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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 6-9 July 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 will be published in the PRAC meeting highlights once the procedures are finalised.

Of note, the 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 6-9 July 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 Marina Dimov Di Giusti, as the new member for Croatia, replacing Viola Macolić Šarinić who becomes the alternate for Croatia replacing Marin Banovac. The PRAC Chair also welcomed Kimmo Jaakkola, replacing Terhi Lehtinen, as the new alternate for Finland. Finally, the PRAC noted a further change in the membership for Sweden: Ulla Wändel Liminga became the member and Qun-Ying Yue the alternate.

Finally, the PRAC welcomed the new Luxembourg presidency of the Council of the EU.

1.2. Adoption of agenda for the meeting on 6-9 July 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 on 8-11 June 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 8-11 June 2015 were published on the EMA website on 21 July 2015 ([EMA/PRAC/443961/2015](#)).

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

- 3.1.1. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP)
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP), SILGARD (CAP)
Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) – GARDASIL 9 (CAP)

MAH(s): GlaxoSmithKline Biologicals S.A. (Cervarix), Sanofi Pasteur MSD SNC (Gardasil, Gardasil 9), Merck Sharp & Dohme Limited (Silgard)

PRAC Rapporteur: Julie Williams

PRAC Co-rapporteurs: Jean-Michel Dogné, Qun-Ying Yue

Scope: Review to further clarify the safety profile of human papillomavirus vaccines following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

Background

Human papillomavirus vaccines are indicated for the prevention of premalignant genital (cervical, vulvar and vaginal) lesions and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) types. Other indications include the active immunisation against premalignant lesions and cancer affecting the anus as well as against genital warts (*condyloma acuminata*) causally related to specific HPV types.

The European Commission sent a letter of [notification](#) dated 09/07/2015 of a referral under Article 20 of Regulation (EC) No 726/2004 for the review of human papillomavirus vaccines to further assess spontaneous reports and the available literature on cases of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) and their potential association with the vaccines.

Discussion

The PRAC noted the notification letter from the European Commission requesting a review of all available data for human papillomavirus vaccines regarding POTS and CRPS and an assessment of their impact on the safety profile for these medicinal products. The PRAC

discussed a list of questions to be addressed by the relevant MAHs as well as a timetable for conducting the review.

The PRAC appointed Julie Williams as Rapporteur and Qun-Ying Yue and Jean-Michel Dogné as Co-Rapporteurs for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions to the MAHs of human papillomavirus vaccines ([EMA/PRAC/454436/2015](#)) and a timetable for the procedure ([EMA/PRAC/454661/2015](#)).

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

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

None

3.5. Others

3.5.1. Ambroxol (NAP); bromhexine (NAP)

MAH(s): Boehringer Ingelheim, various

PRAC Rapporteur: Margarida Guimarães

PRAC Co-rapporteurs: Jean-Michel Dogné, Jan Neuhauser

Scope: Review of recommendations of a referral procedure under Article 31 of Directive 2001/83/EC adopted in January 2015, at the request of the European Commission

Background

The PRAC recommendation (see [PRAC minutes January 2015](#)), followed by the adoption by majority vote of the CMDh position in February 2015 (see [EMA/162540/2014](#)) on the ambroxol- and bromhexine-containing products referral procedure under Article 31 of Directive 2001/83/EC was transmitted to the European Commission for a final legally binding decision valid throughout the European Union (EU). At its current plenary meeting, the PRAC was informed that the decision-making process at the level of the EC Standing Committee (SC) had been put on hold as some Member States raised questions of technical nature considered not sufficiently addressed in the conclusion of the procedure. The EC referred back the PRAC recommendation and CMDh position to the respective Committee/Coordination Group to further consider the relevant questions.

Summary of recommendation(s)/conclusions

The PRAC noted a letter from the EC addressed to the PRAC and CMDh asking for a review by October 2015 of the CMDh position and PRAC recommendations in light of some questions of technical nature. The PRAC discussed the request from the European

Commission, the process and timelines for the revision of the recommendation. It will be further discussed at PRAC in September 2015.

4. Signals assessment and prioritisation¹

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Human fibrinogen, human thrombin – TACHOSIL (CAP)

Applicant: Takeda Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of intestinal obstruction
EPITT 18373 – New signal

Background

Human fibrinogen and human thrombin, local haemostatics, are indicated in combination in adults for supportive treatment in surgery for improvement of haemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient.

The exposure for TachoSil, a centrally authorised medicine containing human fibrinogen/human thrombin, is estimated to have been more than 4.8 million patients worldwide, in the period from first authorisation in 2004 until December 2014.

Following the publication² of one case of intestinal obstruction attributed to TachoSil, a signal of intestinal obstruction was identified by the EMA, based on four cases retrieved from EudraVigilance (including one case reported in the literature). 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 after an extended search. Taking into account that surgical treatment was required in five out of a total of six cases and that a causal relationship between intestinal obstruction and TachoSil in four cases is possible, the PRAC agreed to request the MAH for TachoSil to provide a cumulative review of cases of intestinal obstruction, small bowel obstruction and ileus associated with the use of TachoSil.

Summary of recommendation(s)

- The MAH for TachoSil (human fibrinogen/human thrombin) should submit to the EMA, within 60 days, a cumulative review of all cases referring to 'intestinal obstruction', 'small bowel obstruction' and 'ileus' associated with the use of TachoSil from spontaneous reporting, clinical studies and from published literature including an individual causality assessment of these reports. The MAH should also provide an estimation of the frequency of intestinal obstruction associated with the intestinal

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

² Vázquez Ruiz J et al. Intestinal obstruction due to the use of a surgical hemostatic agent. *Cir Esp.* 2013 Nov;91(9):620-1

adhesion to TachoSil. Regarding the spontaneously reported cases, the MAH should make every effort to obtain additional information. The MAH should discuss the potential mechanism of intestinal obstruction associated with TachoSil and effective risk minimisation measures to avoid intestinal adhesion to the TachoSil matrix.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Ipilimumab – YERVOY (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Signal of Vogt-Koyanagi-Harada syndrome (VKH)
EPITT 18403 – New signal

Background

Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

The post-marketing exposure for Yervoy, a centrally authorised medicine containing ipilimumab, is estimated to have been more than 30,540 patients worldwide, in the period from first authorisation in 2011 until March 2015.

Following the publication³ of one case of Vogt-Koyanagi-Harada (VKH) syndrome (uveitis with accompanying dermatologic, neurologic, and auditory involvement) associated with ipilimumab, a signal of VKH syndrome was identified by EMA, based on a total of three cases (including two literature cases and one spontaneous post-marketing case). 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 the literature. Taking this into account, the PRAC agreed to request the MAH to provide a cumulative review of cases of VKH in association with ipilimumab.

Summary of recommendation(s)

- The MAH for Yervoy (ipilimumab) should submit to the EMA, by 9 September 2015 in the framework of the ongoing PSUR procedure (DLP: 24/03/2015) (PSUSA/00009200/201503), a cumulative review of cases of VKH, taking into account all sources of information (studies, literature, spontaneous reports), and discuss the need for an update of the product information as applicable.

4.1.3. Palifermin – KEPIVANCE (CAP)

Applicant: Swedish Orphan Biovitrum AB

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of infection

³ Crosson JN, Laird PW, Debiec M, Bergstrom CS, Lawson DH, Yeh S. Vogt-Koyanagi-Harada-like Syndrome After CTLA-4 Inhibition With Ipilimumab for Metastatic Melanoma. *J Immunother* [Internet]. 2015; 38(2):80–4

EPITT 18401 – New signal

Background

Palifermin is a detoxifying agent indicated to decrease the incidence, duration and severity of oral mucositis in adult patients with haematological malignancies receiving myeloablative radiochemotherapy associated with a high incidence of severe mucositis and requiring autologous haematopoietic stem cell support.

The post-marketing exposure for Kepivance, a centrally authorised medicine containing palifermin, is estimated to have been more than 21,000 patients, in the period from first authorisation in 2005 until January 2015.

A signal of infection was identified by the United Kingdom, based on new non-clinical data communicated by the MAH. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available information provided by the MAH from a new non-clinical study and available clinical data. Taking into account all available evidence, the PRAC agreed to request the MAH to provide responses to a list of questions.

Summary of recommendation(s)

- The MAH for Kepivance (palifermin) should submit to the EMA, within 60 days, responses to a list of questions focusing on possible mechanisms and risk factors for infection, serious adverse events of bacterial, fungal or viral infections in clinical trials and further studies to investigate the risk of infection.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.4. Saxagliptin – ONGLYZA (CAP); saxagliptin, metformin – KOMBOGLYZE (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Signal of acute kidney injury
EPITT 18379 – New signal

Background

Saxagliptin is a dipeptidyl peptidase 4 (DPP4) inhibitor indicated alone or in combination with metformin, a biguanide, for the treatment of type 2 diabetes under certain conditions.

The post-marketing exposure for Onglyza, a centrally authorised medicine containing saxagliptin, is estimated to have been more than 1,689,003 patient-years worldwide, in the period from first authorisation in 2009 until July 2014. The post-marketing exposure for Komboglyze, a centrally authorised medicine containing saxagliptin and metformin, is estimated to have been more than 354,944 patient-years worldwide, in the period from first authorisation in 2011 until November 2014.

During routine signal detection activities, a signal of acute kidney injury was identified by the EMA, based on fifteen cases retrieved from EudraVigilance. 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. Taking into account that the cases in EudraVigilance are supportive of a signal and that a post-authorisation safety study (PASS) is currently ongoing comparing the risk of hospitalisation for acute kidney injury between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments, the PRAC agreed to request the MAH to provide a cumulative review of cases of acute kidney injury at the same time as the submission of the final clinical study report for this PASS due in October 2015.

Summary of recommendation(s)

- The MAH for Onglyza (saxagliptin) and Komboglyze (saxagliptin/metformin) should submit to the EMA, by 1 October 2015, at the same time as the final clinical study report of the PASS CV181-157ST, a cumulative review of cases reported of acute renal failure in association with saxagliptin and saxagliptin/metformin. The MAH should include clinical data from all sources including clinical trials, post marketing, relevant literature and evaluate the biological plausibility for a possible association taking into account any concomitant medications used by the patients and their potential interactions. Based on both the cumulative review and the results of the study, the MAH should discuss the need for any potential amendment to the product information and/or the risk management plan if applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab – HUMIRA (CAP) – EMEA/H/C/00000481/SDA/0242

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of convulsion
EPITT 18211 – Follow-up to March 2015

Background

For background information, see [PRAC minutes March 2015](#). The MAH replied to the request for information on the signal of convulsion and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. The PRAC agreed that the submitted analysis from clinical trials and post-marketing data does not suggest any safety concern regarding adalimumab and convulsions/seizure. Nevertheless, some aspects of the reported cases should still be clarified by the MAH.

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should submit to the EMA, within 30 days, responses to a list of questions.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.2. Amiodarone (NAP)

Applicant: Sanofi, various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of pancreatitis
EPITT 18216 – Follow-up to March 2015

Background

For background information, see [PRAC minutes March 2015](#). The MAH replied to the request for information on the signal of pancreatitis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review of cases concerning pancreatitis associated with amiodarone as well as the literature review. The spontaneous case reports of pancreatitis are suggestive of a causal association with amiodarone. Two case control studies were recently published which are consistent in their findings and conclude that amiodarone users have an increased risk of pancreatitis. Having considered the available data, the PRAC agreed that there is sufficient evidence to support a causal association between amiodarone and pancreatitis/acute pancreatitis and that the product information should be updated to include this new undesirable effect.

Summary of recommendation(s)

- The MAHs of amiodarone-containing medicinal products should update their product information to include pancreatitis (acute) as a new undesirable effect with an unknown frequency. This update of the product information should be addressed within the scope of the ongoing amiodarone PSUR single assessment procedure (PSUSA/00000166/201412).

4.3.3. Donepezil (NAP)

Applicant: Eisai Ltd.

PRAC Rapporteur: Julie Williams

Scope: Signal of rhabdomyolysis
EPITT 18261 – Follow-up to March 2015

Background

For background information, see [PRAC minutes March 2015](#). The MAH replied to the request for information on the signal of rhabdomyolysis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review of all cases of rhabdomyolysis from post-marketing spontaneous reports and clinical trials. Whilst the individual cases do not provide strong evidence of a causal association between donepezil and rhabdomyolysis, based on the cumulative information from 11 cases in particular (in 3 cases there was no concomitant use with statins), a causal or contributory role for donepezil in these cases of rhabdomyolysis and other less serious muscle disorders including weakness and pain cannot be excluded. Therefore, the PRAC agreed that the product information should be updated to include rhabdomyolysis as a new undesirable effect.

