7 May 2015
EMA/PRAC/332948/2015
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 07-10 April 2015

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

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

Of note, these minutes are a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 7-10 April 2015 meeting by welcoming all participants.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members in upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion (see Annex II). No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chair welcomed Miroslava Matíková, replacing Jana Nováková, as the new alternate for Slovakia. The PRAC also noted that Marcel Bruch replaces Jacqueline Genoux-Hames as the member for Luxembourg and that John Joseph Borg is the new alternate for Malta.

1.2. Adoption of agenda of the meeting of 07-10 April 2015

The agenda was adopted with some modifications upon request from the members of the Committee and the EMA secretariat.

1.3. Adoption of minutes of the previous meeting of 09-12 March 2015

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 9-12 March 2015 were published on the EMA website on 20 April 2015 (EMA/PRAC/257790/2015).

2. EU Referral Procedures for Safety Reasons: Urgent EU Procedures

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

3. EU Referral Procedures for Safety Reasons: Other EU Referral procedures

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

3.3.1. Dexibuprofen (NAP); ibuprofen (NAP) - EMEA/H/A-31/1401

Applicant: various

PRAC Rapporteur: Dolores Montero Corominas; PRAC Co-rapporteur: Julie Williams

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for ibuprofen- and dexibuprofen-containing medicines, systemic formulations (see PRAC Minutes March 2015), is to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs, together with the available evidence on the cardiovascular risk of ibuprofen/dexibuprofen at high dose (2,400mg or above per day for ibuprofen, 1,200mg or above per day for dexibuprofen) and the potential interaction with low dose aspirin (acetylsalicylic acid). The evidence considered included the evaluation of the MAHs' responses to the second list of outstanding issues (LoOI) and the responses from the Coxib and traditional NSAID[1] Trialists' (CNT) Collaboration, who had been consulted during the procedure.

Based on the available data from randomised clinical trials, observational studies and individual epidemiological studies, including meta-analysis thereof, the PRAC considered that ibuprofen at high doses is associated with an increased risk of arterial thrombotic events. It was observed that this risk may be similar to that of selective cyclooxygenase

[1] Non-steroidal anti-inflammatory drugs

(COX)-2 inhibitors. The available data did not suggest that ibuprofen at low doses (equal to or below 1,200mg per day) is associated with an increased risk of arterial thrombotic events. In addition, the PRAC considered that although no specific data about the cardiovascular risk of dexibuprofen is available, a similar cardiovascular risk to that of high-dose of ibuprofen is expected when dexibuprofen is used at equipotent doses. With regard to the interaction between ibuprofen/dexibuprofen and acetylsalicylic acid, the PRAC considered that the pharmacodynamic studies available to date showed that ibuprofen/dexibuprofen inhibit the antiplatelet effect of acetylsalicylic acid when it is administered concurrently. Nevertheless, the epidemiological data available to date did not demonstrate a clinically significant interaction but the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid could not be excluded.

Overall, the PRAC concluded that the benefit-risk balance for ibuprofen- and dexibuprofen-containing medicinal products (systemic formulations) remains favourable, subject to the amendment of the information on the risks associated with the use of high doses of ibuprofen/dexibuprofen in certain populations with pre-existing cardiovascular disease and/or risk factors for arterial thrombotic events and the inclusion of some additional information on the potential clinical effect of the pharmacodynamic interaction when taken with acetylsalicylic acid to the product information[2].

Summary of recommendation(s)/conclusions

The PRAC adopted by consensus a recommendation, to be considered by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), to vary the marketing authorisations for ibuprofen- and dexibuprofen-containing medicines – see 'PRAC recommends updating advice on use of high-dose ibuprofen' EMA/217862/2015.

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

None

3.5. Others

None

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Etanercept – ENBREL (CAP)

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

[2] Update of SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a final position

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

Scope: Signal of diarrhoea
EPITT 18257 – New signal
Lead Member State: UK

Background

Etanercept is a tumour necrosis factor alpha (TNF-α) inhibitor indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis (JIA), psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis, and plaque psoriasis under certain conditions.

The exposure for Enbrel, a centrally authorised medicine containing etanercept, is estimated to have been more than 4,500,000 patient-years worldwide, in the period from first authorisation in 2000 to January 2015.

During routine signal detection activities, a signal of diarrhoea was identified by Portugal, based initially on a case reported in Portugal. A further search in EudraVigilance returned over a thousand cases of diarrhoea in association with etanercept.
The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from a systematic review of the literature on the efficacy and harms of disease-modifying anti-rheumatic drugs (DMARDs) included 143 articles, analysing data from clinical trials, observational studies and other systematic reviews and meta-analyses. Authors concluded that diarrhoea had been reported in between 7% and 18% of patients treated with biological DMARDs[4] (Donahue et al. 2008). However, this review did not provide specific data for patients taking etanercept.
Taking into account these data, the fact that the EU product information does not list diarrhoea as an undesirable effect independently from infections, and considering that a causal relationship with etanercept intake cannot be excluded, the PRAC agreed to request the MAH for the originator product to provide a cumulative review of cases of diarrhoea associated with etanercept.

Summary of recommendation(s)

- The MAH for Enbrel (etanercept) should submit to the EMA, with the next PSUR (DLP: 02/02/2015), a cumulative review of cases of diarrhoea in association with etanercept and comment on the confounding role of other medicines, especially methotrexate. The MAH should also propose to update the product information as appropriate.

4.1.2. Leflunomide – ARAVA (CAP)

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Sabine Straus

Scope: Signal of pulmonary hypertension

[4] Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, Hansen RA, Morgan LC, Lohr KN. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med. 2008 Jan 15;148(2):124-34. Epub 2007 Nov 19

EPITT 18221 – New signal
Lead Member State: NL

Background

Leflunomide is an immunosuppressant indicated for the treatment of adult patients with active rheumatoid arthritis as a 'disease-modifying antirheumatic drug' (DMARD) or with active psoriatic arthritis.

The exposure for Arava, a centrally authorised medicine containing leflunomide, is estimated to have been over 2 million patient-years worldwide in the period from first authorisation in 1999 until September 2014.

During routine signal detection activities, a signal of pulmonary hypertension was identified by the EMA, based on eight cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the eight cases of pulmonary hypertension, including three cases also described in the literature[5]. After leflunomide treatment was withdrawn, a positive dechallenge was observed for three cases. The possible confounding factors identified for some cases were noted but it was recognised that a causal relationship could not be excluded. Therefore, the PRAC considered that the MAH for the originator product (Arava) should be requested to provide a cumulative review and analysis of cases of pulmonary hypertension.

Summary of recommendation(s)

- The MAH for Arava (leflunomide) should submit to the EMA, within 90 days, a cumulative review and detailed analysis of all cases of pulmonary hypertension and related terms, including data from pre-clinical and clinical studies, spontaneous reports, ongoing registries and from the literature. In addition, the MAH should discuss the possible pathophysiological mechanism leading to pulmonary toxicity associated with leflunomide. Depending of the outcome of the review, the MAH should propose an update of the product information and the RMP as appropriate. The MAH should propose a Direct Healthcare Professional Communication (DHPC) and a communication plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Sitagliptin - JANUVIA (CAP), RISTABEN (CAP), TESAVEL (CAP), XELEVIA (CAP) Sitagliptin, metformin hydrochloride – EFFICIB (CAP), JANUMET (CAP), RISTFOR (CAP), VELMETIA (CAP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

[5] Alvarez PA et al. Leflunomide-induced pulmonary hypertension in a young woman with rheumatoid arthritis: a case report. Cardiovasc Toxicol. 2012 Jun;12(2):180-3 (EV case 4)
Votavova R et al. Therapy of pulmonary arterial hypertension. Lekarske listy, Extra 2012:10 Toxicology 2012;12:180-183 (EV case 3)
Martinez-Taboada VM et al. Pulmonary hypertension in a patient with rheumatoid arthritis treated with leflunomide. Rheumatology (Oxford). 2004 Nov;43(11):1451-3

Scope: Signal of intestinal obstruction
EPITT 18251 – New signal
Lead Member State: NL

Background

Sitagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor available both as single active ingredient and in fixed combination with metformin, belonging to the class of biguanides, which is indicated for the treatment of type 2 diabetes mellitus under certain conditions.

The exposure for Januvia, Ristaben, Tesavel and Xelevia, centrally authorised medicines containing sitagliptin, is estimated to have been more than 27,020,375 patient years worldwide, in the period from first authorisation in 2007 until August 2014.

During routine signal detection activities, a signal of intestinal obstruction was identified by the EMA, based on thirty-six cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and from the literature, the PRAC agreed that the MAH of Januvia (sitagliptin) should perform a cumulative review of all cases of 'intestinal stenosis and obstruction'. Since for vildagliptin, another DDP-4 inhibitor, eight cases have been identified for which a causal relationship could not be ruled out, the PRAC agreed to extend the review of sitagliptin and intestinal obstruction to vildagliptin.

Summary of recommendation(s)

- The MAH for Januvia (sitagliptin) should submit to the EMA, within 90 days, a cumulative review of all cases of 'intestinal stenosis and obstruction', both from clinical trials and spontaneous data reported with sitagliptin containing products. With this cumulative review, the MAH should also provide a discussion of relevant non-clinical data and scientific literature. Based on the findings, the MAH should discuss the need for an update of the product information and the necessity for any additional pharmacovigilance activities as appropriate. A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.
- The MAH for Galvus (vildagliptin) should submit to the EMA within the next PSUR (DLP: 28/02/2015) a cumulative review of all cases concerning 'intestinal stenosis and obstruction', both from clinical trials and spontaneous data reported with vildagliptin containing products. With this cumulative review, the MAH should also provide a discussion of relevant non-clinical data and scientific literature. Based on the findings, the MAH should discuss the need for an update of the product information and the necessity for any additional pharmacovigilance activities as appropriate.

4.2. New signals detected from other sources

4.2.1. Clopidogrel – ISCOVER (CAP), PLAVIX (CAP)

Applicant: Sanofi-aventis groupe (Iscover), Sanofi Clir SNC (Plavix)

PRAC Rapporteur: Margarida Guimarães

Scope: Signal of drug interaction with grapefruit juice leading to potential impairment of therapeutic efficacy
EPITT 18289 – New signal
Lead Member State: PT

Background

Clopidogrel is a platelet aggregation inhibitor indicated for the prevention of atherothrombotic events in adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease under certain conditions, in adult patients suffering from acute coronary syndrome under certain conditions and for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation.

The exposure for clopidogrel is estimated to have been more than 165 million patients worldwide, in the period from October 2000 to November 2013.

A signal of drug interaction with grapefruit juice leading to potential impairment of therapeutic efficacy was identified by Finland, based on the study by *Holmberg et al.*[6] published in Clinical Pharmacology and Therapeutics in March 2014. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information provided in the literature article by *Holmberg et al.* and considered that this signal merited further review. Therefore, the PRAC requested a cumulative review of all literature and case reports of lack of efficacy/effect, cardiovascular events, and/or drug interaction concerning the concomitant use of clopidogrel and grapefruit juice.

Summary of recommendation(s)

- The MAH for Plavix and Iscover (clopidogrel) should submit to the EMA, within 90 days, a cumulative review of all literature and case reports of lack of efficacy/effect, cardiovascular events, and/or drug interaction concerning the concomitant use of clopidogrel and grapefruit juice. The MAH should make a proposal to update the product information as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Oestrogens, selective oestrogen-receptor modulators and tibolone indicated in menopausal hormone decrease: Bazedoxifene – CONBRIZA (CAP), bazedoxifene, oestrogens conjugated – DUAVIVE (CAP); ospemifene – SENSHIO (CAP); raloxifene - EVISTA (CAP), OPTRUMA (CAP);NAP Chlorotrianisene; conjugated estrogens; dienestrol; diethylstilbestrol; estradiol; Estriol; estrogen; estrone; ethinylestradiol; lasofoxifene; methallenestril; Moxestrol; ormeloxifene; promestriene; tibolone - NAP

Applicant: Pfizer Limited (Duavive, Conbriza), Daiichi Sankyo Europe GmbH (Evista), Eli Lilly Nederland B.V. (Optruma), Shionogi Limited (Senshio), various

[6] Holmberg MT, Tornio A, Neuvonen M, Neuvonen PJ, Backman JT, Niemi M. Grapefruit juice inhibits the metabolic activation of clopidogrel. Clin Pharmacol Ther. 2014 Mar;95(3):307-13

PRAC Rapporteur: Menno van der Elst

Scope: Signal of increased risk of ovarian cancer
EPITT 18258 – New signal
Lead Member State: DE

Background

Bazedoxifene, raloxifene, ospemifene, lasofoxifene, ormeloxifene are selective estrogen receptor modulators (SERMs). Chlorotrianisene, conjugated oestrogens, dienestrol, diethylstilbestrol, estradiol, estriol, estrogen, estrone, ethinylestradiol, methallenestril, moxestrol, promestriene and tibolone are oestrogens or agonists of oestrogen receptors. These active substances are among others contained in medicinal products indicated as hormone replacement therapy in post-menopausal women.

