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) - PSUSA/00010388/201704

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

[7] EC decision dated 29 July 2016 on the MA withdrawal of Chondrocelect

[8] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.11. Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/201704

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.12. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/201704

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.13. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/201704

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.14. Entecavir - BARACLUDE (CAP) - PSUSA/00001224/201703

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.15. Ertapenem - INVANZ (CAP) - PSUSA/00001256/201703

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.16. Everolimus[9] - AFINITOR (CAP) - PSUSA/00010268/201703

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.17. Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/201703

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.18. Fenofibrate, pravastatin - PRAVAFENIX (CAP) - PSUSA/00001363/201704

Applicant: Laboratoires SMB S.A.

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.19. Ferric citrate coordination complex - FEXERIC (CAP) - PSUSA/00010418/201703

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.20. Florbetapir (^{18}F) - AMYVID (CAP) - PSUSA/00010032/201704

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.21. Histamine[10] - CEPLENE (CAP) - PSUSA/00001610/201704

Applicant: Meda AB

PRAC Rapporteur: Almath Spooner

[9] Renal cell carcinoma indication only
[10] Acute myeloid leukaemia indication only

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.22. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/201704

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.23. Insulin degludec, liraglutide - XULTOPHY (CAP) - PSUSA/00010272/201703

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.24. Insulin glulisine - APIDRA (CAP) - PSUSA/00001752/201704

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.25. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/201703

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.26. Irinotecan[11] - ONIVYDE (CAP) - PSUSA/00010534/201704

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

[11] Liposomal formulations only

6.1.27. Japanese encephalitis vaccine (inactivated, adsorbed) - IXIARO (CAP) - PSUSA/00001801/201703

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.28. Mannitol[12] - BRONCHITOL (CAP) - PSUSA/00009226/201704

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.29. Meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to *Corynebacterium diphtheriae* CRM_{197} protein) - MENVEO (CAP) - PSUSA/00001969/201703 (with RMP)

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.30. Meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to tetanus toxoid carrier protein) - NIMENRIX (CAP) - PSUSA/00010044/201704

Applicant: Pfizer Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.31. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201703

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

[12] Cystic fibrosis indication only

6.1.32. Netupitant, palonosetron - AKYNZEO (CAP) - PSUSA/00010393/201704

Applicant: Helsinn Birex Pharmaceuticals Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.33. Nintedanib[13] - OFEV (CAP) - PSUSA/00010319/201704

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.34. Ocriplasmin - JETREA (CAP) - PSUSA/00010122/201704

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.35. Oestrogens conjugated, bazedoxifene - DUAVIVE (CAP) - PSUSA/00010321/201704

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.36. Olaratumab - LARTRUVO (CAP) - PSUSA/00010541/201704

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.37. Para-aminosalicyic acid[14] - GRANUPAS (CAP) - PSUSA/00010171/201704

Applicant: Lucane Pharma

PRAC Rapporteur: Patrick Batty

[13] Respiratory indication only
[14] Centrally authorised product only

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.38. Pitolisant - WAKIX (CAP) - PSUSA/00010490/201703

Applicant: Bioprojet pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.39. Raltegravir - ISENTRESS (CAP) - PSUSA/00010373/201703 (with RMP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.40. Regadenoson - RAPISCAN (CAP) - PSUSA/00002616/201704

Applicant: Rapidscan Pharma Solutions EU Ltd.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.41. Sofosbuvir, ledipasvir - HARVONI (CAP) - PSUSA/00010306/201704

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.42. Tacrolimus[15] - PROTOPIC (CAP) - PSUSA/00002840/201703

Applicant: Leo Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

[15] Topical formulations only

6.1.43. Tocilizumab - ROACTEMRA (CAP) - PSUSA/00002980/201704

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.44. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/201704

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.1.45. Zonisamide - ZONEGRAN (CAP) - PSUSA/00003152/201703

Applicant: Eisai Ltd

PRAC Rapporteur: Almath Spooner

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. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/201702

Applicants: Clinigen Healthcare Ltd (Savene), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

6.2.2. Tenofovir disoproxil - TENOFOVIR DISOPROXIL MYLAN (CAP); TENOFOVIR DISOPROXIL ZENTIVA (CAP), VIREAD (CAP); NAP - PSUSA/00002892/201703

Applicants: Mylan S.A.S (Tenofovir disoproxil Mylan), Zentiva k.s. (Tenofovir disoproxil Zentiva), Gilead Sciences International Limited (Viread), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CHMP