Summary of recommendation(s)

- The MAHs of donepezil-containing medicinal products should submit to the relevant EU national competent authorities (NCAs), within 60 days, a variation to include rhabdomyolysis as a new undesirable effect.

For the full PRAC recommendations, see [EMA/PRAC/450903/2015](#) published on the EMA website.

4.3.4. [Infliximab - INFLECTRA \(CAP\) - EMEA/H/C/002778/SDA/020, REMICADE \(CAP\) - EMEA/H/C/000240/SDA/152, REMSIMA \(CAP\) - EMEA/H/C/002576/SDA/019](#)

Applicant: Hospira UK Limited (Inflectra), Janssen Biologics B.V. (Remicade), Celltrion Healthcare Hungary Kft. (Remsima)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of rhabdomyolysis
EPITT 18129– Follow-up to March 2015

Background

For background information, see [PRAC minutes November 2014](#) and [PRAC minutes March 2015](#). The MAH replied to the request for information on the signal of rhabdomyolysis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses as well as the in-depth analysis of rhabdomyolysis from the ongoing national rheumatoid arthritis registry and from the Spanish and British registries provided by the MAHs.

Taking into account the available evidence from clinical trials, spontaneous case reports in EudraVigilance and data from a number of observational studies, the PRAC concluded that there is insufficient evidence for adding rhabdomyolysis to the product information or the RMP. Having considered this, the PRAC agreed that the MAHs of infliximab-containing medicinal products should continue to monitor reports of rhabdomyolysis as part of routine safety surveillance including through analysis of registry data.

Summary of recommendation(s)

- The MAHs of infliximab-containing medicinal products should continue to monitor reports of rhabdomyolysis as part of routine safety surveillance including through analysis of registry data.

4.3.5. 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 April 2015

Background

For background information, see [PRAC minutes November 2014](#) and [PRAC minutes April 2015](#).

The MAHs for medicinal products containing proton pump inhibitors (PPIs) (Takeda GmbH, Janssen-Cilag and AstraZeneca UK Limited) provided comments on the wording proposed by the PRAC to reflect in the product information the risk of subacute cutaneous lupus erythematosus (SCLE) and these responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the feedback received from the MAHs of PPIs-containing medicinal products on the wording proposed by the PRAC to reflect the risk of SCLE as well as the cumulative reviews and interpretation of case reports from the MAHs' global safety databases and of case reports published in the literature provided by the MAHs. Having considered this, the PRAC confirmed that there is sufficient evidence to indicate that SCLE is likely to be a class effect for PPIs. Taking into consideration the relevant data across all substances in the class, including the cases with positive re-challenge, the evidence from published literature, and the likelihood of under-reporting given that photosensitivity is a known side effect of PPIs, the PRAC agreed that the product information of medicinal products containing PPIs should be amended to reflect the very infrequent risk of SCLE.

Summary of recommendation(s)

- The MAHs of medicinal products containing omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole and dexlansoprazole should submit, within 90 days, to the EMA or to the EU national competent authorities (NCAs) as applicable, a variation to update the product information to include a new warning on subacute cutaneous lupus erythematosus (SCLE) and to include it as a very infrequent undesirable effect.

For the full PRAC recommendations, see [EMA/PRAC/450903/2015](#) published on the EMA website.

4.3.6. [Warfarin \(NAP\)](#)

Applicant: various

PRAC Rapporteur: Torbjörn Callreus

Scope: Signal of bone density decrease
EPITT 18173 – Follow-up to March 2015

Background

For background information, see [PRAC minutes March 2015](#). Following the March 2015 PRAC discussion, it was agreed that it would be important to seek the views of the paediatric committee (PDCO) on the clinical relevance of the magnitude of the decreased bone mineral density described in the studies in children treated with warfarin, and whether this should warrant further investigation by the PRAC. The PDCO discussed this at their May 2015 meeting and feedback on these discussions was provided to the PRAC.

Discussion

The PRAC considered the conclusions and recommendations from the PDCO regarding the need to further assess the potential effects on bone mineral density associated with long term treatment with warfarin in children. The PRAC agreed that further investigations are needed to fully evaluate the strengths and limitations of the evidence described in the studies by *Monagle et al.*⁴, *Barnes et al.*⁵, *Avgeri et al.*⁶, *Irastorza et al.*⁷, and *Bendaly et al.*⁸ with regard to the risk of reduced bone mineral density in this particular population. Therefore the PRAC endorsed a list of questions to be addressed by the warfarin brand leaders and innovator MAHs on the strengths and limitations of the evidences including the clinical relevance of the reported observations, asking the MAHs to provide a proposal for monitoring and update to the product information if justified by the available scientific evidence.

Summary of recommendation(s)

- Bristol Myers Squibb, Takeda, Nycomed and Teofarma (MAHs brand leaders and innovators for warfarin in the European Union) should submit to the EMA, within 60 days, responses to a list of questions.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

5. Risk management plans (RMPs)

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.

⁴ Monagle K., Jones S, King I et al. Anticoagulation of cardiomyopathy in children. *Thrombosis research*. May 10, 2014; 134:255-258.

⁵ Barnes C, Newall F, Ignjatovic V, et al. reduced bone density in children on long-term warfarin. *Pediatric Res* 2005; 57:578-581.

⁶ Avgeri M, Papadopoulou A, Platokouki H, Douros K, Rammos S, Nicolaidou P, Aronis S. Assessment of bone mineral density and markers of bone turnover in children under long-term oral anticoagulant therapy. *J Pediatr Hematol Oncol*. 2008 Aug;30(8):592-7.

⁷ Irastorza, I. X., B. Krishnamurthy, et al. (2010). Anticoagulant therapy with warfarin does not interfere with bone mineral density and growth of children on home parenteral nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 50: E180.

⁸ Bendaly EA1, DiMeglio LA, Fadel WF, Hurwitz RA. Bone density in children with single ventricle physiology. *Pediatr Cardiol*. 2015 Apr;36(4):779-85.

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

See also Annex I 14.1.

5.1.1. Alirocumab - EMEA/H/C/003882

Scope: Reduction of low-density lipoprotein cholesterol (LDL-C) and increase high-density lipoprotein cholesterol (HDL-C)

5.1.2. Fentanyl - EMEA/H/C/002715

Scope: Treatment of acute moderate to severe post-operative pain

5.1.3. Ferric citrate coordination complex - EMEA/H/C/003776

Scope: Treatment of hyperphosphataemia

5.1.4. Guanfacine - EMEA/H/C/003759

Scope: Treatment of attention deficit hyperactivity disorder (ADHD)

5.1.5. Methotrexate - EMEA/H/C/003756

Hybrid

Scope: Treatment of rheumatological and dermatological diseases

5.1.6. Pegaspargase - EMEA/H/C/003789

Scope: Treatment therapy in acute lymphoblastic leukaemia (ALL)

5.1.7. Pemetrexed - EMEA/H/C/003788

Generic

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

5.1.8. Pemetrexed - EMEA/H/C/003970

Generic

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

5.1.9. Pemetrexed - EMEA/H/C/004114

Generic

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

5.1.10. Pemetrexed - EMEA/H/C/003905

Generic

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

5.1.11. Pemetrexed - EMEA/H/C/004011

Generic

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

5.1.12. Sufentanil - EMEA/H/C/002784

Hybrid

Scope: Management of pain

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

See also Annex I 14.3.

5.3.1. Dabrafenib - TAFINLAR (CAP) – EMEA/H/C/002604/WS0736/0011 trametinib – MEKINIST (CAP) - EMEA/H/C/002643/WS0736/0008

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to add a new therapeutic indication for the use in combination of trametinib and dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3 of the SmPC are updated. The Package Leaflet and RMP are updated accordingly

Background

Dabrafenib and trametinib are protein kinase inhibitors and each of them is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

The CHMP is evaluating an extension of the therapeutic indication for Tafinlar and Mekinist, centrally authorised products containing dabrafenib and trametinib respectively, to include their use in combination for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The respective RMPs version 11 for Mekinist (trametinib) and version 7.0 for Tafinlar (dabrafenib) in the context of the worksharing extension of indication under evaluation by the CHMP were considered acceptable provided that updated RMPs and satisfactory responses to the PRAC list of questions are submitted.
- With regard to dabrafenib, the PRAC considered that neutropenia should be included as an important identified risk under combination therapy only. In addition, photosensitivity should be kept as a potential risk and the risk minimisation should be updated accordingly. Moreover, the MAH should further substantiate the addition of

non-interventional studies 201709⁹ and 201710¹⁰ to the pharmacovigilance plan. With regard to trametinib, the PRAC considered that neutropenia should be included as an important identified risk under combination therapy only, while use in the elderly should be added as an important potential risk for trametinib monotherapy. Finally, studies BRF117277¹¹ and 115532¹² should be included as additional pharmacovigilance activities (category 3) to address the important identified risk of haemorrhagic events.

5.3.2. Deferasirox – EXJADE (CAP) - EMEA/H/C/000670/X/0043

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Corinne Fechant

Scope: Extension application for a new pharmaceutical form and new strengths (Exjade 90, 180 mg and 360 mg film-coated tablets)

Background

Deferasirox is an iron chelating agent indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major, for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in some specific sub-populations, as well as for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes under certain conditions.

The CHMP is evaluating a line extension for Exjade, a centrally authorised product containing deferasirox, for a new pharmaceutical form and new strengths (Exjade 90, 180 mg and 360 mg film-coated tablets). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this line extension procedure.

Summary of advice

- The RMP version 10 for Exjade (deferasirox) in the context of the line extension under evaluation by the CHMP was considered acceptable provided that an updated RMP and satisfactory responses to the PRAC list of questions are submitted.
- The PRAC considered that medication error should be added to the safety specification as an important potential risk. As for the ongoing study F2201¹³, the PRAC advised that the final results should be submitted as an imposed additional pharmacovigilance activity. In addition, the MAH should perform a survey 6 months after the launch of the film-coated tablet formulation to assess awareness amongst healthcare professionals and patients and to measure the appropriate use of both formulations. The MAH should also provide a single set of educational material for both formulations and all indications, for patients and healthcare professionals. This material should include as a key element the dose converting table for safe switching from one formulation to

⁹ ECHO analyses from randomized controlled trials of dabrafenib to evaluate the potential for cardiac valve abnormalities

¹⁰ Evaluation of secondary malignancies in patients treated with dabrafenib in randomized controlled trials

¹¹ Study to evaluate treatment of dabrafenib plus trametinib in subjects with BRAF mutation-positive melanoma that has metastasized to the brain

¹² Study of the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection (COMBI-AD)

¹³ Study evaluating adverse event incidence between formulations in a patient population over a 6 months treatment period

another. It should also ensure that patients switched from one formulation to another are instructed on the proper use of the new formulation.

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

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.4 of the SmPC in order to add a recommendation to consider interruption of treatment in patients with low lymphocyte counts ($<0.5 \times 10^9/L$) persisting for more than six months and to monitor lymphocyte counts until recovery. Update of section 4.8 of the SmPC with information on observed low lymphocyte counts in clinical studies with Tecfidera and progressive multifocal leukoencephalopathy (PML) occurrence in the setting of severe and prolonged lymphopenia. Furthermore, the due dates of two commitments as part of the RMP have been revised

Background

Tecfidera is a centrally authorised product containing dimethyl fumarate, indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). Other medicinal products containing dimethyl fumarate (Fumaderm, Fumaderm Initial) authorised nationally in Germany are indicated for the treatment of psoriasis.

The CHMP is evaluating a worksharing variation procedure for Tecfidera and Fumaderm/Fumaderm Initial, to update the product information to add progressive multifocal leukoencephalopathy (PML) and recommendations following previous signal evaluation. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this worksharing variation. For background, see [PRAC minutes February 2015](#) and [PRAC minutes April 2015](#). At the current meeting, the Scientific Advisory Group (SAG)-Neurology Chair reported to the PRAC the outcome of their SAG meeting held on 11 June 2015.

Summary of discussion

- The PRAC noted the report from the SAG. The SAG advised on risk factors for developing PML as well as on parameters to be studied on the potential risks of lymphopenia and PML. Furthermore, the SAG commented on monitoring algorithms to minimise the risk of developing PML for patients with MS or psoriasis receiving fumarates/dimethylfumarate. The SAG experts supported further investigation on the posology for patients experiencing lymphopenia in view of efficacy and safety.