During routine signal detection activities, a recent publication of a meta-analysis in the Lancet[7] on the risk of ovarian cancer with menopausal hormone use was identified by the EMA. Ovarian cancer is a known risk with hormone replacement therapy in post-menopausal women and reflected in the product information. Since the publication may contain additional information, a signal was validated by the EMA. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the meta-analysis of fifty-two epidemiological studies in over 21,000 women based on collected information from epidemiological studies, published and unpublished since 1998, which confirms an increase in the risk of ovarian cancer in current or recent hormone replacement therapy users compared with never-users. The PRAC considered that a review of the meta-analysis was required in order to assess the implications of the new data. As the meta-analysis described hormone replacement therapy medicinal products containing oestrogens and did not address selective oestrogen receptor modulators, the PRAC agreed to focus the review on hormone replacement therapy medicinal products containing oestrogens or oestrogens and progestogens in combination.

The PRAC appointed Menno van der Elst (NL) as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed to further assess the new information from this study, focusing on hormone replacement therapy medicinal products containing oestrogens or oestrogens and progestogens in combination, which were assessed within the new meta-analysis. The PRAC Rapporteur will circulate an assessment report on this signal.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3. Sildenafil – REVATIO (CAP)

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

[7] Collaborative group on epidemiological studies of ovarian cancer. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies; Collaborative Group on Epidemiological Studies of Ovarian Cancer; The Lancet, February, 13, 2015

Scope: Signal of non-arteritic anterior ischaemic optic neuropathy (NAION)
EPITT 18253 – New signal
Lead Member State: NL

Background

Sildenafil is a phosphodiesterase type 5 (PDE5) inhibitor indicated[8] for the treatment of patients with pulmonary arterial hypertension (PAH) under certain conditions.

The exposure for Revatio, a centrally authorised medicine containing sildenafil, is estimated to have been more than 376,000 patient-years worldwide of exposure to sildenafil in this indication in the period from first authorisation to May 2014.

During routine signal detection activities, a signal of non-arteritic anterior ischaemic optic neuropathy (NAION) was identified by the EMA in patients taking sildenafil in the PAH indication, based on a recent publication in the BMJ by *Gaffuri at al.*[9] which triggered a further search in EudraVigilance resulting in a total of five cases of NAION together with twenty-two cases of blindness for taking sildenafil in the PAH indication. NAION is a known adverse drug reaction for sildenafil when used for erectile dysfunction. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and from the literature, the PRAC noted that all patients had underlying cardiovascular risk factors possibly contributing to the ischaemia. Nevertheless, a causal relationship with sildenafil in the PAH indication could not be excluded.
NAION is a rare condition and a cause of decreased vision or loss of vision and has been reported rarely in post-marketing with the use of PDE5 inhibitors, including sildenafil. Product information for sildenafil-containing products includes information relating to this condition, specifying that cases have been reported in patients taking sildenafil for the treatment of male erectile dysfunction. Currently NAION is included in the RMP for Revatio as an important potential risk. Therefore, the PRAC considered that the MAH for Revatio should be requested to provide a cumulative review and analysis of cases of NAION reported with sildenafil.

Summary of recommendation(s)

- The MAH of Revatio (sildenafil) should submit to the EMA, within the next PSUR (DLP: 31/05/2015), a cumulative review of all cases suggestive of non-arteritic anterior ischaemic optic neuropathy (NAION) in the pulmonary hypertension indication, including preclinical and clinical data and provide a detailed discussion of the relevant literature. Based on the findings, the MAH should propose to amend the product information as appropriate.

4.2.4. Temsirolimus – TORISEL (CAP)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

[8] Sildenafil is also indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance (but this indication is excluded from the current signal review)
[9] Gaffuri M, Cristofaletti A, Mansoldo C, Biban P. Acute onset of bilateral visual loss during sildenafil therapy in a young infant with congenital heart disease. BMJ Case Rep. 2014 Jun 3

Scope: Signal of myocardial infarction
EPITT 18263 – New signal
Lead Member State: DE

Background

Temsirolimus is a protein kinase inhibitor indicated for the treatment of renal cell carcinoma under certain conditions and for the treatment of mantle cell lymphoma under certain conditions.

The exposure for Torisel, a centrally authorised medicine containing temsirolimus, is estimated to have been more than 30,600 patients worldwide, in the period from first authorisation in 2007 until October 2011.

A signal of myocardial infarction with temsirolimus was identified by the World Health Organization (WHO) in the WHO Pharmaceuticals Newsletter 2015, No. 1, based on seventeen cases retrieved from their global individual case safety reports (ICSR) database VigiBase. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of myocardial infarction from the WHO Pharmaceuticals Newsletter 2015, No.1, VigiBase and EudraVigilance and agreed that a potential causal association of myocardial infarction and other closely associated terms with temsirolimus should be further discussed by the MAH in the next PSUR.

Summary of recommendation(s)

- The MAH for Torisel should submit to the EMA, within the next PSUR (DLP: 31/03/2015), a cumulative review of cases of myocardial infarction and closely related terms in association with temsirolimus. The MAH should discuss all available cases including the ones mentioned in the WHO Pharmaceuticals Newsletter 2015, No. 1. In addition, the MAH should review clinical trials data and the literature. The MAH should provide the Council for International Organizations of Medical Sciences (CIOMS) forms. If applicable the MAH should make a proposal to update the product information and/or the risk management plan.

4.2.5. Ziprasidone (NAP)

Applicant: Pfizer, various

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)
EPITT 18222 – New signal
Lead Member State: SE

Background

Ziprasidone is an atypical antipsychotic indicated for the treatment of schizophrenia and for the treatment of manic or mixed episodes of moderate severity in bipolar disorder.

During routine signal detection activities, a marketing authorisation holder Actavis, identified three cases describing an association between ziprasidone and drug reaction with eosinophilia and systemic symptoms (DRESS) in its Pharmacovigilance database, which

were also reported in the scientific literature, and brought this signal to the attention of EMA and the Member States where its product is authorised. Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of DRESS reported by Actavis. The PRAC considered also the information that in December 2014, the FDA published a warning about the association between ziprasidone and severe skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) based on six reports and requested the MAH of Geodon (brand name of ziprasidone marketed by Pfizer) to add a new warning for DRESS to the warnings and precautions section of the US product information. As a consequence, the MAH for Zeldox/Geodon is in the process of submitting national variations in the EU to update the product information to include DRESS. Therefore the PRAC agreed that following completion of this variation, MAHs of ziprasidone-containing generic products are expected to align their product information to that of reference product.

Summary of recommendation(s)

- The PRAC agreed that the risk of DRESS should not be handled as a signal. However, following completion of the variation for the reference medicinal product (Zeldox/Geodon), MAHs of ziprasidone-containing generic products are expected to align their product information to that of the reference medicinal product.

4.3. Signals follow-up

4.3.1. Daclatasvir – DAKLINZA (CAP) - EMEA/H/C/003768/SDA/013 Sofosbuvir – SOVALDI (CAP) - EMEA/H/C/002798/SDA/019; sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/SDA/001

PRAC Rapporteur: Margarida Guimarães

Scope: Signal of arrhythmia
EPITT 18177 – Follow-up to January 2015

Background

For background information, see PRAC Minutes January 2015.
The MAHs for Daklinza (daclatasvir), Sovaldi (sofosbuvir) and Harvoni (sofosbuvir/ledipasvir) replied to the request for information on the signal of arrhythmia and the responses were assessed by the Rapporteur.

Discussion

The PRAC assessed cases of severe arrhythmia associated with the use of sofosbuvir (including in combination with ledipasvir) and/or daclatasvir, in particular in patients with established cardiac disorders and treated with bradycardic medications. The PRAC noted that amiodarone was involved in cases most suggestive of a causal relationship.

Summary of recommendation(s)

- The MAHs of Sovaldi, Harvoni and Daklinza should submit to EMA, within 30 days, a variation to amend their product information (warnings and precautions for use, interaction with other medicinal products and other forms of interaction and undesirable effects sections of the SmPC and the package leaflet).

- The MAHs should distribute a direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the PRAC and CHMP.
- The MAHs should closely monitor all cardiac events with and without the concomitant use of amiodarone, beta-blocking agents and other antiarrhythmic agents and present updates of the cumulative safety reviews in the next PSURs. The long half-life of amiodarone should be considered when deciding on cases for review.
- Taking into account that the mechanism for the drug-drug interaction with amiodarone remains unclear, the MAHs should ensure that planned non-clinical studies investigate both the potential pharmacodynamic and pharmacokinetic effects.

For the full PRAC recommendations, see EMA/PRAC/234960/2015 published on the EMA website.

4.3.2. Interferon alfa-2a (NAP) Interferon alfa-2b – INTRONA (CAP) - EMEA/H/C/000281/SDA/053 Interferon beta-1a – AVONEX (CAP) - EMEA/H/C/000102/SDA/086, REBIF (CAP) - EMEA/H/C/000136/SDA/042 Interferon beta-1b - BETAFERON (CAP) - EMEA/H/C/000081/SDA/023, EXTAVIA (CAP) - EMEA/H/C/000933/SDA/021 Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000381/SDA/052 Peginterferon alfa-2b - PEGINTRON (CAP) - EMEA/H/C/000280/SDA/086, VIRAFERONPEG (CAP) - EMEA/H/C/000329/SDA/083 Peginterferon beta-1a – PLEGRIDY (CAP) – EMEA/H/C/002827/SDA/006

Applicant: Biogen Idec (Avonex, Plegridy), Merck Serono Europe Limited (Rebif), Bayer Pharma AG (Betaferon), Novartis Europharm Ltd (Extavia), Merck Sharp & Dohme Limited (IntronA, PegIntron, ViraferonPeg), Roche Registration Ltd (Pegasys, Roferon-A)

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of pulmonary arterial hypertension
EPITT 18059 – Follow-up to December 2014

Background

For background information, see PRAC Minutes September 2014 and PRAC Minutes December 2014.

The MAHs for interferon alfa and beta–containing products provided comments on the wording proposed by the PRAC to reflect in the product information the risk of pulmonary arterial hypertension and these responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the comments received from the MAHs of interferon alfa and beta–containing products on the wording proposed by the PRAC to reflect in the product information the risk of pulmonary arterial hypertension. Based on published clinical and non-clinical data and on spontaneous reports, the PRAC considered that a causal relationship between the use of interferons alfa and beta and the development of pulmonary arterial hypertension, a rare but severe event, could not be excluded. Therefore, the PRAC concluded that the product information should be amended accordingly.

Summary of recommendation(s)

- The MAHs of interferon alfa and beta containing medicinal products should submit within 60 days to the EMA or to the EU NCAs as applicable, a variation to update the product information to include 'pulmonary arterial hypertension' as an undesirable effect with an unknown frequency together with a description of the reported cases.

For the full PRAC recommendations, see EMA/PRAC/234960/2015 published on the EMA website.

4.3.3. Pantoprazole – CONTROLOC CONTROL (CAP) - EMEA/H/C/001097/SDA/014, PANTECTA CONTROL (CAP) - EMEA/H/C/001099/SDA/014, PANTOLOC CONTROL (CAP) - EMEA/H/C/001100/SDA/013, PANTOZOL CONTROL (CAP) - EMEA/H/C/001013/SDA/014, SOMAC CONTROL (CAP) - EMEA/H/C/001098/SDA/019

Applicant: Takeda GmbH

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of subacute cutaneous lupus erythematosus (SCLE)
EPITT 18119 – Follow-up to November 2014

Background

For background information, see PRAC Minutes November 2014.

The MAH for centrally authorised medicines containing pantoprazole replied to the request for information on the signal of subacute cutaneous lupus erythematosus (SCLE) and the responses were assessed by the Rapporteur.

Discussion

Based on the evidence from published literature including an epidemiological study, spontaneous reporting and data submitted by Takeda GmbH (the MAH for centrally authorised medicines containing pantoprazole), the PRAC agreed that there was sufficient evidence that subacute cutaneous lupus erythematosus (SCLE) is likely to be a class effect for proton pump inhibitors (PPIs), although it has been reported only very rarely. Therefore the PRAC considered that the risk of SCLE should be reflected in the product information of all PPIs, with a common wording for prescription and non-prescription PPIs.

Summary of recommendation(s)

- Takeda GmbH, Janssen-Cilag and AstraZeneca UK limited, MAHs for medicinal products containing PPIs should submit to the EMA within 30 days comments on the wording proposed by the PRAC to reflect in the product information the risk of subacute cutaneous lupus erythematosus (SCLE).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: following a request from MAHs which was considered justified, the PRAC agreed for a modification of the timetable for submission of responses by 60 days.

