5 September 2013
EMA/575955/2013 Rev. 2
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the 8-11 July 2013 meeting

Chair: June Raine – Vice-Chair: Almath Spooner

Explanatory notes

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

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

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

Signals assessment and prioritisation
(Item 4 of the PRAC 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 reports of adverse events from healthcare professionals or patients (so called 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.
After evaluation of a safety signal the conclusion could be that the medicine caused the adverse reaction, that a causal relationship with the adverse event was considered unlikely, or that no clear answer could be given and the signal therefore is to be further investigated. 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 product information (the summary of product characteristics and the package leaflet).
For completeness the information on signals is complemented, when available, by information on worldwide population exposure.

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Risk Management Plans (RMPs)
(Item 5 of the PRAC Minutes)

The RMP describes what is known and not known about the safety of a medicine and states how the side effects 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 summarise data on the benefits and risks of a medicine and include 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 minimisation activities that have been introduced. The results of a PASS help regulatory agencies to further evaluate the safety and benefit-risk profile of a medicine already in use.

Product-related pharmacovigilance inspections
(Item 9 of the PRAC Minutes)
These are inspections carried out by regulatory agencies to ensure that marketing authorisation holders have systems in place that enable them to comply with their obligations to closely follow the safety of a medicine after authorisation.

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

The use and indications of some of the medicines mentioned as background information in the minutes is described in abbreviated form. We recommend the readers to refer to the EMA website: 'Search for medicines' to find the full product information (Summary of the Product Characteristics and Package Leaflet) of all centrally authorised medicines included.

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1. Introduction

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

The Chairperson opened the meeting, welcoming all participants to the 8-11 July 2013 meeting of the PRAC, and extending a special welcome to Viola Macolić Šarinić and Marin Banovac, the PRAC member and alternate member for Croatia, which joined the European Union on 1 July 2013, as well as to Ruchika Sharma, the new PRAC alternate for Ireland. In addition, the PRAC welcomed the new Lithuanian presidency of the EU.

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 for the 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 the already declared interests on 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.

1.2. Adoption of agenda of the meeting on 8-11 July 2013

The agenda was adopted with the addition of the following topics upon request from the members of the Committee and the EMA secretariat: aclidinium bromide 7.1.1. and other topics relating to organisational matters.

1.3. Minutes of the previous PRAC meeting on 10-13 June 2013

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 on 10-13 June 2013 were published on 24 July 2013

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

2.1. Newly triggered procedures

2.1.1. **Hydroxyethyl starch (HES), solutions for infusion** (NAP)

- Review of the benefit-risk balance following notification by the United Kingdom of a referral under Article 107i of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Jana Mladá (CZ)
PRAC Co-Rapporteur: Julie Williams (UK)

Background

Following the June 2013 PRAC meeting, in light of the PRAC conclusion on a negative benefit-risk for these products, the UK Medicines Agency (MHRA) took action to suspend the marketing authorisations for all hydroxyethyl starch (HES) containing products. As currently required when considering national action to suspend the marketing and the use of a medicine, the UK sent a letter of notification on 27 June 2013 along with a rationale for triggering a referral under Article 107i of Directive 2001/83/EC for hydroxyethyl starch (HES), solutions for infusion (see also New review of hydroxyethyl starch-containing solutions for infusion started).

Discussion

The PRAC noted the rationale for triggering the referral provided by the UK Medicines Agency and discussed the list of questions to be addressed during the procedure as well as a timetable for conducting the review. A list of questions for stakeholders' submission was agreed.

The PRAC appointed Jana Mladá (CZ) as Rapporteur and Julie Williams (UK) as Co-Rapporteur for the procedure.

The PRAC emphasised that an aligned timetable for the re-examination procedure under Article 31 for the same medicines (see 3.4.1.) would be desirable.

Summary of recommendation(s)/conclusions

A list of questions should be addressed by the MAHs (published on the EMA website EMA/PRAC/411968/2013) and data will be gathered from stakeholders (healthcare professionals, patients' organisations and the general public) by means of responses to a list of questions (EMA/PRAC/411967/2013). The procedure will follow the adopted timetable (EMA/PRAC/411881/2013).

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

3.1. Newly triggered Procedures

3.1.1. **Zolpidem** (NAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)
PRAC Co-Rapporteur: Carmela Macchiarulo (IT)

Background

The Italian Medicines Agency (AIFA) sent a letter of notification dated 4 July 2013 of a referral under Article 31 of Directive 2001/83/EC for the review of zolpidem-containing medicines indicated for the treatment of short-term relief of insomnia. This review follows discussion of the signal of next-morning impaired mental alertness, including impaired driving ability, discussed at the June 2013 meeting of the PRAC (see PRAC Minutes June 2013).

Discussion

The PRAC noted the notification letter from the Italian Medicines Agency and discussed a list of questions to be addressed during the procedure as well as a timetable for conducting the review.

The PRAC discussed whether there was a rationale for initiating a review for pharmacologically related substances, but concluded that at this time the available evidence justified a focus on zolpidem.