5.3.4. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/000717/II/0079

Applicant: Celgene Europe Limited

PRAC Rapporteur: Corinne Fechant

Scope: Extension of indication to add treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). As a consequence, SmPC sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. A revised version of the RMP (version 25.0) was provided

Background

Lenalidomide is an anti-neoplastic, anti-angiogenic, pro-erythropoietic immunomodulator indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant, and indicated in combination for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. In addition, lenalidomide is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

The CHMP is evaluating an extension of the therapeutic indication for Revlimid, a centrally authorised product containing lenalidomide, to include the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see [PRAC minutes March 2015](#).

Summary of advice

- The RMP version 26.0 for Revlimid (lenalidomide) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable, provided an updated RMP and satisfactory responses to the PRAC list of questions are submitted.
- The PRAC considered that the MAH should discuss and propose ways to document the risks in patients with RRMCL treated with lenalidomide in order to obtain real life data on the identified safety risks: second primary malignancies (SPM), tumour flare reaction (TFR), venous thromboembolism (VTE) and arterial thromboembolism (ATE). In addition, the MAH should discuss whether existing PASS protocols can be revised to also include patients with RRMCL to address these risks and propose a revision as applicable. Alternatively, the MAH should propose a new PASS protocol.

6. Periodic safety update reports (PSURs)

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

See also Annex I 15.1.

6.1.1. Avanafil – SPEDRA (CAP) - PSUSA/10066/201412

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

Background

Avanafil is a highly selective and potent, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) indicated for the treatment of erectile dysfunction in adult men.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Spedra, a centrally authorised medicine containing avanafil, 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 Spedra (avanafil) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new contraindication for the co-administration of PDE5 inhibitors including avanafil with guanylate cyclase stimulators, such as riociguat as it may cause symptomatic hypotension. Additional information on this contraindication should also be included in the interaction with other medicinal products and other forms of interaction section. Therefore the current terms of the marketing authorisation(s) should be varied¹⁴.
- In the next PSUR, the MAH should provide information regarding the cumulative enrolment of patients in the new ongoing non-interventional study that has been submitted by the MAH during this interval. The MAH should also remove 'adult males with significant pre-existing cardiovascular diseases' from the missing information in the RMP and as a consequence the MAH should no longer include it under the evaluation of risks and new information section in the next PSUR. The MAH should finally provide information regarding the 40 treatment-emergent adverse events (apart from headache) reported in the phase IV clinical trial studying the effects of avanafil on vision.

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.

6.1.2. Caspofungin – CANCIDAS (CAP) - PSUSA/00576/201412

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Veerle Verlinden

Scope of procedure: Evaluation of a PSUSA procedure

Background

Caspofungin is a semi-synthetic lipopeptide (echinocandin) compound which inhibits the synthesis of beta (1,3)-D-glucan, an essential component of the cell wall of many filamentous fungi and yeasts. It is indicated for the treatment of invasive candidiasis in adult or paediatric patients, invasive aspergillosis in adult or paediatric patients under certain conditions and empirical treatment for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropaenic adult or paediatric patients.

¹⁴ Update of SmPC sections 4.3 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Candidas, a centrally authorised medicine containing caspofungin, 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 Candidas (caspofungin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- As new cases of drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were reported during this PSUR covering period, the MAH should in the next PSUR closely monitor cases of serious cutaneous adverse reactions (SCAR) and discuss all reported cases.
- The MAH should be requested to submit to the EMA, within 6 months, a cumulative analysis of the risk of SCARs (including SJS, TEN and DRESS).

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.

6.1.3. Clofarabine – EVOLTRA (CAP) - PSUSA/00805/201412

Applicant: Genzyme Europe BV

PRAC Rapporteur: Corinne Fechant

Scope of procedure: Evaluation of a PSUSA procedure

Background

Clofarabine is a purine nucleoside anti-metabolite (antineoplastic agent) indicated for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Evoltra, a centrally authorised medicine containing clofarabine, 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 Evoltra (clofarabine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning on discontinuation of treatment if substantial increase in liver enzymes is observed. In addition the product information should also be updated to include hepatic failure as a new undesirable effect with a common frequency and hepatitis as a new undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied¹⁵.

¹⁵ 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

- In the next PSUR, the MAH should present a review of the off-label use in pediatric acute myeloblastic leukaemia (AML), in ALL patients with less than two prior regimens, or in combination with other drugs. The MAH should also provide a detailed analysis of cases pertaining to renal failure, acute renal failure and acute kidney injury/nephrotoxicity reported spontaneously or collected from clinical trials, and a literature review. The MAH should discuss the need to update sections 4.4 and 4.8 of the SmPC with renal failure/acute renal failure. Finally the MAH should provide a review of any new reported cases (solicited and unsolicited cases) with a fatal outcome received during the next PSUR reporting period.
- The MAH should be requested to submit an updated RMP with the next PSUR removing the important identified risk 'off-label use in pediatric AML, in ALL patients with less than two prior regimens, or in combination with other drugs' but including 'hepatitis' and 'hepatic failure' as new important identified 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.

6.1.4. Ferumoxytol – RIENSO - PSUSA/01386/201412

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Martin Huber

Scope of procedure: Evaluation of a PSUSA procedure (EC decision on MA withdrawal dated 13 April 2015)

Background

Ferumoxytol is a colloidal iron-carbohydrate complex indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD). Following due submission and start of this PSUR procedure, the marketing authorisation of Rienso was withdrawn on 13 April 2015. In addition, the MAH informed EMA that the product was recalled from the EU market. As a consequence, the PRAC did not adopt a recommendation, but only noted the Rapporteur's preliminary assessment report.

Summary of conclusions

The PRAC noted that during the reporting period of this PSUR no changes in characteristics of listed or unlisted adverse drug reactions or increase in reporting frequency associated with ferumoxytol were identified. The safety profile of Rienso remained unchanged in the reporting period. The PRAC also noted that the marketing authorisation for the product had been withdrawn at the request of the MAH ([Commission Implementing Decision of 13.04.2015](#)) and that the product had been recalled from the EU market.

6.1.5. Fingolimod – GILENYA (CAP) - PSUSA/01393/201502

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope of procedure: Evaluation of a PSUSA procedure

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (MS) under certain conditions.

The PRAC is currently reviewing the benefit-risk balance of Gilenya (fingolimod), a centrally authorised medicine, in the framework of the assessment of a PSUR procedure due for PRAC recommendation in September 2015.

Summary of conclusions

- The PRAC noted the report from the neurology scientific advisory group (SAG) meeting held on 11 June 2015. The SAG advised on risk factors for developing progressive multifocal leukoencephalopathy (PML) as well as on parameters to be studied on the potential risks of lymphopenia and PML. The experts agreed that further data were needed on the impact of T-helper and regulator cells on PML development. Furthermore the SAG commented on monitoring algorithms to minimise the risk of developing PML and their general applicability. No clear advice could be given on the fingolimod treatment strategy for high risk PML patients or patients diagnosed with PML.

6.1.6. Human fibrinogen, human thrombin – EVICEL (CAP); TACHOSIL (CAP) - PSUSA/01627/201412

Applicant: Omrix Biopharmaceuticals N. V. (Evicel), Takeda Austria GmbH (TachoSil)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

Background

Human fibrinogen, a glycoprotein, and human thrombin, a serine protease, used in combination are indicated in adults for supportive treatment in surgery for improvement of haemostasis, to promote tissue sealing, and for suture support in vascular surgery and for suture line sealing in dura mater closure.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Evicel and TachoSil, centrally authorised medicines containing human fibrinogen and human thrombin, 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 Evicel and TachoSil (human fibrinogen, human thrombin) in the approved indications remains favourable.
- The current terms of the marketing authorisations should be maintained.
- The MAH for TachoSil should be requested to analyse spontaneous reports and other reports regarding immunogenicity from all studies, including observational and clinical studies and to submit a variation to amend the product information as appropriate.

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.

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

Background

Mirabegron is a potent and selective beta 3-adrenoceptor agonist indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Betmiga, a centrally authorised medicine containing mirabegron, 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 Betmiga (mirabegron) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new contraindication in patients with severe uncontrolled hypertension and to revise the current warning on hypertension to reflect the recommendation to measure blood pressure. In addition the product information should be updated to include urinary retention as a new undesirable effect with a rare frequency and insomnia as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied¹⁶.
- The MAH should inform healthcare professionals of these changes via a Direct Healthcare Professional Communication (DHPC).
- In the next PSUR, the MAH should provide a cumulative review of cases of hypertensive crisis after the use of mirabegron including an analysis by dose. Based on the output of this review, an update to the product information should be considered. The MAH should also provide a cumulative review of cases of acute renal failure, including an analysis by dose. Based on the output of this review, an update to the product information should also be considered. The MAH should provide a review of headache, focused on cases with serious adverse events. The MAH should further consider, therefore, if warnings could be strengthened for patients with severe headache. The MAH should provide a comparative analysis between the adverse drug reactions collected in the elderly (>65 years old) and the adverse drug reactions collected in non-elderly patients including an analysis by dose. Finally, the MAH should discuss the results of the ongoing non-interventional studies
- The MAH should be requested to revise the RMP in the next update to upgrade blood pressure and urinary retention from important potential risks to important identified risks, to include cerebrovascular events as a new important potential risk, to remove decreased lymphocytes and severe uncontrolled hypertension as missing information.

¹⁶ Update of SmPC sections 4.3, 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

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. Omalizumab – XOLAIR (CAP) - PSUSA/02214/201412

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

Background

Omalizumab is a recombinant deoxyribonucleic acid (DNA)-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE) indicated for the treatment of asthma in adults and children over 6 years of age under certain conditions and for the treatment of chronic spontaneous urticaria in adults and adolescents aged 12 and above under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xolair, a centrally authorised medicine containing omalizumab, 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 Xolair (omalizumab) 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 closely monitor reports of herpes zoster, systemic lupus erythematosus and events in children between 6 and 12 years of age.
- The MAH should be requested to submit to EMA, within 60 days, a cumulative review of all reported cases of venous thromboembolism (VTE) (separately for clinical trial and post-marketing cases) including a discussion if any actions are needed.

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. Pertuzumab – PERJETA (CAP) - PSUSA/10125/201412

Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope of procedure: Evaluation of a PSUSA procedure

Background

Pertuzumab is a recombinant humanised monoclonal antibody indicated for use in combination with trastuzumab and docetaxel in adult patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Perjeta, a centrally authorised medicine containing pertuzumab, 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 Perjeta (pertuzumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new warning on severe diarrhoea. Therefore the current terms of the marketing authorisation(s) should be varied¹⁷.
- In the next PSUR, the MAH should review the case of cellulitis gangrenosa, as well as all the cases of renal failure and acute renal failure.

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.

6.1.10. Ponatinib – ICLUSIG (CAP) - PSUSA/10128/201412

Applicant: Ariad Pharma Ltd

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

Background

Ponatinib is a protein kinase inhibitor indicated in adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) under certain conditions and with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Iclusig, a centrally authorised medicine containing ponatinib, 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 Iclusig (ponatinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to revise the current warning on vascular occlusions to include retinal vascular occlusions and refer to the possibility of permanent visual loss, on hypertension to include hypertensive crisis and on hepatotoxicity to include that hepatic failure has been observed. In addition, the product information should be updated to include hypertensive crisis and hepatic failure as new undesirable effects with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied¹⁸.

¹⁷ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

¹⁸ 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

- In the next PSUR, the MAH should provide a review of cases of bone marrow transplant, and stem cell transplant. The MAH should also comment on the status of the phase 2 dose-ranging study, which was imposed as a condition of the marketing authorisation as part of the Article 20 referral procedure. The MAH should provide a review of all cases involving halving or splitting of tablets, a discussion of the potential risks to patients when tablets are divided in this way, and consideration of whether any changes to the product information are required to minimise these risks. The MAH should discuss the following literature articles: *Zhang et al.*¹⁹, *Mayer et al.*²⁰, *Palani et al.*²¹ and consider whether any action is required in relation to these articles, especially in relation to thyroid dysfunction (*Palani et al*), as this is a known side effect of other members of this drug class.
- The MAH should be requested to submit a variation, within 90 days, to EMA to discuss proposals for dose modifications for hepatic toxicity and the possible revision of starting dose recommendations for patients with hepatic impairment, in support of any dose modification recommendations for hepatic toxicity. This variation should include a discussion on all the available evidence (pharmacokinetic (PK) data or other).

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.