4.3.4. Sodium containing formulations of effervescent, dispersible and soluble medicines (NAP)

Applicant: various

PRAC Rapporteur: Julie Williams

Scope: Signal of cardiovascular events
EPITT 17931 – Follow-up to March 2015

Background

For background information, see PRAC Minutes April 2014, PRAC Minutes September 2014, PRAC Minutes February 2015 and PRAC minutes March 2015.
Following the March 2015 PRAC discussions, it was agreed that it would be important to have input from the CMDh on the implementation of the PRAC recommendations for this signal of cardiovascular risk related to the sodium content of effervescent, soluble and dispersible medicines. The CMDh discussed this at their March meeting and feedback on these discussions was provided to the PRAC and factored into the consideration of this issue.

Discussion

The PRAC was informed of the advice of the CMDh to align the implementation of the recommendation with the future publication of the revised EC guideline on 'Excipients in the label and package leaflet of medicinal products for human use'[10].

The PRAC recommended that the product information of medicines containing sodium should be updated to make the sodium content clearer for patients and healthcare professionals (HCPs). The PRAC noted that currently the Excipients Guideline and the EC Guideline on Summary of Products Characteristics (SmPC) provide advice about how sodium content should be presented in the product information. However, none of these guidelines encourages the amount of sodium contained in a medicine to be presented in a way that is meaningful or immediately understandable for patients or HCPs.

A study by *George et al* [11](BMJ, 2013) showed that high sodium in medicines might increase the risk of cardiovascular disease and in particular hypertension. Whilst the limitations of the study were acknowledged, the association for hypertension was extremely strong and is biologically plausible given the established link between dietary sodium and hypertension. The PRAC considered that this study highlighted that medicines especially effervescent and soluble analgesics can contain high levels of sodium.

Therefore, it was agreed that medicines which contain above a certain threshold should be clearly labelled as being high in sodium. The PRAC recommended that ≥17mmol of sodium from active and/or excipients in the maximum daily dose of a product should be considered as 'high sodium'. This is equivalent to ≥20% of the WHO maximum recommended daily intake for sodium for an adult. Defining this threshold for high sodium in medicines took into account both the recommended daily amounts of dietary sodium and the fact that sodium from medicines is in addition to sodium from the diet. As a general guidance, long term use is to be considered as continuous daily use for > 1 month and regular exposure is to be considered repeated use for more than 2 days every week.

Summary of recommendation(s)

[10] Or 'Excipients Guideline'
[11] George et al. Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study. BMJ2013; 347 doi: http://dx.doi.org/10.1136/bmj.f6954 (published 26 November 2013)

- Having considered the available evidence in the literature, the PRAC agreed that the MAHs with formulations that meet the identified criteria i.e. ≥ 17mmol sodium in the maximum daily dose and that are for long term use or regular exposure, should submit a variation to update the warnings and precautions section of the SmPC, the package leaflet and the label regarding sodium content.[12]. As a general guidance, long term use is to be considered as continuous daily use for > 1 month and regular exposure is to be considered repeated use for more than 2 days every week.
- The Excipients Guideline will be updated with the new sodium-labelling requirements. Therefore, the updates should occur following the publication of the updated Excipients Guideline, either at the subsequent routine regulatory opportunity or within 12 months, of publication of the guideline whichever is sooner.
- The updated wording should be implemented for active ingredients and excipients and should replace any existing wording based on the current Excipients Guideline.

For the full PRAC recommendations, see EMA/PRAC/234960/2015 published on the EMA website.

4.3.5. Trabectedin – YONDELIS (CAP) - EMEA/H/C/000773/SDA/028

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Torbjorn Callreus

Scope: Signal of capillary leak syndrome
EPITT 18115 – Follow-up to December 2014

Background

For background information, see PRAC Minutes December 2014.
The MAH replied to the request for information on the signal of capillary leak syndrome and the responses were assessed by the Rapporteur.

Discussion

In the light of available evidence from case reports in EudraVigilance and from data submitted by the MAH, the PRAC agreed that there is a reasonable possibility of a causal relationship between capillary leak syndrome and the use of trabectedin. Considering the seriousness of the condition, the PRAC concluded that an update of the product information is warranted.

Summary of recommendation(s)

- The MAH for Yondelis (trabectedin), a centrally authorised product, should be requested to submit to the EMA within 60 days a variation to update the product information to include 'capillary leak syndrome' as an undesirable effect with an uncommon frequency.

For the full PRAC recommendations, see EMA/PRAC/234960/2015 published on the EMA website.

[12] High sodium-containing effervescent and soluble products that are most commonly used to treat short term conditions for example cystitis, cold and flu, diarrhoea and bowel preparations would be generally be excluded by the scope as products like these should ordinarily never need to be used on a long term basis, given that the conditions they treat should always be short lived or self-limiting. However, if the indication and/or posology provides for long term or regular use then they should be considered within scope.

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the CHMP on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

Please refer to the CHMP pages for upcoming information (http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights).

5.1.1. Alirocumab - EMEA/H/C/003882

Scope: Treatment of hypercholesterolaemia and mixed dyslipidaemia

5.1.2. Duloxetine - EMEA/H/C/003935, Generic

Scope: Treatment of depressive disorder, diabetic neuropathic pain, anxiety disorder

5.1.3. Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - EMEA/H/C/004042

Scope: Treatment of human immunodeficiency virus (HIV-1)

5.1.4. Evolocumab - EMEA/H/C/003766

Scope: Treatment of hypercholesterolaemia and mixed dyslipidaemia and homozygous familial hypercholesterolaemia

5.1.5. Pembrolizumab - EMEA/H/C/003820

Scope: Treatment of melanoma

5.1.6. Sebelipase alfa - EMEA/H/C/004004, Orphan

Applicant: Synageva BioPharma Ltd

Scope: Treatment of lysosomal acid lipase (LAL) deficiency

5.1.7. Susoctocog alfa - EMEA/H/C/002792

Scope: Treatment of haemophilia A

5.2. Medicines in the post-authorisation phase – PRAC-led procedures

See Annex I 14.2.

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

5.3.1. Capecitabine – XELODA (CAP) - EMEA/H/C/000316/II/0067

Applicant: Roche Registration Limited

PRAC Rapporteur: Martin Huber

Scope: Update of SmPC sections 4.3 and 4.4 in order to delete the contraindication regarding patients with known dihydropyrimidine dehydrogenase (DPD) deficiency and add information with regard to patients with DPD deficiency. The package leaflet is updated accordingly

Background

Capecitabine is a cytostatic indicated for the adjuvant treatment of patients following surgery for stage III (Dukes' stage C) colon cancer, for the treatment of metastatic colorectal cancer and for first-line treatment of advanced gastric cancer in combination with a platinum based regimen. Capecitabine is also indicated in combination for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy as well as indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer under certain conditions.

The CHMP is evaluating a type II variation procedure for Xeloda, a centrally authorised product containing capecitabine, to delete the contraindication regarding patients with known dihydropyrimidine dehydrogenase (DPD) deficiency and add information with regard to patients with DPD deficiency. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 7 for Xeloda (capecitabine) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that an updated risk management plan and satisfactory responses to the questions detailed in the assessment report are submitted.
- The PRAC supported distributing a DHPC according to an agreed communication plan and considered that some refinements were needed. Further amendments following the discussion at CHMP of the clinical aspects will be necessary.

5.3.2. Dimethyl fumarate – TECFIDERA (CAP) - EMEA/H/C/002601/WS0689/0011/G

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Update of SmPC sections 4.4 to add a recommendation to consider interruption of treatment in patients with low lymphocyte counts (<0.5 x 109/L) persisting for more than six months and to monitor lymphocyte counts until recovery. Update of SmPC section 4.8 with information on observed low lymphocyte counts in clinical studies with Tecfidera and the risk of progressive multifocal leukoencephalopathy (PML) in the setting of severe and prolonged lymphopenia. Furthermore, the due dates of two commitments as part of the RMP have been revised

Background

For background information, see PRAC Minutes February 2015.

Further information as requested by the PRAC was received and assessed by the PRAC Rapporteur. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this worksharing variation.

Summary of advice

- The RMP version 6.2 for Tecfidera (as well as Fumaderm and Fumaderm Initial) was not considered acceptable in the context of the ongoing worksharing[13] variation under CHMP's evaluation. The PRAC agreed that the MAH should provide an updated RMP and satisfactory responses to the request for supplementary information.
- The PRAC considered that the MAH should propose adequate pharmacovigilance activities to further characterise the risk of progressive multifocal leukoencephalopathy (PML) taking into consideration possible key risk factors, such as exposure time, John Cunningham virus (JCV) serology and prior immunosuppressant use. The MAH should also propose adequate additional risk minimisation measures, such as educational material. Moreover, the PRAC underlined the need to have a complete overview of all PML cases, including those associated with off-label and unlicensed use in the treatment of psoriasis, and considered that the MAH should provide further clarity on the magnitude of the risk for developing PML. Finally, the MAH should give consideration to how emerging cases inform thinking around risk factors for development of PML with dimethyl fumarate including the case recently published in the New England Journal of Medicine (NEJM)[14] in April 2015.

The PRAC acknowledged that any final recommendation on the RMP will be informed by the CHMP's changes to the product information and following the consultation of an ad-hoc expert group in the field as agreed by the CHMP (see CHMP Minutes February 2015).

6. Periodic Safety Update Reports (PSURs)[15]

6.1. PSUR procedures including Centrally Authorised Products only

6.1.1. Afatinib – GIOTRIF (CAP) - EMEA/H/C/002280/PSUSA/10054/201409

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Afatinib is a protein kinase inhibitor indicated for the treatment of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Giotrif, a centrally authorised medicine containing afatinib, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

[13] Article 20 of Commission Regulation (EC) N° 1234/2008
[14] PML in a patient without severe lymphocytopenia receiving dimethyl fumarate, Nieuwkamp et al, N Engl J Med 2015; 372: 1474-1476
[15] PRAC is responsible for adopting recommendations are on PSUR assessment for single centrally authorised product and of EU PSUR single assessment. The EU PSUR single assessment, referred also as PSUSA, is the assessment of PSURs for medicinal products subject to different marketing authorisations containing the same active substance or the same combination of active substances

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Giotrif (afatinib) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a summary of all cases of pancreatitis reported in clinical trials, including information on seriousness and investigator assessment of relatedness with study drug, any available information on dechallenge/rechallenge reactions, time to onset, laboratory or radiological assessments, outcome and an MAH assessment of each case with regard to relatedness. In addition, full narratives of all cases should be provided, including also all available post-marketing cases. The MAH should provide their conclusion on whether pancreatitis should be included as an adverse drug reaction in the product information, and upgraded from an important potential risk to an important identified risk in the RMP. In addition, the MAH should also discuss whether there is a pharmacological/biological rationale to address gastrointestinal ulceration in the context of gastrointestinal perforation (important potential risk in the risk management plan) in future PSURs. Finally, the MAH should continue to monitor off-label use in breast cancer as well as use in combination with chemotherapy and provide all available information (e.g. post marketing reports, sales data, and literature reports) on this type of use outside of the authorised EU indication.
- The MAH should be requested to update the RMP within 60 days to include 'poor survival following off-label use in breast cancer' and 'use in combination with chemotherapy' as important potential risks.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.2. Aliskiren - RASILEZ (CAP) - EMEA/H/C/000780/PSUSA/00089/201409; aliskiren, amlodipine – RASILAMLO (CAP) - EMEA/H/C/002073/PSUSA/00089/201409; aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/PSUSA/00089/201409