The PRAC appointed Menno van der Elst (NL) as Rapporteur and Carmela Macchiarulo (IT) as Co-Rapporteur for the procedure.

Summary of recommendation(s) / conclusions

The Committee adopted a list of questions (EMA/PRAC/418738/2013) and a timetable for the procedure (EMA/PRAC/418739/2013).

3.2. Ongoing Procedures

3.2.1. Combined hormonal contraceptives:
desogestrel, **gestodene, norgestimate**, **etonogestrel, drospirenone**, **dienogest**, **chlormadinone**, **norgestimate** (NAP), **nomegestrol acetate / estradiol – IOA** (CAP), **ZOELY** (CAP), **norelgestromin / ethinylestradiol** - **EVRA** (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

A referral procedure under Article 31 is ongoing for combined hormonal contraceptives (see PRAC Minutes June 2013). An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable and an ad-hoc expert meeting took place on 2 July 2013.

Summary of recommendation(s) / conclusions

The PRAC heard feedback from the Chair of the ad-hoc expert meeting, which took place on 2 July 2013, on the Group's views and position on the questions of the PRAC.

The PRAC discussed the available evidence on the risks of venous thromboembolism (VTE) and ATE for all the medicines included within the review, as well as the diagnosis, extent of recognition and management of VTE and ATE in daily practice based on the assessment of the Rapporteurs and taking account of the feedback from the expert group on the latter point. The PRAC agreed a list of outstanding issues to be addressed by the MAHs. The MAHs will be invited to address the outstanding issues in an oral explanation at the October 2013 PRAC meeting, in accordance with the updated timetable for the review (EMA/PRAC/122032/2013 - Rev 3).

3.2.2. Diacerein (NAP)

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

Regulatory details:
PRAC Rapporteur: Miguel-Angel Macia (ES)
PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

A referral procedure under Article 31 of Directive 2001/83/EC for diacerein-containing medicines for oral administration is ongoing (see PRAC minutes 26-29 November 2012). An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and agreed on a list of outstanding issues to be addressed by the MAHs, regarding the benefit-risk balance of diacerein indicated as a symptomatic treatment in patients with osteoarthritis. The MAHs will be invited to address the outstanding issues in an oral explanation at the October 2013 PRAC meeting, in accordance with an updated timetable for the review.

Post-meeting note: a final timetable was adopted via written procedure on Friday 25 July 2013 2013 (EMA/PRAC/747322/2012 Rev.2).

3.2.3. **Domperidone** (NAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
PRAC Co-Rapporteur: Jean-Michel Dogné (BE)

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for domperidone-containing medicines (see PRAC minutes 4-7 March 2013). An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and agreed on a list of outstanding issues to be addressed by the MAHs. The MAHs will be invited to address the outstanding issues in writing, in accordance with an updated timetable for the review (EMA/PRAC/127280/2013 Rev.1).

3.2.4. **Substances related to nicotinic acid: acipimox** (NAP)

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

Regulatory details:

PRAC Rapporteur: Julia Pallos (HU)
PRAC Co-Rapporteur: Line Michan (DK)

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for acipimox-containing medicines (see PRAC minutes 8-11 April 2013). An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs.

The PRAC noted that xantinol nicotinate-containing products are only indicated as vasodilators in the EU and this use falls outside the scope of this referral procedure. The PRAC therefore agreed to remove these products from the current review.

Regarding medicines containing nicotinic acid as a mono-component, it was confirmed that such products are no longer marketed in the EU. Regarding the fixed-combination products, these were investigated in the HPS2-THRIVE[1] trial, which was prematurely terminated in December 2012 because of failure to reach the primary outcome. The combination products were subsequently suspended following a review under Article 20 of Regulation (EC) No 726/2004 (see European Medicines Agency confirms recommendation to suspend Tredaptive, Pelzont and Trevaclyn). Therefore, products containing nicotinic acid are no longer part of the procedure.

Regarding acipimox-containing medicines, the PRAC agreed a list of outstanding issues to be addressed by the MAH in an oral explanation at the October 2013 meeting, in accordance with a revised timetable for the review (EMA/PRAC/138312/2013rev1).

The PRAC also agreed that an expert meeting should be convened to discuss in greater detail some aspects of the main findings, such as the role of the medicine in clinical practice and its therapeutic effect. A list of questions to the experts was agreed, including how the results of the studies HPS2-THRIVE and AIM-HIGH[2] (see PRAC Minutes January 2013) would apply to acipimox. The date of the expert meeting was confirmed as 6 September 2013 and PRAC members were invited to nominate experts.

Post-meeting note: a list of participants to the expert meeting was adopted via written procedure on 26 August 2013.

3.2.5. Strontium ranelate – **OSSEOR** (CAP), **PROTELOS** (CAP)

- Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20(8) of Regulation (EC) No 726/2004, following procedural steps of Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)
PRAC Co-Rapporteur: Harald Herkner (AT)

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 – following procedural steps of Article 31 of Directive 2001/83/EC – is ongoing for Osseor and Protelos (strontium ranelate) (see PRAC Minutes May 2013).

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary list of participants of the ad-hoc expert meeting to be held on 10 September 2013. The PRAC discussed the need for further experts at the meeting. Members were invited to propose nominations from the Member States.