6.1.11. Reteplase – RAPILYSIN (CAP) - PSUSA/02623/201411

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Martin Huber

Scope of procedure: Evaluation of a PSUSA procedure

Background

Reteplase is a recombinant plasminogen activator indicated for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 12 hours after the onset of acute myocardial infarction (AMI) symptoms.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rapilysin, a centrally authorised medicine containing reteplase, 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 Rapilysin (reteplase) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a cumulative review or variation, as appropriate, regarding the potential risk of cholesterol embolisation. This submission

¹⁹ Zhang M, Hassan KM, Musiek A, Rosman IS. Ponatinib-induced neutrophilic panniculitis. *J Cutan Pathol*. 2014 Jul; 41(7):597-601

²⁰ Mayer K, Gielen GH, Willinek W, Müller MC, Wolf D. Fatal progressive cerebral ischemia in CML under third-line treatment with ponatinib. *Leukemia*. 2014 Apr; 28(4):976-7.

²¹ Palani R, Apperley J, Reid A, Foroni L, Deplano S, Milojkovic D. Thyroid Function Abnormalities Associated with Ponatinib Therapy in Patients with Chronic Myeloid Leukemia. *Thyroid*. 2015; 25,6: 1-2

should include a discussion of the scientific evidence and a discussion around the relevance of the inclusion of this adverse reaction in the product information of Rapilysin in light of the information available in published literature.

- As part of the next variation of the product information, the MAH is requested to reformat section 4.8 of the SmPC in order to enable a direct oversight to both frequencies and SOCs²².

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.

6.1.12. Verteporfin – VISUDYNE (CAP) - PSUSA/03110/201412

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope of procedure: Evaluation of a PSUSA procedure

Background

Verteporfin, a semisynthetic mixture of porphyrins also known as benzporphyrin derivative monoacid ring A (BPD-MA), is a 1:1 mixture of the equally active regioisomers BPD-MA_C and BPD-MA_D indicated for the treatment of adults with exudative (wet) age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularisation (CNV) or adults with subfoveal choroidal neovascularisation secondary to pathological myopia.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Visudyne, a centrally authorised medicine containing verteporfin, 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 Visudyne (verteporfin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to revise the current warning on hypersensitivity reactions in the 'special warnings and precautions for use', and in the 'undesirable effects' sections to include 'convulsions' in the symptoms potentially associated with vasovagal and hypersensitivity reactions related to Visudyne infusion. Therefore the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAH should provide a cumulative review and an analysis of the cases of pulmonary oedema.

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.

²² System Organ Class from the Medical Dictionary for Regulatory Activities (MedDRA)

²³ 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

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

See Annex I 15.2.

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

See also Annex I 15.3.

6.3.1. Amiodarone (NAP) - PSUSA/00000166/201412

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Amiodarone is a Vaughan Williams Class III anti-arrhythmic agent indicated for the treatment of severe rhythm disorders not responding to other therapies or when other treatments cannot be used.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing amiodarone, 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 amiodarone-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information of oral amiodarone-containing medicinal products should be updated to include anaphylactic reaction, anaphylactic shock, pancreatitis (acute), decreased appetite, parkinsonism, parosmia, delirium (including confusion), severe skin reactions as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), bullous dermatitis, drug reaction with eosinophilia and systematic symptoms (DRESS) as new undesirable effects with an unknown frequency, constipation and eczema as new undesirable effects with a common frequency and dry mouth as a new undesirable effect with an uncommon frequency. The product information of intravenous (IV) amiodarone-containing medicinal products should also be updated to include pancreatitis (acute), delirium (including confusion), TEN/SJS, bullous dermatitis and DRESS as new undesirable effects with an unknown frequency and eczema as a new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied²⁴.

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.

²⁴ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.2. Hydroxyethyl starch (NAP) - PSUSA/00001694/201501

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Hydroxyethyl starch (HES) products derive from potato or corn with different molecular weights and substitution ratios (e.g. 200/0,5; 130/0,4). They are approved for intravenous use for infusion and are indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing hydroxyethyl starch, 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 hydroxyethyl starch-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all the MAHs should discuss the use of HES in perioperative settings. In this context, the MAHs should provide a comprehensive review of the use of HES in perioperative settings using databases (among others MAHs' own databases, XMEDALL database group in particular EMBASE, MEDLINE), including a detailed description and assessment of individual case reports (if available) which occurred since marketing authorisation. Based on the results of this review, the MAHs should discuss whether further action is needed and whether the issue should be reflected in the product information. Concerning the potential dose dependency of HES administration in relation to acute kidney injury the MAHs should discuss the study from *Kashy et al.*²⁵ and provide their conclusions on whether its results should be reflected in the product information. The MAHs should also provide a full overview of the status of the fulfilment of the conditions imposed on their marketing authorisations following the [Article 107i referral procedure](#) finalised in 2013.

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.

6.3.3. Methylprednisolone (NAP) - PSUSA/00002026/201411

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

²⁵ Kashy BK, Podolyak A, Makarova N, M.S., Dalton J, Sessler D., Kurz A: Effect of Hydroxyethyl Starch on Postoperative Kidney Function in Patients Having Noncardiac Surgery. *Anesthesiology*. 2014 Oct; 121(4): 730-9. doi: 10.109

Background

Methylprednisolone is a glucocorticoid with potent anti-inflammatory and immunosuppressive effects. It is indicated in the treatment of patients with endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, oedematous states, trichinosis, tuberculous meningitis, and cerebral oedema.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing methylprednisolone, 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 methylprednisolone-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information of all methylprednisolone-containing medicinal products for systemic use should be updated to include a new warning on the need for appropriate monitoring of hepatobiliary disorders, to include leukocytosis, thrombotic events, epidural lipomatosis, chorioretinopathy and increased liver enzymes as new undesirable effects with an unknown frequency. In addition the product information of parenteral formulation of methylprednisolone-containing medicinal products should be updated to include hepatitis as a new undesirable effect. Finally the product information for all methylprednisolone-containing medicinal products for systemic use (contraindications, special warnings and precautions for use, interactions with other medicinal products and other forms of interactions and effects on ability to drive and use machines sections) should be updated to include relevant safety information based on cumulated information for the substance as necessary. Therefore the current terms of the marketing authorisation(s) should be varied²⁶.

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.

Post-meeting note: following comments raised by the CMDh during their July 2015 plenary meeting, a revised recommendation will be adopted at PRAC in September 2015.

6.3.4. [Rabbit anti-human thymocyte \(concentrate for solution for infusion\) \(NAP\) - PSUSA/00010252/201412](#)

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

²⁶ 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 CMDh for adoption of a position

Rabbit anti-human thymocyte (concentrate for solution for infusion) is a concentrated, highly purified, polyclonal anti-human T-lymphocyte immunoglobulin preparation derived from rabbits after immunisation with a T-lymphoblast cell line (Jurkat) and belongs to the pharmacological class of immunosuppressive agents. It is indicated for the prevention of acute transplant rejection after solid organ transplantation in combination with other immunosuppressive drugs, the treatment of acute steroid resistant rejections and the prevention of graft-versus-host disease (GvHD) in stem cell transplantation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing rabbit anti-human thymocyte (concentrate for solution for infusion), 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 rabbit anti-human thymocyte (concentrate for solution for infusion)-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should closely monitor and provide a comprehensive review regarding coagulopathy/disseminated intravascular coagulation (DIC) cases, discuss in addition the plausible mechanism of coagulopathy/DIC in association with rabbit anti-human thymocyte (concentrate for solution for infusion) use and consider updating the product information to include it as a new undesirable effect. The MAH should also closely monitor the signal of hepatic disorders, and provide a review of this signal. The MAHs should consider updating the product information to include it as a new undesirable effect.

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.

6.3.5. Rabbit anti-human thymocyte (powder for solution for infusion) (NAP) - PSUSA/00010184/201412

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Rabbit anti-human thymocyte (powder for solution for infusion) is a concentrated, highly purified, polyclonal anti-human T-lymphocyte immunoglobulin preparation derived from rabbits after immunisation with human thymocytes and belongs to the pharmacological class of immunosuppressive agents. It is indicated in the prevention and the treatment of graft rejection after solid organ transplantation, as well as the treatment of aplastic anaemia, the prevention of acute and chronic graft-versus-host disease (GvHD) after hematopoietic stem cell transplantation, and the treatment of steroid resistant, acute GvHD.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing rabbit anti-human thymocyte (powder for solution for infusion), 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 rabbit anti-human thymocyte (powder for solution for infusion)-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new warning on the need for monitoring of thrombocytes and coagulation parameters in patients with hepatic diseases, to include transaminases increased as a new undesirable effect with a common frequency and to include hepatocellular injury, hepatotoxicity, and hepatic failure as new undesirable effects with an uncommon frequency. Additionally, the product information should be updated to include a single table listing all adverse reactions including cases from clinical trials and from post-marketing period with their respective frequency category in the undesirable effects section, in line with the [Guideline on Summary Product Characteristics](#). Therefore the current terms of the marketing authorisation(s) should be varied²⁷.
- In the next PSUR, the MAHs should add hepatic impairment to the list of important identified risks. The MAHs should also discuss the plausible mechanism for the increased risk of coagulopathy and disseminated intravascular coagulation (DIC) in association with thymoglobulin use and to consider updating the product information to include it as a new undesirable effect.

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.

6.3.6. Testosterone undecylate (injection) (NAP) - PSUSA/00010161/201411

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Testosterone undecylate is an ester of the naturally occurring androgen, testosterone, which is released by cleavage of the side chain. Testosterone undecylate (injection) is indicated for testosterone replacement in primary and secondary male hypogonadism.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing testosterone undecylate (injection), and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

²⁷ 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 CMDh for adoption of a position

- Based on the review of the data on safety and efficacy, the risk-benefit balance of testosterone undecylate (injection)-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include pulmonary oil microembolism as a new undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied²⁸.
- In the next PSUR, the MAHs of all testosterone-containing products should discuss the signal of venous thromboembolism (VTE). A full assessment of the VTE and cardiovascular risk should be provided by all the MAHs within the next PSUR.

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.

6.4. 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 also Annex I 16.1.

7.1.1. Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/0014.2

Applicant: Fresenius Kabi Deutschland GmbH (Volulyte, Voluven Fresenius, Voluven, HyperHAES, HAES-steril), Serumwerk Bernburg AG (VitaHES, Vitafusal, Plasma Volume Redibag, PlasmaHES Redibag, Hesra, Hesra infuusioneste)

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a revised PASS protocol (drug utilisation study) to assess the effectiveness of the risk minimisation taken following the European Commission decision dated 19 December 2013 for the referral procedure EMEA/H/A-1071/1376

Background

For background, see [PRAC minutes July 2014](#), [PRAC minutes October 2014](#) and [PRAC minutes February 2015](#). The Rapporteur assessed the draft revised protocol submitted in accordance with the agreed timetable.

Endorsement/Refusal of the protocol

The PRAC, having considered the joint draft protocol version 1.4 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for PASS study for the above listed medicinal products.

²⁸ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

²⁹ In accordance with Article 107n of Directive 2001/83/EC

7.1.2. Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/0024

Applicant: B. Braun Melsungen AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a new PASS protocol (drug utilisation study) to assess the effectiveness of the risk minimisation taken following the European Commission decision dated 19 December 2013 for the referral procedure EMEA/H/A-1071/1376

Background

Hydroxyethyl starch (HES) products derive from potato or corn with different molecular weights and substitution ratios (e.g. 200/0,5; 130/0,4). They are approved for intravenous use for infusion and are indicated for treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

A protocol for a post-authorisation safety study to assess the effectiveness of the risk minimisation taken was submitted to the PRAC by the MAH in accordance with conditions to the marketing authorisation included in the EC decision [Annex IV](#) for the referral under 107i of ([EMA/606303/2013](#)) for hydroxyethyl starch-containing medicines.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that that the design of the study did not fulfil the study objectives. The PRAC considers that 3,000 patients is the required sample size for this drug utilisation study and therefore does not agree with the MAH's proposal to only include 1,000 patients. The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied.

7.1.3. Valproate (NAP) - EMEA/H/N/PSP/j/0029

Applicant: Sanofi R&D, various

PRAC Rapporteur: Sabine Straus

Scope: Protocol for a drug utilisation study to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate

Background

According to the conclusions of a referral under Article 31 of Directive 2001/83/EC for valproate-containing medicines, marketing authorisation holders are to conduct a post-authorisation safety study to evaluate the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate. A consortium of MAHs submitted a draft protocol for this study for assessment by the PRAC.

Conclusion

The PRAC appointed Sabine Straus as PRAC Rapporteur for the assessment of the protocol and agreed a timetable for this procedure.

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

See Annex I 16.2.

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

None

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

See also Annex I 16.4.