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Aliskiren is a selective direct inhibitor of human renin, indicated in the treatment of essential hypertension in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rasilez, Rasilamlo and Rasilez HCT, centrally authorised medicines containing aliskiren, aliskiren/amlodipine and aliskiren/hydrochlorothiazide respectively, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Rasilez (aliksiren), Rasilamlo (aliskiren/amlodipine) and Rasilez HCT (aliksiren/ hydrochlorothiazide) in the approved indications remains favourable.
- Nevertheless, the product information of the medicinal products containing aliskiren, should be updated to include hyponatraemia and dyspnoea as undesirable effects with an unknown frequency. For the fixed dose combination products affected by this procedure (aliskiren/amlodipine and aliskiren/ hydrochlorothiazide), in case the event occurred with unknown frequency for one of the components, and a known frequency was assigned for another component or a combination, the event is only listed once under the already known frequency and an index is added to indicate the component with which the event occurs. Therefore the current terms of the marketing authorisations should be varied[16].
- The MAH should submit a variation to update the sections on 'posology and method of administration', 'interaction with other medicinal products and other forms of interaction' and 'pharmacokinetic properties' of the product information based on the results of study CSPP100A2413.
  The MAH should submit a variation to reflect in the product information of aliskiren-containing medicinal products the higher risk of angioedema when aliskiren is co-administered with angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers based on the results from study SPP100A2415 and as recommended by the PRAC and the CHMP in September 2014 as an outcome of the worksharing procedure WS/561[17].
- In the next PSUR, the MAH should closely monitor cases of gastritis, pancreatitis, syncope/loss of consciousness with hypotension and injury, cardiovascular events only from randomized clinical trials, acute myocardial infarction only from randomized clinical trials, cardiac arrhythmia in randomized clinical trials and epidemiologic studies, gastrointestinal haemorrhage for cases with diarrhoea, and cases of concomitant administration of non-steroidal anti-inflammatory drugs, hepatitis and chyloperitoneum, fatal cases for cardiovascular events, colorectal hyperplasia, hyperkalaemia for greater severity and for renal impairment, renal dysfunction and gastrointestinal bleeding with diarrhoea and with concomitant use of non-steroidal anti-inflammatory drugs, drug-drug interaction with furosemide, severe renal dysfunction, hyponatraemia, dyspnoea, cardiovascular morbidity and mortality reduction, long term data on concomitant use of calcium channel blockers, long term data on use of angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, long term data in the subgroup of patients with eGFR[18]< 60 ml/min, long term data in the subgroup of patients with pre-existing cardiovascular disease, hepatic impairment, very elderly (> 75-years-old), and colorectal hyperplasia.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[16] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[17] Final study report for the non-interventional study CSPP100A2415: a cohort study including a nested case-control analysis using data from the United States IMS PharMetrics PlusTM health plan claims database – assessing the prevalence and incidence of angioedema among patients with hypertension treated with aliskiren or other antihypertensive medications in the US
[18] Estimated glomerular filtration rate (eGFR)

6.1.3. Alogliptin - VIPIDIA (CAP) - EMEA/H/C/002182/PSUSA/10061/201410; alogliptin, metformin - VIPDOMET (CAP) - EMEA/H/C/002654/PSUSA/10061/201410; alogliptin, pioglitazone – INCRESYNC (CAP) - EMEA/H/C/002178/PSUSA/10061/201410

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Alogliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated for the treatment of type 2 diabetes mellitus under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vipidia, Vipdomet and Incresync, centrally authorised medicines containing alogliptin, alogliptin/metformin and alogliptin/pioglitazone respectively, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Vipidia (alogliptin), Vipdomet (alogliptin/metformin) and Incresync (alogliptin/pioglitazone) in the approved indications remains favourable.
- The current terms of the marketing authorisations should be maintained.
- The MAH should be requested to submit to EMA within 60 days a discussion on the feasibility of amending the ongoing drug utilisation study for pioglitazone-containing medicinal products (study Pioglitazone_5019) instead of cancelling the requested drug utilisation study to measure the effectiveness of the risk minimisation for Incresync. With this discussion on feasibility, the MAH should submit a revised protocol for study Pioglitazone_5019 and an updated RMP for Incresync as appropriate.
  In addition due to uncertainties with regard to an association between alogliptin and hospitalisation for heart failure, this safety concern should be kept under review. Therefore the MAH should submit to EMA, within 60 days, a revised RMP for all alogliptin-containing medicinal products to include heart failure as an important potential risk and to propose adequate pharmacovigilance activities.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.4. Bivalirudin – ANGIOX (CAP) - EMEA/H/C/000562/PSUSA/00421/201409

Applicant: The Medicines Company UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Bivalirudin is a direct and specific thrombin inhibitor indicated as an anticoagulant in adult patients undergoing percutaneous coronary intervention under certain conditions and in the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction planned for urgent or early intervention.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Angiox, a centrally authorised medicine containing bivalirudin, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Angiox (bivalirudin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide an update on intracoronary thrombosis during percutaneous coronary intervention following stasis, slow flow or dissection. The MAH should continue to closely monitor acute stent thrombosis following percutaneous coronary intervention.
- The MAH should submit to EMA within 90 days a variation to amend the posology in patients undergoing percutaneous coronary intervention based on available clinical trial data. This variation should address all patients and include all data from the EUROpean aMbulance Acs angioX trial (EUROMAX) and the Bivalirudin in Acute Myocardial Infarction *vs* Glycoprotein IIb/IIIa and Heparin Undergoing Angioplasty (BRIGHT) trials, a review of the literature and post-marketing data. An update of the RMP should also be included within this variation application. In addition, the MAH should address the potential impact of recent advances in stent technology on the use of bivalirudin.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.5. Dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/PSUSA/00918/201409

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Dabigatran is a direct thrombin inhibitor indicated for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) under certain conditions and the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Pradaxa, a centrally authorised medicine containing dabigatran, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Pradaxa (dabigatran) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should report specifically on the clinical outcome of all pregnancies that come to its attention where women have been treated with dabigatran. The MAH should provide a detailed review of serious ischaemic colitis cases. In addition, the MAH should provide a detailed review of post-marketing cases of lack of efficacy as no information about possible drug interaction is available. The MAH should also provide a detailed analysis of all reported cases of leucocytoclastic vasculitis. Moreover, the MAH should provide a detailed cumulative review and analysis of reported cases of dabigatran associated renal disorders, in particular renal failure. Impairment of renal function should be considered as a potential risk of dabigatran. Finally, the MAH should submit a safety/efficacy review and analysis of all cases with a history of gastric bypass surgery (malabsorption/lack of efficacy). The MAH should also discuss the benefit-risk balance of dabigatran in this population.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.6. Denosumab – PROLIA (CAP) - EMEA/H/C/001120/PSUSA/00954/201409

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Denosumab is a human monoclonal antibody used for the treatment of osteoporosis under certain conditions and bone loss in men with prostate cancer under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prolia, a centrally authorised medicine containing denosumab, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Prolia (denosumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include in the posology and method of administration section that patients treated with Prolia should be given the package leaflet and the patient reminder card, to reflect the current knowledge on osteonecrosis of the jaw as set out in the warnings and undesirable effects sections. Therefore the current terms of the marketing authorisation(s) should be varied[19]. See

[19] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

'PRAC recommends further measures to minimise risk of osteonecrosis of the jaw with bisphosphonate medicine' EMA/169618/2015.

- Moreover, the conditions of the marketing authorisation should be amended regarding the patient information pack (additional risk minimisation measure). The patient information pack should include the package leaflet and a patient reminder card on osteonecrosis of the jaw.
- In the next PSUR, the MAH should discuss the available data on the safety of treatment with Prolia if preceded by treatment with bisphosphonates. The optimal cumulative treatment duration with Prolia alone and with bisphosphonates in combination with Prolia should be discussed by the MAH in light of any new information from clinical trials, epidemiological studies and post-marketing experience on the increased risk of osteonecrosis of the jaw with longer exposure. The MAH should also comment on whether there is a need to update the product information. The MAH should provide a cumulative review of cases of systemic lupus erythematous. The MAH should provide a cumulative review of diarrhoea and discuss including this adverse event in the product information. Finally, the MAH should provide a cumulative review of hyperhidrosis as well as a discussion on whether the product information should be appropriately updated.
- The MAH should submit to the EMA, within 60 days, a revised RMP to reflect the introduction of the reminder card on osteonecrosis of the jaw as a new additional risk minimisation measure and should propose indicators to measure the effectiveness of this new measure.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.7. Denosumab – XGEVA (CAP) - EMEA/H/C/002173/PSUSA/09119/201409

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Denosumab is a human monoclonal antibody indicated in the prevention of skeletal related events in adults with bone metastases from solid tumours under certain conditions and in the treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xgeva, a centrally authorised medicine containing denosumab, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Xgeva (denosumab) in the approved indication(s) remains favourable.

- Nevertheless, the product information should be updated to include a new contraindication in case of unhealed lesions from dental or oral surgery, to include in the posology and method of administration section that patients treated with Xgeva should be given the package leaflet and the patient reminder card, and to reflect the current knowledge on osteonecrosis of the jaw as set out in the warnings and undesirable effects sections. Therefore the current terms of the marketing authorisation(s) should be varied[20]. See 'PRAC recommends further measures to minimise risk of osteonecrosis of the jaw with bisphosphonate medicine' EMA/169618/2015.
- The MAH should inform healthcare professionals of these changes via a Direct Healthcare Professional Communication (DHPC).
- The conditions of the marketing authorisation should be amended regarding the patient information pack (additional risk minimisation measure). The patient information pack should include the package leaflet and a patient reminder card on osteonecrosis of the jaw.
- In the next PSUR, the MAH should discuss the available data on the safety of treatment with Xgeva if preceded by treatment with bisphosphonates. The optimal cumulative treatment duration with Xgeva alone and with bisphosphonates in combination with Xgeva should be discussed by the MAH in light of any new information from clinical trials, epidemiological studies and post-marketing experience of the increased risk of osteonecrosis of the jaw with longer exposure. The MAH should also comment on whether there is a need to update the product information. The reporting rates for cases of osteonecrosis of the jaw should be closely followed and discussed in the future PSURs. As the number of cases of osteonecrosis of the jaw or osteonecrosis that fail adjudication is substantial, a detailed account of the reasons for failing adjudication should be presented by the MAH. The MAH should review and discuss the reported cases of osteosclerosis. Finally, the MAH should provide an in-depth discussion regarding infections, including whether the product information should be appropriately updated.
- The MAH should submit to the EMA, within 60 days, a revised RMP to reflect the introduction of the reminder card on osteonecrosis of the jaw as a new additional risk minimisation measure and should propose indicators to measure the effectiveness of this new measure.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.8. Dibotermin alfa – INDUCTOS (CAP) - EMEA/H/C/000408/PSUSA/01034/201409

Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUR/PSUSA procedure

[20] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Background

Dibotermin is an osteoinductive protein that results in the induction of new bone tissue at the site of implantation, indicated for single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease under certain conditions and for the treatment of acute tibia fractures in adults under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of InductOs, a centrally authorised medicine containing dibotermin, and issued a recommendation on its marketing authorisation(s).

The PRAC noted that after data lock point of this PSUR, a FDA warning against off-label use of dibotermin alfa in children was published on 21 January 2015.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of InductOs (dibotermin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- Since the data provided with this PSUR indicate that the product is sometimes used in children in the European Union, albeit to a limited extent, the MAH should discuss the relevance of the FDA information on paediatric use for the EU marketing authorisation of dibotermin alfa and whether any changes to the product information or RMP would be justified.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.9. Iloprost – VENTAVIS (CAP) - EMEA/H/C/000474/PSUSA/01724/201409

Applicant: Bayer Pharma AG

PRAC Rapporteur: Arnaud Batz

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Iloprost is a synthetic prostacyclin analogue indicated for the treatment of adult patients with primary pulmonary hypertension, classified as New York Heart Association (NYHA) functional class III, to improve exercise capacity and symptoms.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ventavis, a centrally authorised medicine containing iloprost, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ventavis (iloprost) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.

- In the next PSUR, the MAH should include all worldwide patient support programs in the section on non-interventional studies as cases from these programs are considered solicited. If the designs of the support programme are similar in all countries, a global description of safety findings would be more relevant. Moreover, fatal cases reported from patient support programs are mostly poorly documented and no relationship with the use of Ventavis could be drawn. Nevertheless, the MAH should provide an analysis comparing the incidence of death observed in these patient support programs with the known epidemiology for pulmonary arterial hypertension (PAH). The MAH should provide an updated cumulative review for each signal considered as ongoing (i.e. hearing loss, pulmonary oedema, left heart failure decompensation, respiratory tract infections and fatal cases). The MAH should also provide an analysis of the incidence of respiratory tract infections observed in iloprost observational studies (including patient support program) compared with the incidence of respiratory tract infections in the pulmonary arterial hypertension population if such data are available. Regarding the signal of pulmonary embolism, the MAH should provide further information and discuss the pathophysiology in the context of Ventavis use, considering that it appears inconsistent with its claimed antiplatelet aggregation properties. Finally the MAH is requested to submit a summary of the final study report of the AC-063A501-Respire registry.
- The MAH should submit to EMA, within 60 days, a sub-analysis of the Registry to EValuate Early And Long-term PAH and PAH disease management (REVEAL registry) within patients with comparable characteristics regarding age, sex and disease characteristics (New York Heart Association functional group) by matching Ventavis patients with comparable non Ventavis patients (at least 1:1) as requested in the previous PSUR and within this PSUR.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.10. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/PSUSA/09200/201409

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Ipilimumab is a monoclonal antibody enhancing the T-cell mediated immune response indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yervoy, a centrally authorised medicine containing ipilimumab, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Yervoy (ipilimumab) in the approved indication(s) remains favourable.