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

6.3.1. Acetyl salicylic acid, atorvastatin, ramipril (NAP) - PSUSA/00010280/201702

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.2. Amoxicillin (NAP) - PSUSA/00000187/201703

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.3. Amoxicillin, clavulanate (NAP) - PSUSA/00000188/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.4. Bicalutamide (NAP) - PSUSA/00000407/201702

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.5. Clodronic acid (NAP) - PSUSA/00000804/201702

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.6. Cromoglicic acid (NAP) - PSUSA/00000883/201702

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.7. Eplerenone (NAP) - PSUSA/00001236/201703

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.8. Fexofenadine (NAP) - PSUSA/00001388/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.9. Fish oil, olive oil, soybean oil, triglycerides medium chain (NAP) - PSUSA/00010223/201702

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.10. Fluconazole (NAP) - PSUSA/00001404/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.11. Fluticasone propionate (NAP) - PSUSA/00001454/201702

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.12. Frovatriptan (NAP) - PSUSA/00001484/201703

Applicant(s): various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.13. Germanium (^{68}Ge) chloride, gallium (^{68}Ga) chloride (NAP) - PSUSA/00010364/201703

Applicant(s): various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.14. Human plasma[16] (NAP) - PSUSA/00001635/201702

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.15. Hydroquinidine (NAP) - PSUSA/00001688/201703

Applicant(s): various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.16. Ibuprofen (NAP); ibuprofen lysine[17] (NAP) - PSUSA/00010345/201702

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.17. Influenza vaccine (split virion, inactivated)[18] (NAP) - PSUSA/00010298/201703

Applicant(s): various

[16] Pooled and treated for virus inactivation only
[17] All indications except ductus arteriosus
[18] Non-centrally authorised products only

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.18. Influenza vaccine (split virion, inactivated, prepared in cell cultures) (NAP) - PSUSA/00010299/201703

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.19. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/201703

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.20. Influenza vaccine (surface antigen, inactivated, adjuvanted) (NAP) - PSUSA/00010300/201703

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.21. Mannitol[19] (NAP) - PSUSA/00010005/201702

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.22. Lanthanum (NAP) - PSUSA/00003175/201703

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Action: For discussion

[19] All indications except cystic fibrosis

6.3.23. Mefloquine (NAP) - PSUSA/00001955/201702

Applicant(s): various

PRAC Lead: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.24. Nabumetone (NAP) - PSUSA/00002101/201703

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.25. Naratriptan (NAP) - PSUSA/00002126/201702

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.26. Pimecrolimus (NAP) - PSUSA/00002411/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.27. Promestriene[20] (NAP) - PSUSA/00009271/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.28. Sodium iodide (^{131}I) (NAP) - PSUSA/00002753/201703

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

[20] Cream and vaginal capsules only

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.29. Technetium (^{99m}Tc) pertechnetate (NAP) - PSUSA/00002866/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.30. Triamcinolone[21] (NAP) - PSUSA/00010292/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.3.31. Zolmitriptan (NAP) - PSUSA/00003150/201703

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/LEG 014

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Cumulative review on severe cutaneous adverse reactions (SCARs) in patients treated with the combination of dabrafenib and trametinib as well as the dabrafenib monotherapy as requested in the conclusions of PSUSA/00010084/201608 adopted in March 2017

Action: For adoption of advice to CHMP

6.4.2. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/LEG 155

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

[21] Intraocular formulations only

Scope: Summary of available data on response to common vaccines, including pneumococcal vaccines, in patients on Remicade (infliximab) for the different approved indications as requested in the conclusions of PSUSA/00010231/201608 adopted in April 2017

Action: For adoption of advice to CHMP

6.4.3. Rituximab – MABTHERA (CAP) –EMEA/H/C/000165/LEG 0096

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Cumulative review of T lymphocyte decrease overall, CD4+ and CD8+ lymphocyte decrease using all relevant data sources (spontaneous reports, clinical trials, literature) split by indication, focussing on data in which rituximab was used as monotherapy. In addition, cumulative review on the incidence of progressive multifocal leukoencephalopathy (PML) in rituximab treated patients stratified by indication and clinical setting using all available information, including an in-depth review of all risk factors for PML in rituximab treated patients, a discussion on the need for PML risk stratification strategies and proposals for a risk stratification algorithm and risk minimisation measures depending on the risk level, as requested in the conclusions of PSUSA/00002652/201611 adopted in June 2017