7.4.1. Etanercept – ENBREL (CAP) - EMEA/H/C/000262/II/0179 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of final report from the Organisation of Teratology Information Specialists (OTIS) registry, as listed in part III of the RMP

Background

Enbrel is a centrally authorised medicine containing etanercept, indicated for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), axial spondyloarthritis, ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis, plaque psoriasis and paediatric plaque psoriasis.

The MAH had committed to perform a non-interventional PASS to be conducted using the Organization of Teratology Information Specialists (OTIS) registry, as listed in Part III of the Risk Management Plan. The Rapporteur assessed the final results from the Rheumatic Diseases and Psoriasis Pregnancy Registry study (a prospective, observational, exposure cohort study of pregnancy outcome in women with RA, JIA, AS, PsA, or psoriasis who are exposed to etanercept in the first trimester of pregnancy, designed to evaluate the possible teratogenic effect of etanercept when used in the first trimester of pregnancy with respect to major structural birth defects of newborns).

Summary of advice

The PRAC discussed the final results of the OTIS registry study as well as the MAH's responses to the request for supplementary information. The adjusted odds ratio (OR) estimated a greater than 2-fold relative risk of major birth defects in the etanercept cohort, compared with diseased controls. An analysis excluding genetic events still showed a greater than 2-fold increased risk, with the greater part of the confidence intervals compatible with an increased risk. The women in the etanercept and diseased-exposed cohorts were receiving different treatments, and could potentially have different disease severity. But this was not supported by the data on measures of disease severity at baseline. For other factors that could be expected to influence the rate of major birth defects (e.g. maternal comorbidities, smoking status, and previous pregnancies a

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

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

malformation), there were no major differences between the cohorts. According to the MAH's responses, there is not currently a clearly established mechanism by which tumour necrosis factor (TNF)-alpha inhibition is known to cause major congenital malformation. Further examination of the types of birth defect occurring in the OTIS registry did not provide sufficient evidence to conclude on whether there is a pattern of major malformations that indicates that the relative risk of certain types of major birth defects is increased more than others. This may be due to the number of major birth defects in the OTIS registry being too low to detect any unusual patterns in the type of events. The MAH's cumulative spontaneous reporting data for etanercept did not show an obvious unexpected excess of reports for any particular types of major malformation. The presence of an increased risk of major congenital abnormalities, without an obvious explanation for a source of bias or confounding that would easily account for this finding, is concerning. However, considering the lack of a clear pattern of congenital malformations, and noting that there are already statements in the current EU SmPC that recommend that women of childbearing potential should be advised to use appropriate contraception to avoid becoming pregnant during therapy, and for three weeks after discontinuation, the PRAC concluded that the results of the OTIS registry should be considered together with any other relevant new study data and literature before conclusions are drawn. The PRAC noted that alternative therapies may also be teratogenic and it would be important not to change the public perception of the safety of this medicine on the basis of uncertain or conflicting evidence. The PRAC agreed that the MAH should be asked further questions, in particular to comment further on possible mechanisms for a teratogenic effect.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation³³

See also Annex I 16.5.

7.5.1. Mannitol – BRONCHITOL (CAP) - EMEA/H/C/001252/ANX 002.5

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002.4 (fourth interim analysis of the cystic fibrosis (CF) study) request for supplementary information, as adopted in February 2015

Background

Bronchitol is a centrally authorised medicine containing mannitol, indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.

The MAH had committed to perform an interventional PASS to be conducted over 5 years in the UK Cystic Fibrosis Registry according to the conditions included in the Annex II of the marketing authorisation.

Interim results of a PASS examining the rates of identified and potential risks of Bronchitol in CF by comparing mannitol exposed versus unexposed patients in a matched cohort from the CF registry were assessed by the Rapporteur for PRAC review. See [PRAC minutes February 2015](#).

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

Summary of advice

- The PRAC discussed the MAH's responses to the questions raised in February 2015 on the fourth interim summary report of the CF registry study. The clinical trial data on bacterial infection provided by the MAH did not raise a concern and the limitations of the CF registry make findings on bacterial/fungal infections difficult to interpret. The clinical trial data suggest that haemoptysis occurs more frequently with Bronchitol than with controls in younger patients and this is already labelled in the product information. Preliminary data from the fifth interim analysis shows that haemoptysis occurred in 12/199 (6.03%) subjects ≥ 18 years and 2/16 (12.5%) < 18 years with no further paediatric cases reported. The haemoptysis cases reported in children in the CF registry to date do not appear to be severe, and haemoptysis is expected in patients with CF. Further data from the ongoing DPM-CF-204 paediatric/adolescent study may provide further information on risk factors for haemoptysis, which may help in formulating risk management strategies as appropriate. The PRAC agreed to review the data provided in the fifth interim report before reassessing whether additional changes to product information are necessary and whether other sources of data may be necessary to provide further information on the long-term safety of Bronchitol treatment. However the MAH should clarify when analyses of data will become available from exposed patients with 2 or more annual reviews while on Bronchitol treatment with sufficient numbers of patients to allow a robust analysis. The MAH should also justify providing a pooled analysis of studies rather than the requested meta-analysis of randomized controlled trials for the incidence of haemoptysis, fungal infections, and all infections associated with Bronchitol. The MAH should address the above request within two months.

7.6. Others

See Annex I 16.6.

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 17.1.

8.2. Conditional renewals of the marketing authorisation

None

8.3. Renewals of the marketing authorisation

None

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. List of planned pharmacovigilance inspections

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

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Azithromycin (NAP) - FI/H/XXXX/WS/23

Applicant: Pfizer (Zithromax)

PRAC Rapporteur: Kimmo Jaakkola

Scope: PRAC consultation on a variation procedure evaluating the draft PASS protocol (A0661209) for a non-imposed non-interventional study in the Kaiser Permanente databases to examine the effects of azithromycin use on cardiovascular outcome

Background

Azithromycin is a macrolide antibiotic indicated for the treatment of infections caused by susceptible organisms (respiratory, skin and subcutaneous tissue, sexually transmitted disease (STD)). Azithromycin is also indicated for long term use in patients with advanced human immunodeficiency virus (HIV) infection for prophylaxis and treatment against *Mycobacterium avium* intracellular complex (MAC/DMAC).

For background information, see [PRAC minutes March 2015](#). Following previous advice, Finland, RMS for the azithromycin-originator product, further consulted the PRAC on the evaluation of the MAH's updated non-imposed non-interventional study PASS protocol (A0661209) to explore the effects of azithromycin on cardiovascular outcome, as part of an ongoing worksharing type II variation.

Summary of advice

- Based on the review of the available information, the PRAC was informed that the MAH did not fully follow earlier methodological recommendation by PRAC but had proposed alternative methods for controlling the confounding. The PRAC supported the conclusions from the RMS that the alternative methodology can be accepted in order to expedite the study. The PRAC noted the MAH's proposed methods with sensitivity analyses, as well as the option to continue the research in the Veterans Affairs (VA) study database.

11.1.2. Valsartan, hydrochlorothiazide (NAP) - IS/H/0126/001-003/II/021

Applicant: Egis Pharmaceuticals PLC

PRAC Lead: Hrefna Guðmundsdóttir

Scope: PRAC consultation on a variation procedure pertaining to the hydrochlorothiazide component and concomitant use with allopurinol

Background

Valsartan is an angiotensin II antagonist indicated in combination for the treatment of essential hypertension in adults. In combination with hydrochlorothiazide, a diuretic, it is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

In the context of a type II variation for a generic medicinal product containing valsartan/hydrochlorothiazide proposing to refine the product information on concomitant use with allopurinol and the increased risk of hypersensitivity reactions, Iceland requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC noted that the interaction with allopurinol is already included in the product information and supported Iceland's proposal not to add exacerbation of hypersensitivity reactions in patients with renal failure as valsartan/hydrochlorothiazide-containing products are contraindicated in this sub-population. The PRAC agreed to transmit the PRAC advice to the CMDh for information and any further action as necessary.

11.2. Other requests

11.2.1. Clarithromycin (NAP) - IE/H/PSUR/0020/003

Applicant: Abbott (Klacid), various

PRAC Lead: Almath Spooner

Scope: PRAC consultation on a PSUR worksharing procedure regarding the cardiovascular safety of clarithromycin

Background

Clarithromycin is a macrolide antibiotic used to treat various types of infections including infections of the upper and lower respiratory tract, skin and soft tissue infections and in the eradication treatment of *Helicobacter Pylori*.

Following PRAC recommendations for a signal of cardiovascular (CV) adverse events associated with clarithromycin, Ireland as P-RMS, further assessed the MAH's analyses of available clinical trial data relevant to the evaluation of cardiovascular safety and of the published literature within an ongoing PSUR worksharing procedure. Further questions were agreed by PRAC and addressed to the MAH. For further background, see [PRAC minutes November 2014](#).

Following previous advice, the PRAC was further consulted on the evaluation of the MAH's responses to a list of questions.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions of the P-RMS. The Committee acknowledged that the studies in the company's clinical database were designed and powered to investigate the efficacy of clarithromycin and not to investigate short or longer term CV outcomes. This coupled with the low event rate observed and the nature of the events reported within the selected cardiac SMQs³⁴ raised doubts as to whether further exploration of this dataset would help to address the outstanding uncertainties and provide any additional insights at this time. The PRAC endorsed continued routine monitoring of cumulative and any emerging evidence on the cardiovascular safety of clarithromycin as proposed by the P-RMS and also considered that further studies, including ongoing observational studies in clinical practice research datalink (CPRD), may provide further insights into the CV safety of clarithromycin.

11.2.2. Diltiazem (NAP); verapamil (NAP)

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Following the completion of the Article 20 for ivabradine, CMDh's consultation on the consequences on the diltiazem or verapamil product information

Background

Diltiazem is a calcium channel blocker indicated for the treatment of hypertension, angina pectoris, and some types of arrhythmia. Verapamil is also a calcium channel blocker indicated for the treatment of hypertension, angina pectoris, cardiac arrhythmia, and cluster headaches.

In 2014, the safety referral under Article 20 of Regulation (EC) No 726/2004 for ivabradine-containing products ([EMEA/H/A20/1404](#)) concluded, as part of the outcome, that the concomitant use of diltiazem/verapamil and strong CYP3A4 inhibitors should be contraindicated due to the increased incidence of bradycardia events and increased risk of myocardial infarction. The CMDh requested PRAC advice on the relevance of reflecting the contraindication on the concomitant use of ivabradine and verapamil/diltiazem, in the

³⁴ Standardised MedDRA Queries (SMQs)

product information of diltiazem- and verapamil-containing medicinal products. The Netherlands prepared an assessment.

Summary of advice

- The PRAC advised that the contraindication of the concomitant use of ivabradine with verapamil or diltiazem in the product information of diltiazem- and verapamil-containing medicinal products should be reflected accordingly, due to the heart rate lowering associated with the concomitant use of these medicinal products.
- The PRAC considered that the [Guideline on Summary of Product Characteristics](#) could be more explicit on the criteria that could warrant the reciprocal harmonisation of product information of interacting medicinal products.

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

Applicant: various

Lead member: Rafe Suvarna

Scope: PRAC consultation on a post-authorisation measure resulting from the 2010 Article 20 and Article 31 referral procedures for gadolinium-containing contrast agents

Background

Gadolinium-containing contrast agents (GdCAs) are used intravenously as an enhancement for magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). A referral procedure under Article 31 of Directive 2001/83/EC, completed in 2010 ([EMEA/H/A-31/1097](#)), focused on measures to minimise the risk of nephrogenic systemic fibrosis (NSF) in specific patient groups, and investigation of concerns regarding accumulation of gadolinium in bone and skin tissue. As part of the outcome of the referral procedure, the CHMP agreed that further clinical studies were warranted to assess the retention of gadolinium in bone and skin. In May 2015, the UK requested PRAC advice on the issue of recruitment for study GMRA-102. The PRAC considered the MAH's proposals for protocol amendments, and agreed a list of questions to the Scientific Advice Working Party (SAWP) to inform further interaction with the concerned MAHs. For further background, see [PRAC minutes May 2015](#).

At its current plenary meeting, the PRAC discussed the SAWP responses for further consideration. The CHMP will consider the set of questions at its July 2015 meeting with regard to Optimark.