- Nevertheless, the product information should be updated to include in the current warning on immune-related skin adverse reactions that new cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported and also to recommend caution in patients with a history of severe or life-threatening adverse skin reactions on a prior cancer immune stimulatory therapy. In addition, DRESS should be included as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should closely monitor ipilimumab patients predisposed for hypersensitivity reactions, and also posterior reversible encephalopathy syndrome. Finally the MAH should provide a review of cases of rheumatoid arthritis including a discussion on the available information on the patient's medical history.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.11. Lapatinib – TYVERB (CAP) - EMEA/H/C/000795/PSUSA/01829/201409

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Lapatinib is a protein kinase inhibitor indicated for the treatment of adult patients with breast cancer whose tumours overexpress the human epidermal growth factor receptor 2 (HER2) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tyverb, a centrally authorised medicine containing lapatinib, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Tyverb (lapatinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning that serious cutaneous reactions have been reported with lapatinib and to include serious cutaneous reactions as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[22].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from

[21] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[22] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.12. Pneumococcal polysaccharide conjugate vaccine (7-valent, adsorbed) – PREVENAR (CAP) - EMEA/H/C/000323/PSUSA/02452/201408

Applicant: Pfizer Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Pneumococcal polysaccharide conjugate vaccine (7-valent, adsorbed) is a vaccine indicated for active immunisation against disease caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (including sepsis, meningitis, pneumonia, bacteraemia and acute otitis media) in infants and children from 2 months up to 5 years of age.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prevenar, a centrally authorised medicine containing pneumococcal polysaccharide conjugate vaccine (7-valent, adsorbed), and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Prevenar (pneumococcal polysaccharide conjugate vaccine (7-valent, adsorbed)) in the approved indication(s) remains favourable.
- Nevertheless, Annex II of the marketing authorisation(s) should be updated to reflect the next PSUR submission. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should consider Kawasaki's disease as a safety signal for pneumococcal 7-valent conjugate (vaccine) and discuss this safety topic in the signal section in view of the reported cases of Kawasaki's disease, some of which developed after vaccination with pneumococcal 7-valent conjugate (vaccine) only. The MAH should further discuss the risk of hypotonic-hyporesponsive episode when pneumococcal 7-valent conjugate (vaccine) is co-administered with a Diphteria-Tetanus-whole cell Pertussis – Haemophilus influenzae type b vaccine.

The frequency of PSUR submission should be revised from two-yearly to ten-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.13. Strontium ranelate – OSSEOR (CAP) - EMEA/H/C/000561/PSUSA/09301/201409; PROTELOS (CAP) - EMEA/H/C/000560/PSUSA/09301/201409

Applicant: Les Laboratoires Servier

[23] Update of Annex II. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Strontium ranelate is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures and the treatment of severe osteoporosis in adult men at increased risk of fracture.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Protelos and Osseor, centrally authorised medicines containing strontium ranelate, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Protelos and Osseor (strontium ranelate) in the approved indications remains favourable.
- The current terms of the marketing authorisations should be maintained.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly. The justification for a change to a three-yearly PSUR frequency is that the safety profile is considered well characterized, and that the effectiveness of the recently implemented additional risk minimisation measures are to be reviewed annually via the PASS programme in place.

6.1.14. Sulphur hexafluoride – SONOVUE (CAP) - EMEA/H/C/000303/PSUSA/02822/201409

Applicant: Bracco International B.V.

PRAC Rapporteur: Arnaud Batz

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Sulphur hexafluoride is an ultrasound contrast agent used with ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal to noise ratio.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of SonoVue, a centrally authorised medicine containing sulphur hexafluoride, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of SonoVue (sulphur hexafluoride) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to remove the contraindication in pregnant and lactating women from the contraindications section and to add that as a precaution, it is preferable to avoid treatment with SonoVue during pregnancy and that breastfeeding can be resumed two to three hours after

administration of SonoVue. In addition, myocardial infarction and myocardial ischaemia should be included as undesirable effects with an unknown frequency. The frequency of the undesirable effects of chest pain, fatigue, pain and hypersensitivity should be amended to rare and the frequency of the undesirable effect of abdominal pain should be amended to uncommon. Finally the description of the undesirable effect of hypersensitivity has been amended.

- In the next PSUR, the MAH should provide a cumulative review of vomiting and convulsions to assess if there is a causal relationship between SonoVue treatment and these adverse events. Based on the outcome of this review, a proposal for changes in the product information should be provided. The MAH should provide a discussion on the effectiveness of the recent updates of the product information sections on warnings and undesirable effects (variation II/25[24], positive CHMP opinion adopted in May 2014) combined with the education-based risk minimisation strategy implemented in 2014. The MAH should provide a discussion on reported adverse events occurring in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease with a comparison of reporting rates (specifically in patients with conditions suggesting cardiovascular instability) when the contraindication was in effect versus when the contraindication was removed. The MAH should provide the method of calculation leading to the frequency modification of pruritus (from uncommon to rare). Finally, the MAH should provide a detailed and robust justification for proposing to remove the following adverse drug reactions from the product information: sinus headache, blood glucose increased, pharyngitis and insomnia.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.15. Teriflunomide – AUBAGIO (CAP) - EMEA/H/C/002514/PSUSA/10135/201409

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Teriflunomide is a selective immunosuppressant indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aubagio, a centrally authorised medicine containing teriflunomide, and issued a recommendation on its marketing authorisation(s).

[24] Variation II/25: deletion in section 4.3 of the contraindications for use in patients with acute coronary syndrome or clinically unstable ischaem disease and the insertion of these patient populations into Section 4.4 Special warnings and precautions for use, with editing of the wording These changes are also reflected in revised wording for the PIL

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Aubagio (teriflunomide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated in the warnings and precautions for use section and in the undesirable effects sections to include that cases of severe skin reactions have been reported with teriflunomide in post-marketing settings. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should discuss an update of the product information section on undesirable effects to include: pancreatitis, headache, creatinine phosphokinase increase (CPK) increase, arthralgia, and an update of the same section together with a warning on Stevens-Johnson syndrome. In addition, the MAH should further discuss adverse reactions such as cough and dyspnoea in the context of potential signs of interstitial lung disease. The MAH should also discuss if diabetes mellitus/hyperglycaemia should be included in the product information. The MAH should discuss a class effect of immunomodulating substances and the influence on mood within the next PSUR. A substantial number of cases have been identified for the following events, which also reveal some evidence for a causal association with teriflunomide, but have not been discussed within this PSUR: pneumonia, bronchopneumonia and lower respiratory tract infection; sepsis; convulsion and complex partial seizure; chest discomfort and chest pain. Finally, the MAH should discuss all cases which might be suggestive of angioedema.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.16. Trabectedin – YONDELIS (CAP) - EMEA/H/C/000773/PSUSA/03001/201409

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUR/PSUSA procedure

Background

Trabectedin is an antineoplastic agent indicated for the treatment of adult patients with advanced soft tissue sarcoma under certain conditions and for the treatment of patients with relapsed platinum-sensitive ovarian cancer under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yondelis, a centrally authorised medicine containing trabectedin, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Yondelis (trabectedin) in the approved indication(s) remains favourable.

[25] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to include a cross reference to the warnings and precautions for use section in the method of administration for the recommendation to use a central venous access. Therefore the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, the MAH should review the concomitant use of trabectedin and doxorubicin alongside the review of cardiomyopathy and heart failure. The MAH should monitor embolism, phlebitis, and thrombosis. The MAH should review drug interactions with aprepitant in view of a possible extension of the current wording in section 4.5 of the SmPC. The MAH should closely monitor rhabdomyolysis and renal failure.
- The MAH should be requested to revise the overall pregnancy information (including section 5.3 Pre-clinical safety data of the SmPC) in the product information in line with the Quality Review of Documents (QRD) and SmPC guidelines, as well as the Guideline on pregnancy labelling (EMEA/CHMP/203927/2005) in a separate variation upon submission of the non-clinical study report for study PBC040-101.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.2. PSUR procedures including Centrally Authorised Products (CAPs) and Nationally Authorised Products (NAPs)

6.2.1. Leflunomide – ARAVA (CAP) - EMEA/H/C/000235/PSUSA/01837/201409; LEFLUNOMIDE MEDAC (CAP) - EMEA/H/C/001227/PSUSA/01837/201409; LEFLUNOMIDE WINTHROP (CAP) - EMEA/H/C/001129/PSUSA/01837/201409; NAP

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Leflunomide is a selective immunosuppressant indicated for the treatment of adult patients with active rheumatoid arthritis as a disease-modifying antirheumatic drug (DMARD), and for the treatment of active psoriatic arthritis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Arava, Leflunomide Medac and Leflunomide Winthrop, centrally authorised medicines containing leflunomide, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Arava, Leflunomide Medac and Leflunomide Winthrop (leflunomide) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.

[26] Update of SmPC section 4.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAHs should provide a cumulative review and discussion on posterior reversible encephalopathy syndrome (PRES). The MAHs should provide more information on leflunomide use with non-biological disease-modifying antirheumatic drugs at event level in order to better assess what the contribution of each drug to the occurrence of the reactions might be. Finally the signals of hepatotoxicity pregnancy, and renal failure, should be closed as these risks are already included as safety concerns (important potential or identified risk) in the risk management plan.
- The MAHs should be requested to submit to EMA, within 60 days, a detailed review of their evaluation of hyperthyroidism in patients treated concomitantly with thyroid hormones for hypothyroidism. If applicable, a proposal to update the product information should be provided.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.2.2. Zoledronic acid – ZOLEDRONIC ACID MEDAC (CAP) - EMEA/H/C/002359/PSUSA/03149/201408; ZOMETA (CAP) - EMEA/H/C/000336/PSUSA/03149/201408; NAP

Applicant: medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Zoledronic acid is a bisphosphonate indicated in the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone and in the treatment of adult patients with tumour-induced hypercalcaemia (TIH).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zoledronic acid Medac and Zometa, centrally authorised medicines containing zoledronic acid, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Zoledronic acid and Zometa (zoledronic acid) in the approved indications remains favourable.
- Nevertheless, the product information should be updated to include in the posology and method of administration section that patients treated with zoledronic acid (indicated for cancer and fractures) should be given the package leaflet and the patient reminder card, to reflect the current knowledge on osteonecrosis of the jaw as set out in the warnings and undesirable effects sections. Therefore the current terms of the marketing authorisation(s) should be varied[27]. See 'PRAC recommends further

[27] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

measures to minimise risk of osteonecrosis of the jaw with bisphosphonate medicine' EMA/169618/2015.

- In the next PSUR, the MAH for Zometa should justify the current four week administration cycles, as during 12 week therapy cycles fewer adverse events can be expected. This could reduce an unnecessary burden for the patient. The MAH should provide a discussion on the results of the ALLIANCE study[28] and possible impact on the SmPC wording.
- In the next PSUR, all the MAHs should closely monitor and provide reviews of vascular calcification in women under the age of 65 years, radiation induced adverse events, long term safety including long term safety in off label use in postmenopausal women with hormone positive breast cancer receiving anti-hormonal therapy, and medication errors.
- The MAH should be requested to submit to EMA, within 60 days, a revised RMP to reflect the addition of a new additional risk minimisation measure (introduction of the reminder card on osteonecrosis of the jaw) as well as to propose indicators to measure the effectiveness of this new measure.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3. PSUR procedures including Nationally Approved Products (NAPs) only

None

6.4. Follow-up to PSUR procedures

See Annex I 15.4.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[29]

See Annex I 16.

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

See Annex I 16.

7.3. Results of PASS imposed in the marketing authorisation(s)[31]

None

[28] Smith et al. Randomized Controlled Trial of Early Zoledronic Acid in Men With Castration-Sensitive Prostate Cancer and Bone Metastases: Results of CALGB 90202 (Alliance) JCO Apr 10, 2014:1143-1150; published online on March 3, 2014
[29] In accordance with Article 107n of Directive 2001/83/EC
[30] 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
[31] In accordance with Article 107p-q of Directive 2001/83/EC

7.4. Results of PASS non-imposed in the marketing authorisation(s)[32]

See Annex I 16.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[33]

See Annex I 16.

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

8.1. Annual reassessments of the marketing authorisation

None

8.2. Conditional renewals of the marketing authorisation

See annex I 17.

8.3. Renewals of the marketing authorisation

None

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspection

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 minutes.

9.3. Others

None

[32] 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
[33] In line with the revised variations regulation for any submission before 4 August 2013

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 MS safety announcements

None

10.3. Other requests

10.3.1. Adrenaline auto-injectors (NAP) - EMEA/H/A-31/1398

Applicant: PharmaSwiss s.r.o., ALK-Abelló A/S, Aptiv Solutions (Lincoln Medical Ltd), Meda Pharma

Lead PRAC member: Rafe Suvarna
Scope: PRAC consultation on a CHMP referral procedure under Article 31 of Directive 2001/83/EC

Background

Adrenaline, a natural active sympathomimetic hormone from the adrenal medulla, used by self-administration via an auto-injector is indicated in the emergency treatment of severe allergic reactions (anaphylaxis) such as insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis.