Action: For discussion

6.4.4. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/LEG 005.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to LEG 005 [detailed review on suicidal ideation and behaviour providing preclinical, clinical, epidemiology and post-marketing data as requested in the conclusions of EMEA/H/C/PSUSA/00010341/201606 adopted by PRAC in January 2017] as per the request for supplementary information (RSI) adopted in June 2017

Action: For adoption of advice to CHMP

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[22]

7.1.1. Blinatumomab – BLINCYTO (CAP) - EMEA/H/C/PSA/S/0024

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsova

Scope: Amendment to a previously agreed protocol for an observational study of blinatumomab safety and effectiveness, utilisation and treatment practices in order to

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

characterise the safety of blinatumomab in routine clinical practice, its effectiveness, medication errors and utilisation [protocol previously adopted within procedure EMEA/H/C/PSP/0041.1 at the September 2016 PRAC meeting]

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

7.1.2. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/PSA/S/0023

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Doris Stenver

Scope: Amendment to a previously agreed protocol for a prospective, multicentre registry (TED-R-13-002) for patients with short bowel syndrome in order to evaluate the long-term safety profile for patients with short bowel syndrome (SBS) who are treated with teduglutide in a routine clinical setting [protocol previously adopted within procedure EMEA/H/C/002345/ANX 003.7 at the May 2014 PRAC meeting]

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[23]

7.2.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 008.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 008.1 including a revised protocol [assessment of a retrospective, observational cohort study protocol, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus (T2DM) treated with canagliflozin-containing medicines or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted in May 2017

Action: For adoption of advice to CHMP

7.2.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 007.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.1 including a revised protocol [assessment of a retrospective, observational cohort study protocol, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus (T2DM) treated with canagliflozin-containing medicines or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted in May 2017

Action: For adoption of advice to CHMP

[23] 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

7.2.3. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/MEA 002.2

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.1 including a revised protocol [PASS protocol for a multiple sclerosis (MS) pregnancy exposure registry study 109MS402 (category 3) aiming at evaluating prospectively pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product] as per the request for supplementary information (RSI) adopted in June 2017

Action: For adoption of advice to CHMP

7.2.4. Florbetapir (^{18}F) - AMYVID (CAP) - EMEA/H/C/002422/MEA 001.3

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 001.2 including a revised protocol [protocol for study I6E-AV-AVBE: a non-interventional PASS evaluating the effectiveness of Amyvid reader training programme, initially endorsed by PRAC/CHMP in December 2013, amended following the conclusions of variation II/22 finalised at CHMP in December 2016 to allow the optional use of quantitative reading as an adjunct to visual reading leading resulting in changes in the reader training programme [final clinical study report (CSR) due date: Q4/2017-Q1/2018] as per the request for supplementary information (RSI) adopted in June 2017

Action: For adoption of advice to CHMP

7.2.5. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/MEA 005

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised protocol (version 3) for a non-imposed, non-interventional PASS safety study: a drug utilisation study (DUS) of Intuniv (guanfacine extended release) in European countries (DUS-database) and protocol (version 1) for a prescriber survey (DUS-survey) conducted in European countries

Action: For adoption of advice to CHMP

7.2.6. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 007

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study SB2-G41-AS; SB2-G42-CD: a prospective observational cohort study in ankylosing spondylitis (AS) and Crohn's disease (CD) for two years to observe safety, efficacy and immunogenicity of Flixabi with active comparator in AS and CD (as requested in the initial opinion)

Action: For adoption of advice to CHMP

7.2.7. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.2

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 046.1 including a revised protocol [a PASS protocol to further investigate and characterise the associations of lenalidomide and tumour flare reaction (TFR)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL) (as per the conclusions of variation II/79) (final clinical study report (CSR) planned in December 2022)] as per the request for supplementary information (RSI) adopted in June 2017

Action: For adoption of advice to CHMP

7.2.8. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/MEA 004.3

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 004.2 including a revised protocol [study XM22-ONC-50002: a multi-country, multicentre, retrospective observational study 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 of the EU to reflect a revised list of countries] as per the request for supplementary information (RSI) adopted in May 2017

Action: For adoption of advice to CHMP

7.2.9. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.3

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.2 [submission of a draft protocol synopsis for an observational retrospective database study based on secondary data analysis using existing databases, as suitable] as per request for supplementary information (RSI) adopted in May 2017