Summary of advice

- The PRAC agreed with the SAWP and the proposed refined list of questions to the MAHs for NAPs. The MAHs should comment on the effect of these proposed protocol changes on study recruitment and completion. Using the analysis of options suggested by SAWP, the MAHs should make proposals to accelerate patient recruitment and adjust the data requirements, to provide interpretable data against the need for timely completion of the study. Moreover, the MAHs should discuss the feasibility of using a

modelling and simulation approach, as suggested by SAWP, to analyse the data collected so as to make best use of datasets.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. Mandate of Chair and Vice-Chair - prolongation

In line with Article 3³⁵ of the Rules of Procedure of the PRAC ([EMA/PRAC/567515/2012 Rev.1](#)), and following confirmation of the current Chair's and Vice-Chair's interest in prolonging their mandate, the PRAC voted to prolong, for a further three years, June Raine and Almath Spooner as Chair and vice-Chair respectively, taking effect as of September 2015.

12.2. Coordination with EMA scientific committees or CMDh-v

None

12.3. Coordination with EMA working parties/working groups/drafting groups

12.3.1. Pharmacovigilance Inspectors Working Group (PhV IWG) – 2015 training course draft agenda

At the organisational matters teleconference on 23 July 2015, the EMA Secretariat presented to the PRAC the draft agenda for the 2015 PhV IWG 2015 training course due to take place in November 2015.

12.3.2. Post-authorisation efficacy study (PAES) - draft scientific guidance

The EMA Secretariat presented to the PRAC the draft scientific guidance on post-authorisation efficacy studies (PAES). The aim of this draft guidance is to provide scientific guidance for MAHs and national competent authorities on the general need for such studies, on general methodological considerations, on specific situations and on study conduct. PRAC delegates were invited to provide written comments by 15 August 2015. This draft scientific guidance is also being shared with CHMP, CAT, CMDh and PDCO for comments in advance of its adoption by the PRAC. Following its adoption this draft guidance will be released for public consultation (foreseen before the end of the year 2015).

12.4. Cooperation within the EU regulatory network

12.4.1. EUROmediCAT: safety of medication use in pregnancy (7th Framework project) - conclusion

The EMA Secretariat presented to the PRAC the final report of the project of EUROmediCAT on safety medication use in pregnancy in relation to risk of congenital malformations. In

³⁵ The Chair and Vice-Chair of the PRAC shall be elected by and from amongst its members for a term of three years, which may be prolonged once

EUROmediCAT, a project funded by the EU 7th Framework Programme (FP7), 15 European (EUROCAT) congenital anomaly (CA) registries in 13 countries and 7 healthcare databases including prescription information in 5 countries were used and linked to generate powerful datasets for the assessment of medicine use and associated teratogenicity (ability to cause CA). EUROmediCAT's studies focused on four medication groups for chronic conditions: treatment of asthma, epilepsy, diabetes and depression (use of selective serotonin reuptake inhibitors). The PRAC welcomed the report and supported further consideration in the context of the Good Vigilance Practice P.III 'Product- or population-specific considerations: pregnancy'.

12.4.2. European Food Safety Agency (EFSA) – draft guidance document on uncertainty in scientific assessment

At the organisational matters teleconference on 23 July 2015, the EMA Secretariat presented to the PRAC the draft EFSA guidance document on uncertainty in scientific assessment which is currently under public consultation. PRAC delegates were invited to provide written comments by 4 September 2015.

12.5. Cooperation with international regulators

None

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

None

12.7. PRAC work plan

12.7.1. 2015 PRAC work plan - update

The EMA Secretariat presented to the PRAC an update on the status and progress made with the different topics and activities included in the 2015 PRAC work plan. This update was welcomed by the PRAC.

12.7.2. 2016 PRAC work plan - development

The EMA Secretariat presented to the PRAC a brief outline of the next steps regarding the development of the draft 2016 PRAC work plan. PRAC delegates were invited to provide suggestions of new topics and activities for the development of the draft 2016 PRAC work plan by 1 September 2015.

12.8. Planning and reporting

12.8.1. PRAC statistics - overview

At the organisational matters teleconference on 23 July 2015, the EMA Secretariat presented the scope of statistics collected to account for PRAC activities (which statistics are being prepared for each procedure type or indicator and at what frequency). It was proposed to have quarterly statistics generated.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Granularity and Periodicity Advisory Group (GPAG)

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

12.10.2. Periodic safety update reports - network capacity and planning

The EMA Secretariat presented to the PRAC a proposal to address network capacity issues and planning of PSUR assessments. Currently PSUR procedures involving a single centrally authorised product (CAP) are started at the next available start date following actual submission. If a PSUR is submitted before the submission deadline provided for by the EURD list it could result in this procedure starting a month earlier than anticipated. To allow for better planning of upcoming PSUR procedures, it is proposed from now on for single CAP PSURs to use the submission deadlines provided in the EURD list to calculate the start date and the assessment time-table (and not the actual submission date if early). In case of unexpected resource issues at Member State level it was proposed that the PRAC Rapporteur informs the EMA Secretariat who will then liaise with the PRAC Co-Rapporteur to check if they could take on the assessment. If not, it is proposed to launch a call for interest to all PRAC members. Based on available alternative, a new PRAC Rapporteur is appointed for this particular PSUR procedure who will conduct the assessment and the payment of the relevant fees will go to this national competent authority.

12.10.3. Periodic safety update reports – proposal for revised criteria for plenary discussion

The topic was deferred to the October 2015 PRAC meeting.

12.10.4. PSURs repository – conditions for identifying pre-conditions of the network from the pilot phase to switch-on

At the organisational matters teleconference on 23 July 2015, the EMA Secretariat presented a proposal to use the PSUR repository before its use becomes mandatory as of June 2016. This simulated mandatory use (i.e. where the network would rely solely on the repository for the workflow of PSURs and no longer use Eudranet messages) is also referred

to as 'switch-on' phase. This would allow readiness for the mandatory use. In order for the PSUR repository to move from the pilot phase to the 'switch-on' phase a number of pre-conditions agreed by the network should be met. A proposal for pre-conditions for the 'switch-on' was presented to the PRAC following a previous CMDh consultation. Following this network consultation, the pre-conditions were endorsed with two additions. The 'switch-on' phase is currently planned for early 2016.

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

The PRAC endorsed the draft revised EURD list version June 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 July 2015, the updated EURD list was adopted by the CHMP and CMDh at their July 2015 meeting and published on the EMA website on 06/08/2015, 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. Signal management – feedback from Signal Management Review Technical (SMART) Working Group

The PRAC was updated on the outcome of the July 2015 SMART Working Group (SMART WG) meeting. The SMART WG discussed a review conducted by the EMA Secretariat on signals/safety issues from non-EEA regulatory authorities for nationally authorised products (NAPs). The proposal is for such information to be collected by the EMA Secretariat and shared with the network on a monthly basis. For NAPs where there is no lead Member State (MS) for signal monitoring and which is available in more than one MS, the first step will be to identify a MS with knowledge on the issue and when not available, the EMA Secretariat will validate and confirm (as appropriate) any signal. A pilot of the above proposal will run for six months. The SMART WG also discussed a proposal to publish the designated medical event (DME) list, currently included in electronic reaction monitoring reports (eRMRs) and used by EMA and national competent authorities in order to address the legal provision from the [Commission Implementing Regulation \(EU\) No 520/2012](#). The SMART WG will further reflect on the rationale, need and possible impact of publishing the DME list and have a follow-up discussion in September 2015. Finally the SMART WG discussed the mid-2015 deliverables.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Additional monitoring

None

12.12.2. 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 29/07/2015 on the EMA website (see: [Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#))

12.12.3. Management and reporting of adverse reactions to medicinal products – guidance on monitoring of off label use

The EMA Secretariat presented to the PRAC an update on the draft EMA question and answer (Q&A) document on recording and reporting of off-label use which had been presented to the PRAC and discussed in February 2015 (see [PRAC minutes February 2015](#)). As requested by the PRAC, the draft Q&A document has been reviewed and revised by the Project and Maintenance Group (PMG) 1 to provide guidance on the monitoring of off label use while focusing on regulators' needs. PRAC delegates were invited to provide comments on the draft revised Q&A by 31 July 2015.

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.13.2. Article 57 database – demonstration on the new Data Warehouse tool

At the organisational matters teleconference on 23 July 2015, the EMA Secretariat presented a brief update on the current status of the Article 57(2) of Regulation (EC) No 726/2004 database (referred to as Article 57 database). As of beginning of August 2015, national competent authorities will be given priority access to a subset of data fields via the Article 57 data warehouse tool. A short demonstration on how to access the Article 57 medicinal product data was given to the PRAC and to the CMDh.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

12.15.1. Post-authorisation Safety Studies – non-imposed PASS

None

12.15.2. Post-authorisation Safety Studies and additional monitoring imposed on originator products: applicability to generic products

The EMA Secretariat presented to the PRAC the issue of the applicability of PASS and additional monitoring requirements imposed on the originator products to generic medicinal products using a real life example as an illustration. A follow-up discussion is expected at the September 2015 PRAC meeting.

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. Enhanced early dialogue to foster development and facilitate accelerated assessment

The EMA secretariat informed the PRAC of the development of a new scheme designed to facilitate the development and accelerated assessment of innovative medicines of major public health interest, in particular from the viewpoint of therapeutic innovation.

13.2. European Commission report on the performance of pharmacovigilance tasks

The PRAC was updated on the progress on the data collection for the report on the performance of pharmacovigilance tasks by the Member States and the EMA and informed that Member States might be approached for information on certain activities.

13.3. Strategy on impact of pharmacovigilance

The EMA Secretariat presented to the PRAC a draft revised paper on a strategy on impact of the pharmacovigilance system (see [PRAC minutes June 2015](#)) as well as the next steps. PRAC delegates were invited to provide comments on the draft revised paper by 31 July 2015. The paper and the work plan are foreseen to be finalised by the autumn.

13.4. Tender for studies of the impact of the Article 31 referral on combined hormonal contraceptives (CHC) ³⁶

The EMA Secretariat presented to the PRAC a draft consultation document regarding a proposed tender to conduct studies on the effectiveness of communication and impact on drug exposure of regulatory action following the referral on combined hormonal contraceptives for venous thromboembolism which was concluded in January 2014 ([EMA/607314/2013](#)). The studies would be commissioned from an independent research group. The PRAC supported this initiative. The nature of the communication processes could vary between member states and PRAC also commented that additional measures may have been taken in some member states that coincided with the conclusion of the referral. It was suggested that this variation would be investigated via non urgent information (NUI). The PRAC noted that previous NUIs had addressed aspects related to CHCs and suggested that these should be reviewed.

³⁶ Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, EMEA/H/A-31/1356

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(s).

14.1.1. Albutrepenonacog alfa - EMEA/H/C/003955

Scope: Prophylaxis and treatment of bleeding in all patients with haemophilia B, treatment of bleeding in all patients with haemophilia B

14.1.2. Aripiprazole - EMEA/H/C/004021

Generic

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

14.1.3. Blinatumomab - EMEA/H/C/003731 – Orphan

Applicant: Amgen Europe B.V.