A referral procedure under Article 31 of Directive 2001/83/EC for adrenaline auto-injectors is currently under evaluation by the CHMP to review in relation to reports of device failure the available data on the site of delivery of adrenaline from auto-injectors with respect to needle-length, and on whether the product information contains clear and detailed instructions for appropriate use.

The CHMP sought the advice of the PRAC on potential databases or other data sources that might hold information on actual device usage.

Summary of advice

- The PRAC considered that there were no identified data sources that would permit a formal epidemiological approach for assessing actual usage or device failure of adrenaline auto-injectors in the EU. Even if data sources were identified, the limitations of such studies would mean that they could only be exploratory in nature and robust conclusions would be precluded. In addition, the PRAC considered that a simple case series approach would be preferable for gaining further data on the reasons for adrenaline device failure, if there are adequately documented case reports.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

12.2.1. Paediatric Committee (PDCO): Guideline on conduct of pharmacovigilance for medicines used by the paediatric population

Following the departure of Andis Lacis from the PRAC, the EMA Secretariat launched a call for expression of interest to nominate a new PRAC co-Rapporteur for the drafting of the revised guideline on conduct of pharmacovigilance for medicines used by the paediatric population. PRAC delegates were invited to indicate their interest by 16 April 2015.

Post-meeting note: At its May 2015 meeting, the PRAC endorsed the nomination of Amy Tanti as the new PRAC co-Rapporteur for the revised guideline on conduct of pharmacovigilance for medicines used by the paediatric population.

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

12.3.1. Joint Paediatric Committee (PDCO)–PRAC Working Group (WG): Call for nomination

Following the departure of Andis Lacis from the PRAC, the EMA Secretariat launched a call for expression of interest to nominate a new a PRAC delegate to join the joint PDCO/PRAC Working Group. PRAC delegates were invited to indicate their interest by 20 April 2015.

Post-meeting note: At its May 2015 meeting, the PRAC endorsed the nomination of Amy Tanti as a new a PRAC delegate to join the joint PDCO/PRAC Working Group.

12.3.2. Pharmacogenomics Working Party (PGWP): Guideline on key aspects for the use of pharmacogenomics methodologies in the pharmacovigilance evaluation of medicinal products

Following the completion of the public consultation on the draft guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of

medicinal products, Qun-Ying Yue, leading the editorial board, presented to the PRAC an update on the main changes following consultation.
The guideline aims at addressing the influence of pharmacogenomics on pharmacovigilance activities, including consideration of how to evaluate the pharmacovigilance related issues for medicinal products with pharmacogenomics tools and methodologies, and how to translate the results of these evaluations to appropriate treatment recommendations in the product information. Particular emphasis is given to the specific aspects of pharmacovigilance activities and risk minimisation measures in the RMP related to the use of medicinal products in genetic subpopulations.

The PRAC welcome the updated guideline. The PRAC was informed that finalisation of the guideline is targeted before the end of 2015.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance Systems and their Quality Systems

None

12.9.2. Pharmacovigilance Inspections

None

12.9.3. Pharmacovigilance Audits

None

12.10. Periodic Safety Update Reports & Union Reference Date (EURD) List

12.10.1. Periodic Safety Update Reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

The PRAC was updated on the activities of the GPAG, composed of PRAC delegates and EMA staff members, focussing on harmonising and streamlining the EURD list and welcomed the progress being made.

12.10.3. PSURs repository

12.10.3.1. PRAC recommendation on the repository audit outcome

Pursuant to Article 25a of Regulation (EC) No 726/2004, the PRAC was consulted on drawing up the functional specifications for the repository for PSURs on 5 December 2013. These 'PSUR Repository functionalities to be audited' were subsequently endorsed by the EMA Management Board on 12 December 2013. These agreed functionalities are to be understood as the 'full functionality' term. They formed the basis of the first release of the PSUR repository into its live environment on 26 January 2015.

In accordance with the above Article, an independent audit was conducted as to whether the deployed repository meets the functional specifications.

Having considered the independent audit findings, the PRAC concurred that the PSUR repository meets the functional specifications as agreed in the 'PSUR Repository functionalities to be audited' document and concluded therefore that it has achieved its full functionality in the meaning of Article 25a of Regulation (EC) No 726/2004. This recommendation is subject to the EMA implementing the EMA IAP within the stated deadlines, to be confirmed by the independent auditor in June 2015 in advance of endorsement by the EMA Management Board.

12.10.4. Union Reference Date List – Consultation on the draft list

The PRAC endorsed the draft revised EURD list version April 2015 reflecting the PRAC comments impacting on the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC Minutes April 2013).

Post-meeting note: following the PRAC meeting in April 2015, the updated EURD list was adopted by the CHMP and CMDh at their April 2015 meeting and published on the EMA website on 12/05/2015, see:

Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.11. Signal Management

12.11.1. Interstitial lung disease (ILD): analysis of geographic clusters of reports

Following a request from the PRAC, the EMA Secretariat presented to the Committee a detailed analysis of geographic clustering of case reports of interstitial lung disease (ILD). This analysis was performed to provide an insight on the differences in the reporting rates, trends and potential coding practices between different world regions, and to identify methods to improving signal validation for IDL. Some further work is ongoing in order to ensure that an evidence-based approach is conducted to the use of ILD in signal detection and analysis.

12.11.2. Signal Management – Feedback from Signal Management Review Technical (SMART) Working Group

The PRAC was updated on the outcome of the April 2015 SMART Working Group (SMART WG) meeting. The new individual case safety report (ICSR (R3)) form was further discussed following the inclusion of the PRAC requested changes after the plenary discussion during the March 2015 PRAC meeting. In addition, the SMART WG was updated on the results of the survey addressed to all users of the EudraVigilance data analysis system (EVDAS) and users of electronic reaction monitoring reports (eRMR) in EU NCAs aiming at clarifying how these tools are used and perceived and to collect feedback on any improvements needed. In addition, the SMART Working Group was updated on the progress of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) project.

12.12. Adverse Drug Reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional Monitoring

None

12.12.3. List of products under Additional Monitoring – Consultation on the draft list

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on 29/04/2015 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.12.4. Reporting of adverse drug reactions for donated medicines

The EMA Secretariat consulted the PRAC regarding a request from the World Health Organization (WHO) to provide clarification as regards the reporting requirements for MAHs in the EU for suspected adverse reactions occurring with medicinal products which they

donate outside the EU to public health programmes in the area of neglected tropical diseases.

In line with the legal requirements set out in Directive 2001/83/EC and Regulation (EC) 726/2004 and as further detailed in the EU guidelines on good pharmacovigilance practices, the PRAC clarified that suspected adverse reactions brought to the attention of a MAH for a medicinal product donated outside the EU should be recorded and reported by the MAH to the relevant competent authorities in the EU.

12.13. EudraVigilance Database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk Management Plans and effectiveness of risk minimisations

12.14.1. Implementation of the revised RMP assessment process

As a follow-up to the March 2015 PRAC plenary meeting, the PRAC further discussed and endorsed the revised RMP assessment reports templates, process and schedule. The introduction of the revised RMP process and joint templates for PRAC and CHMP starts for any new marketing authorisation procedure starting as of May 2015. The PRAC underlined the need for training assessors from EU national competent authorities on the revised RMP process and suggested joint training with PRAC and CHMP assessors.

12.14.2. Medication errors: risk minimisation strategy with high strength/fixed combination insulins

As a follow-up to the discussion at the March 2015 PRAC, the EMA Secretariat presented the revised draft guidance on medication errors with high strength/fixed combination insulins and the respective draft communication following comments from the PRAC and patients' and consumers' organisations and healthcare professionals' organisations (PCO/HCPO). The PRAC adopted the draft guidance that will be released for a 2 month public consultation as an addendum of the Good Practice Guide on risk minimisation and prevention of medication errors.

12.14.3. Risk Management Systems

None

12.14.4. Tools, Educational Materials and effectiveness measurement of risk minimisations

None

12.15. Post-authorisation Safety Studies

12.15.1. Good pharmacovigilance practices (GVP) module VIII (Post-Authorisation Safety Studies)

Following consolidation by the Project Maintenance group 2 of the pharmacovigilance implementation governance, GVP Module VIII on Post-authorisation safety studies revision 2 as well as its Addendum on requirements for transmission of information on non-interventional post-authorisation safety studies, were circulated to the PRAC for comments with the aim to start public consultation in April 2015.

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

13. Any other business

13.1. Pharmacovigilance programme and revised implementation governance

The PRAC received a further update on the revised implementation governance of the pharmacovigilance legislation and the pharmacovigilance programme, with a special focus on information systems and services, including updates on the Article 57[34] database,

[34] Article 57 of Regulation (EC) No. 726/2004

EudraVigilance auditable requirements, PSUR repository, medical literature monitoring and pharmacovigilance fees.

13.2. Type II variations: revised procedural timetables

As agreed at its March 2015 PRAC, the PRAC further discussed the proposed type II variations timetables. Follow-up discussion will take place in May/June 2015 PRAC.

14. Annex I – Risk management plans

14.1. Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance will be made available following the CHMP opinion on their marketing authorisation.

14.1.1. Aripiprazole - EMEA/H/C/003803, Generic

Scope: Treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder

14.1.2. Aripiprazole - EMEA/H/C/003899, Generic

Scope: Treatment of schizophrenia and prevention of manic episodes in bipolar I disorder

14.1.3. Edoxaban - EMEA/H/C/002629

Scope: Prevention of stroke, embolism and treatment of venous thromboembolism

14.1.4. Brivaracetam - EMEA/H/C/003898

Scope: Treatment of partial-onset seizures

14.1.5. Duloxetine - EMEA/H/C/003981, Generic

Scope: Treatment of major depressive disorder, diabetic peripheral neuropathic pain, and generalised anxiety disorder

14.1.6. Ferric maltol - EMEA/H/C/002733

Scope: Treatment of iron deficiency anaemia

14.1.7. Lutetium, isotope of mass 177 - EMEA/H/C/002749

Scope: Radiolabelling of carrier molecules

14.1.8. Necitumumab - EMEA/H/C/003886

Scope: Treatment of squamous non-small cell lung cancer

14.1.9. Nivolumab - EMEA/H/C/003985

Scope: Treatment of advanced (unresectable or metastatic) melanoma in adults

14.1.10. Octocog alfa - EMEA/H/C/004147; EMEA/H/C/003825

Scope: Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)

14.1.11. Opicapone - EMEA/H/C/002790

Scope: Treatment of Parkinson's disease and motor fluctuations

14.1.12. Pemetrexed - EMEA/H/C/004114, Generic

Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer

14.1.13. Pregabalin - EMEA/H/C/003962; EMEA/H/C/004078, Generics

Scope: Treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD)

14.1.14. Pregabalin - EMEA/H/C/004010; EMEA/H/C/004070, Generics

Scope: Treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD)

14.1.15. Selexipag - EMEA/H/C/003774

Scope: Treatment of pulmonary arterial hypertension (PAH)

14.1.16. Sonidegib - EMEA/H/C/002839

Scope: Treatment of basal cell carcinoma (BCC)

14.1.17. Tasimelteon - EMEA/H/C/003870, Orphan

Applicant: Vanda Pharmaceuticals Ltd

Scope: Treatment of non-24-hour sleep-wake disorder (non-24)

14.2. Medicines in the post-authorisation phase – PRAC-led procedure

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of these updated versions of the RMP for the below mentioned medicines.

14.2.1. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0005/G

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of non-clinical study 100011749 (Study of Ataluren (PTC124) and M4 metabolite in the β3 binding assay) and non-clinical study 100012124 (Study of ataluren (PTC124) and M4 (PTC-0256858-04) functional activity in a beta-3 adrenergic cellular assay) in fulfilment of MEA 006 and MEA 007

14.2.2. Fluticasone furoate, vilanterol – RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS/0713/G; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS/0713/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Miguel-Angel Macia

Scope: Update of the RMP to revise due dates of commitments within the pharmacovigilance plan

14.2.3. Interferon beta-1b – BETAFERON (CAP) - EMEA/H/C/000081/II/0100

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Introduction of an RMP for Betaferon following a signal assessment on thrombotic microangiopathy (TMA) covering the entire class of interferon beta. The RMP for Extavia, informed consent of Betaferon, has already been assessed

14.2.4. Lapatinib – TYVERB (CAP) - EMEA/H/C/000795/II/0041/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Revised RMP in order to include general updates in the RMP regarding posology update, addition of some new studies to pharmacovigilance activities and addition of details of three newly available study reports. Timelines have been also changed for study EGF114299 and study EGF117165 and RMP and Annex II have been updated accordingly

14.2.5. Memantine – AXURA (CAP) - EMEA/H/C/000378/WS0668/0067; EBIXA (CAP) - EMEA/H/C/000463/WS0668/0083; MEMANTINE MERZ (CAP) - EMEA/H/C/002711/WS0668/0004

Applicant: Lundbeck A/S

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised RMP (version 7.1) to reflect the interim results of the prostate cancer study and four finalised studies. This RMP update also introduces changes to the required additional pharmacovigilance activity regarding the identified potential risk of prostate cancer by adjusting the due dates of agreed milestones

14.2.6. Micafungin – MYCAMINE (CAP) - EMEA/H/C/000734/II/0026

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Revised RMP in order to update the important identified risk of drug interaction; include a second survey that will be conducted in Q1 2015 to further assess the effectiveness of risk minimisation measures as requested by the PRAC in May 2014.