Action: For adoption of advice to CHMP

7.3. Results of PASS imposed in the marketing authorisation(s)[24]

7.3.1. Domperidone (NAP) - EMEA/H/N/PSR/J/0010

Applicant(s): Janssen (on behalf of a consortium)

PRAC Rapporteur: Caroline Laborde

Scope: Results for a PASS imposed as an outcome of the Article 31 referral (EMEA/H/A-31/1365) in September 2014, to assess the effectiveness of the risk minimisation measures

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

of domperidone – a physician survey

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

7.3.2. Flupirtine maleate (NAP) - EMEA/H/N/PSR/J/0007

Applicant(s): Meda Pharma GmbH & Co KG, DE and Meda Pharma - Produtos Farmaceuticos, S.A. PT (Flupigil, Metanor); various (on behalf of a consortium)

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to EMEA/H/N/PSR/J/0007 [final study results for an imposed non-interventional PASS EUPAS11134: a retrospective chart review to evaluate the effectiveness of the risk minimisation measures for the use of flupirtine 100 mg immediate-release capsules in daily practice] as per the request for supplementary information (RSI) adopted by PRAC in July 2017

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

7.3.3. Hydroxyethyl starch (NAP) - EMEA/H/N/PSR/S/0009

Applicant(s): Fresenius Kabi Deutschland GmbH (Volulyte, Voluven)

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to EMEA/H/N/PSR/S/0009 [results of a retrospective drug utilisation study (DUS) to investigate the routine use of hydroxyethyl starch (HES)-containing infusion solutions in hospital settings] as per the request for supplementary information (RSI) adopted by PRAC at its October 2017 meeting

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

7.3.4. Thiocolchicoside (NAP) - EMEA/H/N/PSR/J/0008

Applicant(s): Sanofi (on behalf of a consortium)

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of the effectiveness of risk minimisation measures: a joint PASS survey among healthcare professionals (HCPs) to assess their knowledge and attitudes on prescribing conditions of thiocolchicoside containing medicinal products for systemic use in France, Greece, Italy and Portugal

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

7.4. Results of PASS non-imposed in the marketing authorisation(s)[25]

7.4.1. Dronedarone - MULTAQ (CAP) - EMEA/H/C/001043/II/0039/G

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) submission of the final report from study DRONE_C_05917 (listed as a category 3 study in the RMP): a non-interventional epidemiological study aimed for the surveillance of serious liver injuries/diseases (SLD) with the use of dronedarone using multiple databases in the US, including the addendum on surveillance of interstitial lung disease (ILD); 2) submission of the final report from study DRONE_C_05911 (listed as a category 3 study in the RMP): a non-interventional epidemiological study aimed at studying the concomitant use of dronedarone and digoxin (or statins) and the risk of digitalis intoxication (or rhabdomyolysis and myopathy). The RMP (version 11.0) is updated accordingly

Action: For adoption of PRAC Assessment Report

7.4.2. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1261/0212; LIFMIOR (CAP) - EMEA/H/C/004167/WS1261/0010

Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final report for the anti-rheumatic treatment in Sweden Registry-etanercept cohort study (listed as a category 3 study in the RMP): a non-interventional PASS aimed at providing an assessment of a number of pre-specified safety outcomes for Enbrel as used in the treatment of rheumatoid arthritis (RA) in Sweden, using data from the Antirheumatic Therapies in Sweden (ARTIS) system, in total and from 2006

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. Albiglutide - EPERZAN (CAP) - EMEA/H/C/002735/MEA 005.4

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

Scope: Interim report for a phase IV observational drug utilisation and foetal outcome study PRJ2379/201954 (non-interventional cohort, category 3 in the RMP): a retrospective cohort study to assess the utilisation of albiglutide among women of child bearing age in the US

Action: For adoption of advice to CHMP

[25] 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

7.5.2. Dalbavancin - XYDALBA (CAP) - EMEA/H/C/002840/MEA 002

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Second interim report for microbial surveillance study 14-DUR-01: Surveillance of dalbavancin resistance tested against clinical isolates collected in the United States and Europe in 2015 to determine if resistance to dalbavancin has developed in those organisms specific to the indication in the label for ABSSSI and to determine the mechanism(s) of resistance for isolates identified as being resistant to dalbavancin

Action: For adoption of advice to CHMP

7.5.3. Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/MEA 039.6

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope: Fourth annual report for malignant events associated with efavirenz: Diagnostic Consulting Network (DCN) report as a routine risk minimisation measures