Scope: Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia

14.1.4. Bortezomib - EMEA/H/C/004076

Generic

Scope: Treatment of multiple myeloma

14.1.5. Caspofungin - EMEA/H/C/004134

Generic

Scope: Treatment of invasive candidiasis and invasive aspergillosis

14.1.6. Ceftolozane, tazobactam - EMEA/H/C/003772

Scope: Treatment of intra-abdominal urinary tract infections

14.1.7. Daclizumab - EMEA/H/C/003862

Scope: Treatment of relapsing multiple sclerosis (RMS)

14.1.8. Efmoroctocog alfa - EMEA/H/C/003964 - Orphan

Applicant: Biogen Idec Ltd

Scope: Treatment of haemophilia A

[14.1.9. Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - EMEA/H/C/004042](#)

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

[14.1.10. Enoxaparin sodium - EMEA/H/C/004264, EMEA/H/C/003795](#)

Biosimilar

Scope: Prophylaxis of thromboembolic disorders of venous origin

[14.1.11. Idarucizumab - EMEA/H/C/003986](#)

Scope: Prevention and treatment of dabigatran associated haemorrhage

[14.1.12. Infliximab - EMEA/H/C/004020](#)

Biosimilar

Scope: Treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis

[14.1.13. Isavuconazole - EMEA/H/C/002734 - Orphan](#)

Applicant: Basilea Medical Ltd

Scope: Treatment of aspergillosis and mucormycosis

[14.1.14. Levodopa, carbidopa - EMEA/H/C/002611](#)

Scope: Treatment of Parkinson's disease

[14.1.15. Lumacaftor, ivacaftor - EMEA/H/C/003954 - Orphan](#)

Applicant: Vertex Pharmaceuticals (U.K.) Ltd

Scope: Treatment of cystic fibrosis

[14.1.16. Mepolizumab - EMEA/H/C/003860](#)

Scope: Treatment of asthma

[14.1.17. Miglustat - EMEA/H/C/004016](#)

Generic

Scope: Treatment of Gaucher disease

[14.1.18. Pandemic influenza vaccine H5N1 \(live attenuated, nasal\) - EMEA/H/C/003963](#)

Scope: Prophylaxis of influenza

[14.1.19. Plasmodium falciparum circumsporozoite protein fused with hepatitis B surface antigen \(rts\) and combined with hepatitis B surface antigen\(s\) in the form of non-](#)

infectious virus-like particles (vlp) produced in yeast cells (*saccharomyces cerevisiae*) by recombinant DNA technology) - EMEA/H/W/002300

Scope: Active immunisation against malaria

14.1.20. Rasagiline - EMEA/H/C/004064

Generic

Scope: Treatment of idiopathic Parkinson's disease (PD)

14.1.21. Susoctocog alfa - EMEA/H/C/002792 – Orphan

Applicant: Baxter AG

Scope: Treatment of haemophilia A

14.1.22. Trifluridine, tipiracil - EMEA/H/C/003897

Scope: Treatment of colorectal cancer

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. Filgrastim – FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/WS0779/0029/G; ZARZIO (CAP) - EMEA/H/C/000917/WS0779/0030/G

Applicant: Sandoz GmbH

PRAC Rapporteur: Julie Williams

Scope: Submission of long term safety and immunogenicity data in additional studies EP06-302 to address post authorisation measure MEA 005 and submission of a revised RMP (version 11) to include two important potential risks (extramedullary haematopoiesis and venous thrombotic events) following the assessment of PSUR#13

14.2.2. Filgrastim – ACCOFIL (CAP) - EMEA/H/C/003956/II/0002

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP following a product information update with regard to routine risk minimisation measures of for several safety concerns

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

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of a 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 minimization measures as requested by the PRAC in May 2014

14.2.4. Tadalafil – ADCIRCA (CAP) - EMEA/H/C/001021/WS0762/0021; CIALIS (CAP) – EMEA/H/C/000436/WS0762/0078

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Update of the due date of the final study report of the category 3 study LVHQ from 'Q3 2015' to 'Q2 2016', which addresses the specific safety concern of non-arteritic anterior ischemic optic neuropathy (NAION), in the tadalafil EU RMP. In addition, other minor changes have been made to the RMP, mainly to update the exposure numbers in line with an updated data cut-off date.

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

14.3.1. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/II/0089

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.6 of the SmPC in order to update the safety information on the risk of infection associated with live vaccination in infants born to women treated with abatacept during pregnancy. The Package Leaflet is updated accordingly

14.3.2. Alipogene triparvovec – GLYBERA (CAP) - EMEA/H/C/002145/II/0038

Applicant: UniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: Update of section 5.1 of the SmPC based on the final CSR for study CT-AMT-011-05, a retrospective clinical records review study undertaken to generate further long-term follow-up data on the incidence and severity of acute pancreatitis episodes in LPLD subjects who previously participated in clinical studies with alipogene tiparvovec or AMT-10

14.3.3. Ambrisentan – VOLIBRIS (CAP) - EMEA/H/C/000839/II/0041

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include an expanded therapeutic indication for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1). In addition, the MAH took the opportunity to update Annex II to reflect a change in the PSUR cycle. The Package Leaflet is updated accordingly

14.3.4. Atazanavir – REYATAZ (CAP) - EMEA/H/C/000494/X/0094/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Isabelle Robine

Scope: Grouped variation of 1) Line extension covering a new pharmaceutical form (oral powder), a new strength for the oral powder presentation (50 mg), and a new paediatric indication (patients from 3 months of age and weighing at least 5 kg); 2) addition of new paediatric data for the capsules; 3) minor revisions to the RMP with regard to nephrolithiasis following PRAC's assessment of RMP version 7.3

14.3.5. Atazanavir – REYATAZ (CAP) - EMEA/H/C/000494/II/0096

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Isabelle Robine

Scope: Update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 5.1 and 5.2 of the SmPC in order to provide important information and guidance to prescribers when they consider using unboosted atazanavir (ATV) in line with international guidelines based on study INDUMA/AI424-136. In addition, the MAH took the opportunity to make a minor change in section 4.7 of the SmPC for increased clarity, and minor editorial changes to the SmPC and Package Leaflet. The RMP version 9 has been submitted

14.3.6. Bevacizumab – AVASTIN (CAP) - EMEA/H/C/000582/II/0082

Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC to include information regarding osteonechrosis in children. The Package Leaflet is updated accordingly. The RMP is updated accordingly

14.3.7. Capsaicin – QUTENZA (CAP) - EMEA/H/C/000909/II/0039

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Magda Pedro

Scope: Extension of indication to include treatment of diabetic patients with peripheral neuropathic pain based on the results of studies E05-CL-3004 (STEP) and E05-CL-3002 (PACE). As a consequence, sections 4.1, 4.4 and 4.8 of the SmPC have been updated; Annex II (additional risk minimisation measures) and the package leaflet have been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II, labelling and Package Leaflet. An updated RMP (version 18) was submitted accordingly

14.3.8. Ceritinib – ZYKADIA (CAP) - EMEA/H/C/003819/II/0001

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update the safety information after the MAH's assessment of the association between the use of ceritinib and acute pancreatitis. The Package Leaflet is updated accordingly. In addition, the updated RMP version 2.5 is submitted accordingly

14.3.9. Collagenase clostridium histolyticum – XIAPEX (CAP) - EMEA/H/C/002048/II/0059

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC to include information related to the treatment of Dupuytren's contracture with two concurrent injections of Xiapex. The Package Leaflet and RMP have been updated accordingly

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

Applicant: Pharming Group N.V

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of an RMP submitted in the context of a 5-year renewal of the marketing authorisation

14.3.11. Crizotinib – XALKORI (CAP) - EMEA/H/C/002489/II/0024

Applicant: Pfizer Limited

PRAC Rapporteur: Corinne Fechant

Scope: Extension of indication for the first-line treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung carcinoma (NSCLC). This variation is based on results of study A8081014. As a consequence, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been amended. The Package Leaflet is updated accordingly

14.3.12. Daclatasvir – DAKLINZA (CAP) - EMEA/H/C/003768/II/0008/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to update the safety information based on the final results of clinical study AI444043 (daclatasvir (DCV) in combination with peginterferon alfa plus ribavirin in hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infected treatment-naive subjects with genotype 1 (GT-1) infection). The Package Leaflet is updated accordingly.

14.3.13. Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/II/0001/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.4, 4.5 and 4.6 of the SmPC in order to include further information related to pharmacokinetic interactions based on the *in vivo* interaction study D0816C00008 and 4, 3 *in vitro* interaction studies (ADME-AZS-Wave3-140714, ADME-AZS-Wave3-140725 and 140483) and data from previously submitted interaction studies. The provision of the final CSR of study D0816C00008 addresses the post-authorisation measure MEA 004. Further, the MAH provided the study report of *in vitro* study 8305083. In addition, the MAH took the opportunity to add the published ATC code in section 5.1 of the SmPC, and to implement minor editorial changes in the SmPC, labelling and Package Leaflet. A revised RMP version 6 was provided, which includes consequential changes related to data on interactions. Further, the MAH is taking the opportunity to update the due dates for the provision of the final study reports of the category 3 studies D0816C00005 and D0816C00006, and to add the new category 3 study D0816C00010

14.3.14. Pneumococcal polysaccharide conjugate vaccine (adsorbed) – SYNFLORIX (CAP) - EMEA/H/C/000973/II/0096/G

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped application including one type II variation and two type IB variations to update section 5.1 of the SmPC with effectiveness data against pneumococcal vaccine

serotypes and against vaccine related serotype 19A, and update of section 4.4 of the SmPC to include information on the immune response against serotype 19A observed in infants and children. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC, and to request extensions to the due dates for MEA 009: study 10PN-PD-DIT-034 (111634) and MEA 018.5: study 10PN-PD-DIT-064 (114056). A revised RMP version 12 was provided

14.3.15. Ruxolitinib – JAKAVI (CAP) - EMEA/H/C/002464/II/0024

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to add a warning on reported cases of Merkel cell carcinoma in patients treated with ruxolitinib

14.3.16. Thiotepa – TEPADINA (CAP) - EMEA/H/C/001046/II/0021

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

PRAC Rapporteur: Corinne Fechant

Scope: Update of section 4.8 of the SmPC to add the new adverse drug reaction (ADR) 'toxic skin reactions' with unknown frequency. The Package Leaflet is updated accordingly. A revised RMP version 12 was provided

14.3.17. Ticagrelor – BRILIQUE (CAP) - EMEA/H/C/001241X/0029/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Grouped application to 1) extension application to add a new strength of 60mg with a new indication: history of myocardial infarction; 2) update of the product information of the existing Brilique 90 mg license with important clinical information from the PEGASUS study

14.3.18. Tobramycin – VANTOBRA (CAP) - EMEA/H/C/002633/II/0001/G

Applicant: Pari Pharma GmbH

PRAC Rapporteur: Qun-Ying Yue

14.3.19. Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0024/G

Applicant: Roche Registration Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4, 4.5 and 4.8 of the SmPC in order to update information on the risk of potentiation of radiation toxicity and updating the risk of progression of cancers with RAS mutations with information on progression of pre-existing pancreatic adenocarcinoma with KRAS mutation. The Package Leaflet is updated accordingly

14.3.20. Voriconazole – VFEND (CAP) - EMEA/H/C/000387/II/0110/G

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of the SmPC sections 4.4, 4.8 and 5.1 to reflect the safety and efficacy data from studies in paediatric population. The Package Leaflet is updated accordingly. Updated RMP (version 4) is also submitted 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. Amifampridine – FIRDAPSE (CAP) - PSUSA/00141/201412

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.2. Belatacept – NULOJIX (CAP) - PSUSA/00311/201412

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope of procedure: Evaluation of a PSUSA procedure

15.1.3. Besilesomab – SCINTIMUN (CAP) - PSUSA/00385/201501

Applicant: Cis Bio International

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.4. Brimonidine tartrate, brinzolamide – SIMBRINZA (CAP) - PSUSA/10273/201412

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Almath Spooner

Scope of procedure: Evaluation of a PSUSA procedure

15.1.5. Canakinumab – ILARIS (CAP) - PSUSA/00526/201412

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

15.1.6. Concentrate of proteolytic enzymes enriched in bromelain – NEXOBRID (CAP) - PSUSA/10028/201412

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Valerie Strassmann

Scope of procedure: Evaluation of a PSUSA procedure

15.1.7. Darunavir – PREZISTA (CAP) - PSUSA/00934/201412

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

15.1.8. Dextromethorphan hydrobromide, quinidine sulfate – NUEDEXTA (CAP) - PSUSA/10089/201412

Applicant: Jenson Pharmaceutical Services Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.9. Eptacog alfa (activated) – NOVOSEVEN (CAP) - PSUSA/01245/201412

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Sabine Straus

Scope of procedure: Evaluation of a PSUSA procedure

15.1.10. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - PSUSA/01742/201412

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope of procedure: Evaluation of a PSUSA procedure

15.1.11. Lenalidomide – REVLIMID (CAP) - PSUSA/01838/201412

Applicant: Celgene Europe Limited

PRAC Rapporteur: Corinne Fechant

Scope of procedure: Evaluation of a PSUSA procedure

15.1.12. Matrix applied characterised autologous cultured chondrocytes – MACI (CAP) - PSUSA/10116/201412

Applicant: Aastrom Biosciences DK ApS

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.13. Paclitaxel albumin – ABRAXANE (CAP) - PSUSA/10123/201501

Applicant: Celgene Europe Limited

PRAC Rapporteur: Sabine Straus

Scope of procedure: Evaluation of a PSUSA procedure

15.1.14. Roflumilast – DALIRESP (CAP); DAXAS (CAP); LIBERTEK (CAP) - PSUSA/02658/201501

Applicant: Takeda GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

15.1.15. Ticagrelor – BRILIQUE (CAP) - PSUSA/02948/201412

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

15.1.16. Trametinib – MEKINIST (CAP) - PSUSA/10262/201412

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.17. Umeclidinium bromide, vilanterol – ANORO (CAP); LAVENTAIR (CAP) - PSUSA/10264/201412

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope of procedure: Evaluation of a PSUSA procedure

15.1.18. Ustekinumab – STELARA (CAP) - PSUSA/03085/201412

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.19. Ziconotide – PRIALT (CAP) - PSUSA/03142/201412