14.2.7. Temoporfin – FOSCAN (CAP) - EMEA/H/C/000318/II/0036

Applicant: Biolitec pharma Ltd

PRAC Rapporteur: Sabine Straus

Scope: Submission of a new RMP (version 1.0)

14.2.8. Temozolomide – TEMODAL (CAP) - EMEA/H/C/000229/II/0072

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Martin Huber

Scope: Revised RMP (version 5.0) in order to reclassify hepatobiliary disorders from important potential to important identified risk following the request from PRAC/CHMP in the assessment of variation II/63

14.3. Medicines in the post-authorisation phase – CHMP-led procedure

14.3.1. Aprepitant – EMEND (CAP) - EMEA/H/C/000527/X/0049/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication for chemotherapy-induced nausea and vomiting (CINV) in adults to paediatric patients (12 to 17years) for the 80mg and 125mg hard capsules. SmPC section 4.2 and 5.3 of the 165mg hard capsule label, which is consequential. In addition, addition of a new pharmaceutical form (powder for oral suspension) is assessed for 125mg strength. The MAH also submitted a type II variation to reflect the paediatric results for prevention of post-operative nausea and vomiting (PONV) in the clinical sections of 40mg hard capsules label, thus updating SmPC sections 5.1 and 5.2. The Package Leaflet is updated accordingly

14.3.2. Azacitidine – VIDAZA (CAP) - EMEA/H/C/000978/II/0030

Applicant: Celgene Europe Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to add treatment of adult patients aged 65 years or older who are not eligible for hematopoietic stem cell transplantation (HSCT) with acute myeloid leukaemia (AML) with >30% marrow blasts according to the WHO classification, based on the pivotal phase III study AZA- AML-001. As a consequence, SmPC sections 4.1, 4.4, 4.8 and 5.1 have been updated and the package leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. A revised RMP version 10.0 was provided as part of the application. The application includes a request for an additional year of market protection for a new indication in accordance with Article 10(1) of Directive 2001/83/EC

14.3.3. Cabazitaxel – JEVTANA (CAP) - EMEA/H/C/002018/II/0029

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Arnaud Batz

Scope: Update of SmPC sections 4.2 and 5.2 in order to update safety and pharmacokinetic information on the use of cabazitaxel in patients with solid tumours with moderately and severely impaired and with normal renal function. Final study report for study POP12251 supportive of these changes has been submitted. The RMP is updated accordingly. In addition, the MAH took the opportunity to update the RMP also for the on-going variation EMEA/H/C/002018/II/0029

14.3.4. Conestat alfa – RUCONEST (CAP) - EMEA/H/C/001223/R/0023

Applicant: Pharming Group N.V.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of an RMP as part of a five-year renewal of the marketing authorisation

14.3.5. Enzalutamide – XTANDI (CAP) - EMEA/H/C/002639/II/0018

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of SmPC section 5.1 in order to update the pharmacodynamic properties information regarding overall survival (OS) after analysis of data from the PREVAIL (MDV3100-03) study part of the obligation to conduct post-authorisation measures as reported in Annex II. Annex II is updated accordingly

14.3.6. Ingenol mebutate – PICATO (CAP) - EMEA/H/C/X002275/II/0012

Applicant: Leo Pharma A/S

PRAC Rapporteur: Julie Williams

Scope: Update of SmPC sections 4.2, 4.8 and 5.1 to provide new efficacy and safety data supporting a labelling update that introduces repeat treatment of Picato gel (150 mcg/g and 500 mcg/g), based on trial LP0041-22. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor linguistic amendments

14.3.7. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/II/0028/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

14.3.8. Japanese encephalitis vaccine (inactivated, adsorbed) – IXIARO (CAP) - EMEA/H/C/000963/II/0065/G

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1 in order to include data of the clinical trial sponsored by Novartis Vaccines V49_23, testing concomitant use in conventional and accelerated schedules of Ixiaro with Rabipur. Update of SmPC as recommended during the renewal procedure EMEA/H/C/00963/R/0055 with inclusion of relevant data to elderly population

14.3.9. Levetiracetam – KEPPRA (CAP) - EMEA/H/C/000277/R/0154 (with RMP)

Applicant: UCB Pharma SA

PRAC Rapporteur: Veerle Verlinden

Scope: Evaluation of an RMP as part of a five-year renewal of the marketing authorisation

14.3.10. Methylnatrexone bromide – RELISTOR (CAP) – EMEA/H/C/000870/II/0030

Applicant: TMC Pharma Services Ltd

PRAC Rapporteur: Valerie Strassmann

Scope: Extension of the indication for the treatment of opioid induced constipation in adult non cancer pain patients. Consequently, SmPC sections 4.1, 4.2, 4.4 and 5.1 as well as the package leaflet are updated accordingly

14.3.11. Nitisinone – ORFADIN (CAP) - EMEA/H/C/000555/X/0041

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Addition of an oral suspension 4 mg/ml as additional pharmaceutical form

14.3.12. Pazopanib – VOTRIENT (CAP) - EMEA/H/C/001141/II/0029/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Update of SmPC sections 4.4 and 4.8 to add interstitial lung disease (ILD)/pneumonitis. The package leaflet is updated accordingly. Following study VEG 108844 results, update of SmPC section 4.4 to add more information on myocardial dysfunction. Following the review of safety data from the sarcoma studies, the SmPC section 4.4 has been updated to correct the number of reported cases of congestive heart failure (CHF). The RMP is updated accordingly

14.3.13. Peginterferon alfa-2b – PEGINTRON (CAP) - EMEA/H/C/000280/WS0611/0119; VIRAFERONPEG (CAP) - EMEA/H/C/000329/WS0611/0112 interferon alfa-1b – INTRONA (CAP) - EMEA/H/C/000281/WS0611/0099

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of SmPC section 4.4 with updated information on homicidal ideation and for patients with decompensated liver disease, and update in SmPC section 4.8 with pulmonary fibrosis added as post-marketing adverse experience. The package leaflet is updated accordingly. For Intron A only, the MAH takes the opportunity to implement minor linguistic revisions in various languages arising from an internal quality check

14.3.14. Pegvisomant – SOMAVERT (CAP) - EMEA/H/C/000409/X/0072

Applicant: Pfizer Limited

PRAC Rapporteur: Arnaud Batz

Scope: Line extension to add 25 mg and 30 mg powder and solvent for solution for injection

14.3.15. Prucalopride – RESOLOR (CAP) - EMEA/H/C/001012/II/0034

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Extension of indication to include the male population on the basis of the completion of the clinical study SPD555-302. Consequently, the MAH proposed to update SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2. The package leaflet is updated accordingly. An updated RMP (version 12) is also provided with this submission

14.3.16. Sodium oxybate – XYREM (CAP) - EMEA/H/C/000593/R/0054 (with RMP)

Applicant: UCB Pharma Ltd.

PRAC Rapporteur: Magda Pedro

Scope: Evaluation of an RMP as part of a five-year renewal of the marketing authorisation

14.3.17. Thiotepa – TEPADINA (CAP) - EMEA/H/C/001046/II/0018

Applicant: Adienne S.r.l. S.U.

PRAC Rapporteur: Arnaud Batz

Scope: Update of SmPC section 4.8 in order to update the safety information on pulmonary arterial hypertension with an uncommon frequency. The package leaflet is updated accordingly

14.3.18. Tigecycline – TYGACIL (CAP) - EMEA/H/C/000644/II/0092

Applicant: Pfizer Limited

PRAC Rapporteur: Miguel-Angel Macia

Scope: Addition of a new restricted indication in children of eight year-old and older. SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 as well as the package leaflet are updated accordingly

14.3.19. Ulipristal – ESMYA (CAP) - EMEA/H/C/002041/II/0028

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication including updates to SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 in order to extend the current indication to long term (repeated intermittent) treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The package leaflet is updated accordingly

15. ANNEX I - Periodic safety update reports (PSURs)

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated under relevant PSUR procedure(s).

15.1. PSUR procedures including centrally authorised products only

15.1.1. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/PSUSA/10175/201409

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.2. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/003718/PSUSA/10055/201409

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.3. Antithrombin alfa – ATRYN (CAP) - EMEA/H/C/000587/PSUSA/00224/201407

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Arnaud Batz

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.4. Aztreonam – CAYSTON (CAP) - EMEA/H/C/000996/PSUSA/00283/201409

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.5. Bedaquiline – SIRTURO (CAP) - EMEA/H/C/002614/PSUSA/10074/201409

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.6. Belimumab – BENLYSTA (CAP) - EMEA/H/C/002015/PSUSA/09075/201409

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.7. Cabozantinib – COMETRIQ (CAP) - EMEA/H/C/002640/PSUSA/10180/201409

Applicant: TMC Pharma Services Ltd

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.8. Cetuximab – ERBITUX (CAP) - EMEA/H/C/000558/PSUSA/00635/201409

Applicant: Merck KGaA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.9. Cholic acid – ORPHACOL (CAP) - EMEA/H/C/001250/PSUSA/10208/201409

Applicant: Laboratoires CTRS - Boulogne Billancourt

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.10. Colestilan – BINDREN (CAP) - EMEA/H/C/002377/PSUSA/10016/201409

Applicant: Mitsubishi Tanabe Pharma Europe Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.11. Daptomycin – CUBICIN (CAP) - EMEA/H/C/000637/PSUSA/00931/201409

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.12. Eculizumab – SOLIRIS (CAP) - EMEA/H/C/000791/PSUSA/01198/201410

Applicant: Alexion Europe SAS

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.13. Etravirine – INTELENCE (CAP) - EMEA/H/C/000900/PSUSA/01335/201409

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Patrick Maison

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.14. Florbetapir (^{18}F) – AMYVID (CAP) - EMEA/H/C/002422/PSUSA/10032/201410

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.15. Glycopyrronium bromide – ENUREV BREEZHALER (CAP) - EMEA/H/C/002691/PSUSA/10047/201409; SEEBRI BREEZHALER (CAP) -

EMEA/H/C/002430/PSUSA/10047/201409; TOVANOR BREEZHALER (CAP) - EMEA/H/C/002690/PSUSA/10047/201409

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

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

15.1.16. Glycopyrronium bromide, indacaterol – ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/PSUSA/10105/201409; ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/PSUSA/10105/201409; XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/PSUSA/10105/201409

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.17. Hepatitis A (inactivated) and hepatitis B (rDNA) (hab) vaccine (adsorbed) – AMBIRIX (CAP) - EMEA/H/C/000426/PSUSA/01593/201409; TWINRIX ADULT (CAP) - EMEA/H/C/000112/PSUSA/01593/201409; TWINRIX PAEDIATRIC (CAP) - EMEA/H/C/000129/PSUSA/01593/201409

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.18. Human fibrinogen, human thrombin – EVARREST (CAP) - EMEA/H/C/002515/PSUSA/10103/201409

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.19. Insulin degludec, insulin aspart – RYZODEG (CAP) - EMEA/H/C/002499/PSUSA/10036/201409; TRESIBA (CAP) - EMEA/H/C/002498/PSUSA/10036/201409

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.20. Insulin human – INSUMAN (CAP) - EMEA/H/C/000201/PSUSA/10107/201409

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.21. Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) – PANDEMRIX (CAP) - EMEA/H/C/000832/PSUSA/02277/201409

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.22. Panitumumab – VECTIBIX (CAP) - EMEA/H/C/000741/PSUSA/02283/201409

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.23. Para-aminosalicylic acid – GRANUPAS (CAP) - EMEA/H/C/002709/PSUSA/10171/201410

Applicant: Lucane Pharma

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.24. Regorafenib – STIVARGA (CAP) - EMEA/H/C/002573/PSUSA/10133/201409

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.25. Retigabine – TROBALT (CAP) - EMEA/H/C/001245/PSUSA/02624/201409

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.26. Riociguat – ADEMPAS (CAP) - EMEA/H/C/002737/PSUSA/10174/201409

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.27. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/000944/PSUSA/02653/201409

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.28. Telavancin – VIBATIV (CAP) - EMEA/H/C/001240/PSUSA/02879/201409

Applicant: Clinigen Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.29. Tenecteplase – METALYSE (CAP) - EMEA/H/C/000306/PSUSA/02888/201408

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.30. Trastuzumab – HERCEPTIN (CAP) - EMEA/H/C/000278/PSUSA/03010/201409

Applicant: Roche Registration Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.31. Vandetanib – CAPRELSA (CAP) - EMEA/H/C/002315/PSUSA/09327/201410

Applicant: AstraZeneca AB

PRAC Rapporteur: Arnaud Batz

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.32. Vinflunine ditartrate – JAVLOR (CAP) - EMEA/H/C/000983/PSUSA/03123/201409

Applicant: Pierre Fabre Médicament

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUR/PSUSA procedure

15.1.33. Vortioxetine – BRINTELLIX (CAP) - EMEA/H/C/002717/PSUSA/10052/201409

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Veerle Verlinden

Scope: Evaluation of a PSUR/PSUSA procedure

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

15.2.1. Anagrelide – XAGRID (CAP) - EMEA/H/C/000480/PSUSA/00208/201409; NAP

Applicant: Shire Pharmaceutical Contracts Ltd.