Action: For adoption of advice to CHMP

7.5.4. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.6

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Second interim study report for a US category 3, non-interventional PASS (B2311060 study): active surveillance of conjugated estrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data as per the request for supplementary information (RSI) adopted in December 2016. This interim report includes data through the second year of CE/BZA availability

Action: For adoption of advice to CHMP

7.5.5. Everolimus - VOTUBIA (CAP) - EMEA/H/C/002311/MEA 014.3

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Fourth interim analysis for study CRAD001MIC03 (TOSCA): a safety sub-study classified as a PASS entitled: 'international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex (TSC)'

Action: For adoption of advice to CHMP

7.5.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 005.6

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Seventh annual report from the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT): a long-term observational study of the safety of biologic treatments in rheumatoid arthritis

Action: For adoption of advice to CHMP

7.5.7. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 017.10

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Sixth annual interim report on study CA184-143: a multinational prospective, observational study in patients with unresectable or metastatic melanoma to estimate the incidence and severity of adverse reactions in adult patients treated with ipilimumab in the post-approval setting and to describe the management of adverse reactions and their outcomes in ipilimumab-treated patients in the post-approval setting [final clinical study report (CSR) planned in 2017-4Q/2018]

Action: For adoption of advice to CHMP

7.5.8. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 013.3

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Interim yearly report for study No GS-EU-337-1820: a prospective observational on drug utilisation study (DUS) of ledipasvir/sofosbuvir (LDV/SOF) in adults with hepatitis C virus (HCV)/human immunodeficiency virus (HIV) coinfection

Action: For adoption of advice to CHMP

7.5.9. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/SOB 003.3

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Fourth annual report on the Lomitapide Observational Worldwide Evaluation Registry [LOWER] study collecting information on the safety and effectiveness outcomes of patients treated with lomitapide; and Pregnancy Exposure Registry [PER] study collecting data on pregnancies that occur in women exposed to lomitapide at any time within 30 days prior to the first day of the last menstrual period (LMP) prior to pregnancy or during pregnancy

Action: For adoption of advice to CHMP

7.5.10. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - EMEA/H/C/002705/MEA 002.5

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: First annual interim report for study VFMCRP-MEAF-PA21-01-EU or 'Velphoro Evaluation of Real-life saFety, effectIveness and adherence (VERIFIE)': a non-interventional study to investigate the short and long-term real-life safety, effectiveness, and adherence of Velphoro in patients with hyperphosphataemia undergoing haemodialysis (HD) or peritoneal dialysis (PD)

Action: For adoption of advice to CHMP

7.6. Others

7.6.1. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/REC 001

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Amended protocol for label extension study (R668-AD-1225): an open-label study of dupilumab in patients with atopic dermatitis who participated in previous dupilumab clinical trials

Action: For adoption of advice to CHMP

7.6.2. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/LEG 058.2

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to LEG 058.1 [evaluation of Increlex growth forum database (EU-IGFD) post-marketing surveillance: a multicentre, open-label, non-interventional study based in Europe (ENCEPP/SDPP/7708) collecting long term safety and effectiveness data on mecasermin] as per the request for supplementary information (RSI) adopted in July 2017

Action: For adoption of advice to CHMP

7.6.3. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/MEA 093.6

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: MAH's response to MEA 093.5 on the revised statistical analysis plan (SAP) for the RIVAS study [PASS registry protocol for a long-term surveillance study of rituximab (Mabthera)-treated patients with granulomatosis, with polyangiitis (GPA) or microscopic polyangiitis (MPA) (RIVAS)] as per request for supplementary information (RSI) adopted in June 2017

Action: For adoption of advice to CHMP

7.6.4. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/MEA 017

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the primary clinical study report (CSR) (MEA 017) for study BO28408 (KRISTINE): a randomized, multicentre, open-label, two-arm, phase 3 neoadjuvant study evaluating trastuzumab emtansine plus pertuzumab compared with chemotherapy plus trastuzumab and pertuzumab for patients with human epidermal growth factor 2 (HER2)-positive breast cancer

Action: For adoption of advice to CHMP

7.7. New Scientific Advice

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

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)

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

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

8.1. Annual reassessments of the marketing authorisation

8.1.1. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0055 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.2. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0067 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.3. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0026 (without RMP)

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.4. Modified vaccinia ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/S/0029 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

Action: For adoption of advice to CHMP

8.1.5. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0038 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

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. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0024 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.2.2. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/R/0027 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.2.3. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0027 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Conditional renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3. Renewals of the marketing authorisation