Applicant: Eisai Ltd

PRAC Rapporteur: Jean-Michel Dogné

Scope of procedure: Evaluation of a PSUSA procedure

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

15.2.1. Human hepatitis b immunoglobulin – ZUTECTRA (CAP), NAP - PSUSA/01631/201411

Applicant: Biotest Pharma GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

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

15.3.1. Atomoxetine (NAP) - PSUSA/00000262/201411

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.2. Caffeine, drotaverine hydrochloride, metamizol sodium (NAP) - PSUSA/00001996/201411

Applicant: various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

15.3.3. Ciprofloxacin hydrochloride, hydrocortisone (NAP) - PSUSA/00000774/201411

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.3.4. Dapoxetine (NAP) - PSUSA/00000928/201412

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

15.3.5. Diacerein (NAP) - PSUSA/00001026/201412

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.3.6. Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) (NAP) - PSUSA/00001124/201411

Applicant: various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

15.3.7. Drospirenone, estradiol (NAP) - PSUSA/00001184/201412

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.3.8. Estradiol, gestodene (NAP) - PSUSA/00001273/201412

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.3.9. Fluorine (¹⁸F) fludeoxyglucose (NAP) - PSUSA/00001437/201411

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.3.10. Human coagulation factor VIII (antihemophilic factor A) (NAP) - PSUSA/00001620/201411

Applicant: various

PRAC Lead: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

15.3.11. Lisuride (NAP) - PSUSA/00001896/201411

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

15.4. Follow-up to PSUR procedures

15.4.1. Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/LEG 031

Applicant: Roche Registration Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's responses to PSUSA/00009329/201408 as adopted in March 2015

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. Protocols of PASS imposed in the marketing authorisation(s)³⁷

16.1.1. Flupirtine (NAP) - EMEA/H/N/PSP/j/0005.4

Applicant: Meda Pharma GmbH & Co KG

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a revised protocol for a non-interventional post-authorisation safety study to evaluate the effectiveness of the risk minimisation measures for the use of flupirtine 100 mg immediate-release capsules in daily practice

16.1.2. Tolvaptan – JINARC (CAP) - EMEA/H/C/PSP/0028

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for a prospective study of the safety of tolvaptan in ADPKD patients with an additional retrospective component to assess for risks associated with long term use

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)³⁸

16.2.1. Collagenase clostridium histolyticum – XIAPEX (CAP) - EMEA/H/C/002048/MEA 027

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: PASS protocol for a non-interventional survey to evaluate the effectiveness of Xiapex educational material for healthcare professionals in the treatment of Peyronie's disease

³⁷ In accordance with Article 107n of Directive 2001/83/EC

³⁸ 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

16.2.2. Flutemetamol (¹⁸F) – VIZAMYL (CAP) - EMEA/H/C/002557/MEA 002.1

Applicant: GE Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002 [PASS protocol, study no. GE067-027 CPR to assess the effectiveness of the educational training programme] as adopted in February 2015

16.2.3. Linaclotide – CONSTELLA (CAP) - EMEA/H/C/002490/MEA 009.1

Applicant: Almirall S.A

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 009 (linaclotide safety study for the assessment of diarrhoea - complications and associated risk factors in selected European populations with IBS-C) as adopted in March 2015

16.2.4. Linaclotide – CONSTELLA (CAP) - EMEA/H/C/002490/MEA 011

Applicant: Almirall S.A

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 010 (drug utilisation study (DUS) protocol - linaclotide utilisation study in selected European populations study) as adopted in March 2015

16.2.5. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches – VELPHORO (CAP) - EMEA/H/C/002705/MEA 002.1

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002 [PASS protocol for study VFMCRP-MEAF-PA21-01-EU] as adopted in February 2015

16.2.6. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – AFLUNOV (CAP) - EMEA/H/C/002094/MEA 022; prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP) - EMEA/H/C/001208/MEA 026 , PREPANDEMIC INFLUENZA VACCINE (H5N1) (SURFACE ANTIGEN, INACTIVATED, ADJUVANTED) NOVARTIS VACCINES AND DIAGNOSTIC (CAP) - EMEA/H/C/002269/MEA 021

Applicant: Novartis Vaccines Influenza Srl

PRAC Rapporteur: Carmela Macchiarulo

Scope: MAH's responses to MEA 020 /MEA 019 (PASS protocol synopsis V87_27 OB) request for information (RSI) following the PRAC outcome in February 2014

16.3. Results of PASS imposed in the marketing authorisation(s)³⁹

None

³⁹ In accordance with Article 107p-q of Directive 2001/83/EC

16.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁰

16.4.1. Afibercept – EYLEA (CAP) - EMEA/H/C/002392/II/0023 (with RMP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: Submission of final study report for VIEW-1 extension VGFT-OD-0910 to assess the long-term safety and tolerability of VEGF Trap-Eye in patients with neovascular age-related macular degeneration (AMD), in order to fulfil MEA 003 (category 3 study included in the RMP). The RMP has been updated (version 21.0) to reflect the completion of this study

16.4.2. Fentanyl – EFFENTORA (CAP) - EMEA/H/000833/II/0037 (with RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final study report of a PASS: national descriptive and longitudinal study of patients treated with Effentora in France. The RMP has been updated accordingly

16.4.3. Human rotavirus, live attenuated – ROTARIX (CAP) - EMEA/H/C/000639/II/0062 (with RMP)

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report of genetic stability study EPI-ROTA-014 VS BE – 112560 that addresses the post-approval measure MEA 005.2 in which the MAH commits to monitor for the potential occurrence of genetic drifts and shifts in the vaccine strain in post-marketing settings

16.4.4. Indacaterol – HIROBRIZ BREEZHALER (CAP) - EMEA/H/C/001211/WS0777/0036/G; ONBREZ BREEZHALER (CAP) - EMEA/H/C/001114/WS0777/0035/G ; OSLIF BREEZHALER (CAP) - EMEA/H/C/001210/WS0777/0035/G (with RMPs)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final study reports of two PASS studies (UK PASS study QAB149B2433/QAB149BS641859 and EU PASS study QAB149B2431/QAB149AS232863) included in the RMP to monitor off-label use of indacaterol; an updated RMP (version 8.0) has been submitted accordingly. Moreover, the MAH updated the RMP to include changes as agreed by the CHMP in March 2015 (MEA 017/MEA 015/MEA 015 following the review of the fourth US PASS (QAB149B2432/CQAB149BS232861) interim report)

16.4.5. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) – PREVENAR 13 (CAP) - EMEA/H/C/001104/II/0123 (without RMP)

Applicant: Pfizer Limited

⁴⁰ 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

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of final clinical study report (CSR) for study 6096A1-4024 (B1851040), a PASS to assess the impact of 13vPnC on otitis media in children after the introduction of the vaccine in 2010 in the United States

16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation⁴¹

16.5.1. Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/MEA 080.3

Applicant: AbbVie Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First progress report on the P11-292 registry (long-term non-interventional registry to assess safety and effectiveness of Humira (adalimumab) in paediatric patients with moderately to severely active Crohn's disease (CD))

16.5.2. Betaine anhydrous – CYSTADANE (CAP) - EMEA/H/C/000678/MEA 022

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

PRAC Rapporteur: Valerie Strassmann

Scope: Submission of the second progress report on Orphan Europe Cystadane surveillance protocol in collaboration with the network and registry for homocystinurias and methylation defects (E-HOD)

16.5.3. Elosulfase alfa – VIMIZIM (CAP) - EMEA/H/C/002779/MEA 005

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: First annual report for the Morquio registry study (MARS)

16.5.4. Prucalopride – RESOLOR (CAP) - EMEA/H/C/001012/MEA 006.10

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Fourth annual interim safety report for the drug utilisation study to examine the characteristics of patients prescribed prucalopride (Resolor) and a pharmacoepidemiological study of the occurrence of major cardiovascular events, pregnancy, and pregnancy outcomes in the UK Clinical Practice Research Datalink (CPRD) database

16.5.5. Raltegravir – ISENTRESS (CAP) - EMEA/H/C/000860/MEA 048.5

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

⁴¹ In line with the revised variations regulation for any submission before 4 August 2013

Scope: MAH's responses to MEA 048.4 [fourth and final annual report for a post-authorisation safety study in a US managed care network] request for supplementary information (RSI) as adopted in February 2015

**16.5.6. Saxagliptin, metformin – KOMBOGLYZE (CAP) - EMEA/H/C/002059/MEA 010.1
saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 033.1**

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim analysis of PASS study CV181-099ST (comparison of risk of major cardiovascular events between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments)

**16.5.7. Saxagliptin, metformin – KOMBOGLYZE (CAP) - EMEA/H/C/002059/MEA 011.1
saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 034.1**

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim analysis of PASS study CV181-100ST (comparison of risk of hospitalisation with acute liver failure between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments)

**16.5.8. Saxagliptin, metformin – KOMBOGLYZE (CAP) - EMEA/H/C/002059/MEA 012.1
saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 036.1**

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim analysis of PASS study CV181-101ST (comparison of risk of hospitalisation with infection between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments)

**16.5.9. Saxagliptin, metformin – KOMBOGLYZE (CAP) - EMEA/H/C/002059/MEA 013.1
saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 037.1**

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim analysis of PASS study CV181-157ST (comparison of risk of hospitalisation for acute kidney injury between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments)

**16.5.10. Saxagliptin, metformin – KOMBOGLYZE (CAP) - EMEA/H/C/002059/MEA 014.1
saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 035.1**

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Second interim analysis of PASS study CV181-103ST (comparison of risk of hospitalisation for severe hypersensitivity (including severe cutaneous reactions) between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments)

16.5.11. Ulipristal – ESMYA (CAP) - EMEA/H/C/002401/MEA 003.3

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third annual progress report on a non interventional study in pre-operative treatment of moderate to severe symptoms of uterine fibroids (PGL10-014)

16.5.12. Ustekinumab – STELARA (CAP) - EMEA/H/C/000958/MEA 023.6

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Fifth annual interim safety registry report on the Nordic database initiative (protocol CNTO1275PSO4005)

16.5.13. Voriconazole – VFEND (CAP) - EMEA/H/C/000387/MEA 071.11

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of annual status report for PASS study A1501097 (third study progress report) to assess the potential association between voriconazole use and the development of SCC of the skin in patients with lung or heart/lung transplant (LT)

16.6. Others

16.6.1. Brinavess – VERNAKALANT (CAP) - EMEA/H/C/001215/LEG 025

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: From 11/09: A requirement to promptly inform the CHMP of any future serious cases of hypotension, with or without fatal outcome. Such case reports will be accompanied by a causality assessment. With this LEG the MAH provides the details including the causality assessment of a hypotension case related to Brinavess

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. Annual reassessments of the marketing authorisation

17.1.1. Anagrelide – XAGRID (CAP) - EMEA/H/C/000480/S/0064 (without RMP)

Applicant: Shire Pharmaceutical Contracts Ltd

PRAC Rapporteur: Corinne Fechant

Scope: Annual reassessment 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 6-9 July 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	Member	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
Marina Dimov Di Giusti	Member	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
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
Kimmo Jaakkola	Alternate	Finland	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Isabelle Robine	Member	France	No interests declared	Full involvement
Corinne Fechant	Alternate	France	No participation in discussions, final deliberations and voting on	6.1.15 Human fibrinogen, human thrombin
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
Hrefna Guðmundsdóttir	Alternate	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
Zane Neikena	Alternate	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	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
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
Magda Pedro	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to this meeting	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Miguel-Angel Macia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	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 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-Stanislowski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
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
Line Michan	Expert - in person*	Denmark	No interests declared	Full involvement
Triin Leinemann	Expert - in person*	Estonia	No interests declared	Full involvement
Serge Bakchine (SAG neurology chair)	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Carine Condy	Expert - via telephone*	France	No interests declared	Full involvement
Catherine Deguines	Expert - via telephone*	France	No interests declared	Full involvement
Maarten Lagendijk	Expert - in person*	Netherlands	No interests declared	Full involvement
Justyna Paterak	Expert - in person*	Poland	No interests declared	Full involvement
Ružena Kamenská	Expert - in person*	Slovakia	No interests declared	Full involvement
Almudena López Fando	Expert - in person*	Spain	No interests declared	Full involvement
Rolf Gedeberg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Patrick Batty	Expert - in	United Kingdom	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	person*		declared	
Mattia Calissano	Expert - in person*	United Kingdom	No interests declared	Full involvement
John Clements	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Julia Double	Expert - in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Kathryn Ord	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

19. Explanatory notes

The Notes give a brief explanation of relevant minute's 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/