PRAC Rapporteur: Arnaud Batz

Scope: Evaluation of a PSUSA procedure

15.2.2. Measles, mumps, rubella and varicella vaccine (live) – PROQUAD (CAP) - EMEA/H/C/000622/PSUSA/01936/201409; NAP

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.2.3. Memantine – AXURA (CAP) - EMEA/H/C/000378/PSUSA/01967/201409; EBIXA (CAP) - EMEA/H/C/000463/PSUSA/01967/201409; MEMANTINE MERZ (CAP) - EMEA/H/C/002711/PSUSA/01967/201409; NAP

Applicant: Merz Pharmaceuticals GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.3. PSUR procedures including nationally approved products (NAPs) only

None

15.4. Follow-up to PSUR procedures

15.4.1. Rasburicase – FASTURTEC (CAP) - EMEA/H/C/000331/LEG 044

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Sabine Straus

Scope: Provision of cumulative overview of safety data received for the on-going signals of cardiac toxicity, lack of efficacy and hepatobiliary disorders as per CHMP Opinion dated 23 October 2014 for the procedure EMEA/H/C/000331/PSUV/0041

16. ANNEX I – Post-authorisation safety studies (PASS)

Since all comments received on the assessment of these studies were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below without further plenary discussion.

16.1.1. Chlormadinone, ethinylestradiol (NAP) – EMEA/H/N/PSP/J/0012.1

Applicant: Gideon Richter, various

PRAC Rapporteur: Valerie Strassmann

Scope: Revised joint PASS protocol (following conclusion of Article31 referral procedure for combined hormonal contraceptives with CHMP opinion adopted in November 2013) to study the risk of venous thromboembolism (VTE) associated with chlormadinone/ethinylestradiol (CMA/EE) containing products

16.1.2. Cyproterone, ethinylestradiol (NAP) – EMEA/H/N/PSP/J/0006.1

Applicant: Bayer Pharma AG (Bayer 35), various

PRAC Rapporteur: Menno van der Elst

Scope: Revised PASS protocol for a drug utilisation study (database DUS) following EC decision dated 25 July 2013 on a referral procedure (EMEA/H/107i/1357)

16.1.3. Domperidone (NAP) - EMEA/H/N/PSP/J/0016

Applicant: Janssen (Motilium), various

PRAC Rapporteur: Arnaud Batz

Scope: PASS protocol for a study is to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the change in SmPC and the distribution of DHPC. The secondary objective of the study is to characterise the extent to which domperidone is prescribed for conditions that are not labelled

16.1.4. Agomelatine – THYMANAX (CAP) - EMEA/H/C/000916/MEA 023.1; VALDOXAN (CAP) - EMEA/H/C/000915/MEA 023.1

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ingebjørg Buajordet

Scope: Revised PASS protocol for a study using databases in four European countries to assess the incidence of hospitalisation for liver injury in current medical practice in comparison with other antidepressant drugs

16.1.5. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/MEA 002.1

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 002 (PASS protocol for an observational study of the risk of acute pancreatitis in subjects exposed to albiglutide, other GLP-1 agonists or DPP-4 inhibitors compared to other antidiabetic agents (protocol PRJ2335)) request for supplementary information (RSI) as adopted in November 2014

16.1.6. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/MEA 003.1

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 003 (PASS protocol for a study to assess the risk of thyroid and pancreatic cancers, and malignancy when used in combination with insulins in observational databases of sufficient size that provides long term longitudinal follow up of patients (Protocol PRJ2331)) request for supplementary information (RSI) as adopted in November 2014

16.1.7. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/MEA 004.1

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 004 (PASS protocol for a cohort study to investigate the prescribing of albiglutide among women of child bearing age who have type 2 diabetes (Protocol PRJ2376)) request for supplementary information (RSI) as adopted in November 2014

16.1.8. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/MEA 005.1

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 005 (PASS protocol for a retrospective cohort study to assess the utilisation of albiglutide among women of child bearing age in the U.S. (protocol PRJ2379)) request for supplementary information (RSI) as adopted in November 2014

16.1.9. Aripiprazole – ABILIFY MAINTENA (CAP) - EMEA/H/C/002755/MEA 005.1

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to MEA 005 (PASS protocol No. 31-10-270) request for supplementary information (RSI) as adopted in December 2014

16.1.10. Dasabuvir – EXVIERA (CAP) - EMEA/H/C/003837/MEA 001

Applicant: AbbVie Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: PASS protocol for a prospective, observational cohort study utilising the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of Grade 3+ ALT elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (3 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (2-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA Regimens in a real world setting)

16.1.11. Florbetaben (^{18}F) – NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.2

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 001 (revised PASS protocol study no. FBB-01_03_13) adopted in December 2014

16.1.12. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.1

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 026 (protocol MRK-2859, Nordic national register database study) request for supplementary information (RSI) as adopted in April 2014

16.1.13. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/MEA 027.2

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 027.1 (feasibility assessment of Spanish ENEIDA Registry) request for supplementary information (RSI) as adopted in October 2014

16.1.14. Insulin human – INSUMAN (CAP) - EMEA/H/C/000201/MEA 047

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: PASS protocol for an European observational cohort of patients with type I diabetes treated via intraperitoneal route with Insuman Implantable 400 IU/mL in Medtronic MiniMed implantable pump (study HUBIN-C-06380)

16.1.15. Ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 001

Applicant: AbbVie Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Protocol for a prospective, observational cohort study utilising Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ ALT elevations in patients being treated for Hep C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (3-direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (2-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA Regimens in a real world setting)

16.1.16. Voriconazole – VFEND (CAP) - EMEA/H/C/000387/MEA 091

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Non-interventional PASS protocol A1501103 for an active safety surveillance program to monitor selected events in patients with long-term voriconazole use

16.1.17. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/II/0053 (without RMP)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the clinical study report (CSR) of the Eviplera/Edurant. Healthcare Professionals survey undertaken to gain an understanding of the effectiveness of the current prescribing conditions in minimising the risk associated with taking the products without food/a meal, potentially associated with the risk of development of drug resistance

16.1.18. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/002494/II/0035 (with RMP)

Applicant: Vertex Pharmaceuticals (U.K.) Ltd

PRAC Rapporteur: Miguel-Angel Macia

Scope: Submission of the final study VX08-770-105 CSR to fulfil the post-authorisation measure ANX 002 and a revised RMP

16.1.19. Lapatinib – TYVERB (CAP) - EMEA/H/C/000795/II/0042 (with RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of data analysis of the available pharmacokinetic sampling of patients enrolled in LANTERN trial (LAP113130) in comparison to historical data in order to fulfil the MEA 023.4 which is to examine lapatinib dose adjustments with specific CYP3A4 inducers.

16.1.20. Palivizumab – SYNAGIS (CAP) - EMEA/H/C/000257/II/0098 (without RMP)

Applicant: AbbVie Ltd.

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final study report for study A11-632, an observational study carried out to assess the risk of autoimmune and allergic diseases in high risk children exposed to palivizumab, in fulfilment of the Post Authorisation Measure (REC) FU2 032.4

16.1.21. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) – PREVENAR 13 (CAP) - EMEA/H/C/001104/II/0116 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a final report for an observational safety study of 13-valent pneumococcal conjugate vaccine (13vPnC) administered in routine use to infants and toddlers. This observational study was conducted as a post-marketing commitment, MEA 012

16.1.22. Rilpivirine – EDURANT (CAP) - EMEA/H/C/002264/II/0015 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Sabine Straus

Scope: Submission of the clinical study report of the Edurant/Eviplera Healthcare Professionals survey undertaken to gain an understanding of the effectiveness of the current prescribing conditions in minimising the risk associated with taking the products without food/a meal, potentially associated with the risk of development of drug resistance.

16.1.23. Sofosbuvir – SOVALDI (CAP) - EMEA/H/C/002798/II/0015 (with RMP)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report to investigate the safety and efficacy of GS-7977 and ribavirin for 24 weeks in subjects with recurrent chronic HCV post liver transplant (GS-US-334-0126). This submission of this study fulfils MEA 005. An updated RMP (version 3.0) is proposed accordingly.

16.1.24. Adefovir dipivoxil – HEPSERA (CAP) - EMEA/H/C/000485/MEA 070.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Arnaud Batz

Scope: Interim report on the antiretroviral pregnancy registry

16.1.25. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.1 canagliflozin, metformin – VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur (lead): Valerie Strassmann

Scope: Canagliflozin independent data monitoring committee (IDMC) status reports for the DIA3008 CANVAS study

16.1.26. Denosumab – XGEVA (CAP) - EMEA/H/C/002173/MEA 009.2

Applicant: Amgen Europe B.V.

PRAC Rapporteur Ulla Wändel Liminga

Scope: Interim report on an observational cohort study (study 20101363) to monitor the incidence proportion of ONJ and infections leading to hospitalisation in patients with cancer treated with Xgeva or zoledronic acid using health registry data as defined in the protocol

16.1.27. Fingolimod – GILENYA (CAP) - EMEA/H/C/002202/LEG 012.3

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Arnaud Batz

Scope: Evaluation of yearly report of studies CFTY720D2399, D2403, D2404 and D2406 and annual pooled report of D2403 and D2406
Action: For adoption of advice to CHMP

16.1.28. Fingolimod – GILENYA (CAP) - EMEA/H/C/002202/MEA 014.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Arnaud Batz

Scope: Interim results for study D2404: multi-national pregnancy fingolimod exposure registry in multiple sclerosis

16.1.29. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/002494/ANX 001.2

Applicant: Vertex Pharmaceuticals (U.K.) Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Second interim analysis of a five-year long-term observational study with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints

17. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

17.1.1. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/R/0007 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

17.1.2. Everolimus – VOTUBIA (CAP) - EMEA/H/C/002311/R/0033 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 7-10 April 2015 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Viola Macolić Šarinić	Member	Croatia	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Terhi Lehtinen	Alternate	Finland	No interests declared	Full involvement
Arnaud Batz	Member	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Ruchika Sharma	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain	Alternate	Luxembourg	No restrictions applicable to this meeting	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Ingebjørg Buajordet	Member	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Alternate	Romania	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Miguel-Angel Macia	Alternate	Spain	No interests declared	Full involvement
Qun-Ying Yue	Member	Sweden	No interests declared	Full involvement
Ulla Wändel Liminga	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Jane Ahlqvist Rastad	Member	Independent scientific expert	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Hervé Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Filip Babylon	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Marco Greco	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Kimmo Jaakkola	Expert - in person*	Finland	No restrictions applicable to this meeting	Full involvement
Corinne Féchant	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Nathalie Morgensztejn	Expert - via telephone*	France	No interests declared	Full involvement
Wilma Fischer-Barth	Expert - via telephone*	Germany	No interests declared	Full involvement
Maarten Lagendijk	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Alexandra Pacurariu	Expert - in person*	Netherlands	No restrictions applicable to this meeting	Full involvement
Maaike van Dartel	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Sophia Venzke	Expert - via	Netherlands	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*			
Kristin Kvande	Expert - in person*	Norway	No interests declared	Full involvement
Jana Nováková	Expert - in person*	Slovakia	No interests declared	Full involvement
Darius Matusevicius	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Eva Gil Berglund	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Karl-Mikael Kälkner	Expert - via telephone*	Sweden	No interests declared	Full involvement
Ulf Olsson	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Vidar Wendel Hansén	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Claire Davies	Expert - in person*	United Kingdom	No interests declared	Full involvement
Claire Doe	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Katherine Donegan	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Jennifer Matthissen	Expert - in person*	United Kingdom	No interests declared	Full involvement
Dinesh Mehta	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the product(s) they have been invited to talk about.

Explanatory notes

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

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

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 minutes)

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 minutes)

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 minutes)

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 minutes)

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 minutes)

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

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