8.3.1. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/R/0021 (without RMP)

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Caroline Laborde

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.2. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/R/0105 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.3. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type B conjugate vaccine (adsorbed) - HEXYON (CAP) - EMEA/H/C/002796/R/0072 (with RMP)

Applicant: Sanofi Pasteur Europe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.4. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type B conjugate vaccine (adsorbed) - HEXACIMA (CAP) - EMEA/H/C/002702/R/0068 (with RMP)

Applicant: Sanofi Pasteur SA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.5. Imatinib - IMATINIB ACTAVIS (CAP) - EMEA/H/C/002594/R/0015 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.6. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/R/0037 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.7. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/R/0024 (with RMP)

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.8. Memantine - MEMANTINE MYLAN (CAP) - EMEA/H/C/002660/R/0010 (without RMP)

Applicant: Generics UK Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.9. Memantine - NEMDATINE (CAP) - EMEA/H/C/002680/R/0008 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.10. Memantine hydrochloride - MEMANTINE LEK (CAP) - EMEA/H/C/002630/R/0009 (without RMP)

Applicant: Pharmathen S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.11. Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/R/0042 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

8.3.12. Telmisartan, hydrochlorothiazide - TOLUCOMBI (CAP) - EMEA/H/C/002549/R/0020 (without RMP)

Applicant: Krka, d.d., Novo mesto

PRAC Rapporteur: Carmela Macchiarulo

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. Leuprorelin acetate (NAP)

Applicant: Astellas Pharma (Eligard, Eliprogel)

PRAC Lead: Martin Huber

Scope: PRAC consultation on the distribution of a direct healthcare professional communication (DHPC) in the context of safety related type II variations (Eligard: DE/H/0580/001-003/II/072; Eliprogel: DE/H/4014/001-003/II/014) to update the product information with additional reconstitution guidance related to safety needle

Action: For adoption of advice to Member States

11.1.2. Misoprostol[26] (NAP)

Applicant: Ferring Läkemedel AB (Misodel)

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on a safety related variation (MRP SE/H/1224/01/II/04/G) updating of the product information[27] and including a direct healthcare professional communication (DHPC) to ensure the correct use of the medicinal product

Action: For adoption of advice to Member States

[26] Vaginal insert formulation, containing 200 µg of misoprostol
[27] Proposal to update SmPC sections 4.2, 4.4, 4.8, 5.1 and the package leaflet

11.2. Other requests

11.2.1. Ethylmorphine (NAP); tramadol (NAP)

Applicant(s): various

PRAC Lead: Julie Williams

Scope: PRAC consultation on the scientific relevance to update the product information of tramadol-containing products and ethylmorphine-containing products regarding the use in the paediatric population given the metabolism of tramadol and ethylmorphine, available safety data, FDA action taken in April 2017 and the changes made in the context of the codeine referral for pain (EMEA/H/A-31/1342) concluded in 2013 as well as in the codeine referral for cough and/or cold (EMEA/H/A-31/1394) concluded in 2015

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 Brexit ancillary working group

PRAC lead: Almath Spooner

Action: For discussion

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMP)

PRAC lead: Brigitte Keller-Stanislawski, Dolores Montero Corominas, Sabine Straus, Ulla Wändel Liminga, Julie Williams

Action: For discussion

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

12.3.1. Scientific advice working party (SAWP) – re-nomination of PRAC representative(s)

Action: For discussion

12.4. Cooperation within the EU regulatory network

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

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

12.7.1. PRAC work plan 2018 – preparation

PRAC lead: June Raine, Almath Spooner

Action: For discussion

12.8. Planning and reporting

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

Action: For discussion

12.8.2. PRAC workload statistics – Q3 2017

Action: For discussion

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections - union procedure on follow-up of pharmacovigilance inspections

EMA lead: Sophia Mylona, Calogero Cannavo, Agata Aleksandra Lazowska

Action: For discussion

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. PSUR roadmap - explanatory note to Good Pharmacovigilance Practice (GVP) module VII on 'Periodic safety update report' and 'Questions & Answers (Q&A)' document to assessors - update

PRAC lead: Menno Van Der Elst, Ulla Wändel Liminga

Action: For discussion

12.10.5. 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 auditable requirement project – update and next steps

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)

None

12.15.1. 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. Strategy on measuring the impact of pharmacovigilance – revised activities

PRAC lead: Marieke de Bruin

Action: For discussion

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

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

Action: For adoption

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:

http://www.ema.europa.eu/ema/