Post-meeting note: the list of experts and the list of questions to be addressed by the experts were adopted by written procedure on 23 August 2013.

[1] HPS2-THRIVE: Treatment of HDL to Reduce the Incidence of Vascular Events trial
[2] AIM HIGH: Niacin Plus Statin to Prevent Vascular Events

3.3. Procedures for finalisation

3.3.1. Short-acting beta agonists:
hexoprenaline (NAP); **fenoterol** (NAP); **ritodrine** (NAP); **salbutamol** (NAP); **terbutaline** (NAP); **isoxsuprine** (NAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteurs: Jean-Michel Dogné (BE), Carmela Macchiarulo (IT), Jana Mladá (CZ), Julia Pallos (HU)

Background

A referral procedure under Article 31 of Directive 2001/83/EC for short-acting beta agonists (see PRAC Minutes May 2013) was planned for finalisation. It was agreed to finalise the procedure in September 2013 providing the opportunity for an oral explanation by relevant Marketing Authorisation Holders.

Summary of recommendation(s)/conclusions

The PRAC agreed to have an oral explanation from MAH(s) and to finalise the procedure at the September 2013 PRAC meeting.

3.4. Re-examination procedures

3.4.1. Hydroxyethyl starch (HES), solutions for infusion (NAP)

- Re-examination procedure of the PRAC recommendation on the benefit-risk balance of HES-containing products following notification by Germany of a referral under Article 31 of Directive 2001/83/EC based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Tatiana Magálová (SK)
PRAC Co-Rapporteur: Brigitte Keller-Stanislawski (DE-PEI)

Background

A referral procedure under Article 31 of Directive 2001/83/EC for HES-containing solutions for infusion was concluded at the 10-13 June 2013 PRAC meeting (see minutes). The MAHs for some of the products concerned submitted a request for re-examination of the PRAC recommendations.

Summary of recommendation(s)/conclusions

The PRAC appointed Tatiana Magálová (SK) to act as Rapporteur and Brigitte Keller-Stanislawski (DE-PEI) to act as Co-rapporteur for the re-examination procedure to start upon receipt of the grounds for the request. A timetable for the re-examination procedure will also be agreed upon receipt of the grounds.

Post-meeting note: grounds were received on 19 August 2013. Therefore the appointment of the Rapporteurs was confirmed and a timetable was adopted via written procedure on 21 August 2013.

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

None

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Fondaparinux – ARIXTRA (CAP)

- Signal of heparin-induced thrombocytopenia

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Fondaparinux is an anticoagulant that acts as a selective inhibitor of activated factor X. It is used in the prevention of venous thromboembolic events (VTE) in various conditions, and in the treatment of unstable angina, non-ST segment-elevation myocardial infarction (UA/NSTEMI), acute deep-vein thrombosis (DVT) and acute pulmonary embolism (PE).

The exposure for Arixtra, a centrally authorised medicine containing fondaparinux, is estimated to have been more than 10 million patients worldwide, in the period from first authorisation until 2011.

During routine signal detection activities, a signal of heparin-induced thrombocytopenia was identified by the EMA based on 8 cases mostly from the published literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the cases of heparin-induced thrombocytopenia, a life-threatening disorder that follows exposure to unfractionated or (less commonly) low-molecular-weight heparin. Heparin-induced thrombocytopenia is caused by platelet-activating antibodies against platelet factor 4 (PF4)–heparin complexes.

The diagnosis of heparin-induced thrombocytopenia is based on clinical evaluation of the patient using a reference scale (4 T's) based on the platelet count, the time to onset, the occurrence of thrombosis, the exclusion of alternative explanations, the identification of antibodies against platelet factor 4 (PF4)–heparin / fondaparinux complexes and, most importantly, on a functional platelet serotonin-release assay which involves the use of radioactive serotonin.

The PRAC noted that in a recently published article reporting fondaparinux-associated thrombocytopenia, the anti-PF4 enzyme immunoassay had been found positive[4]. In addition, a platelet serotonin-release assay of the patient's serum was found strongly positive for heparin-induced thrombocytopenia antibodies. This information further supported a causal association between fondaparinux and the development of the disease.

The PRAC agreed that this new information should be further evaluated in order to confirm the need for strengthened clinical advice in the current product information.

[3] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required.
[4] Warkentin TE, Chakraborty AK, Sheppard JA, Griffin DK. The serological profile of fondaparinux-associated heparin-induced thrombocytopenia syndrome. Thromb Haemost. 2012 Aug;108(2):394-6. doi: 10.1160/TH12-03-0201. Epub 2012 May 25.

Summary of recommendation(s)

- The MAH for Arixtra (fondaparinux) should submit to the EMA, within 30 days, a cumulative review of the signal and a proposal for amending the product information as appropriate.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Lopinavir/ritonavir – **KALETRA** (CAP), **ALUVIA** (Art 58) **Quetiapine** (NAP)

- Signal of major sedation due to drug interaction between lopinavir/ritonavir and quetiapine

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Lopinavir and ritonavir are protease inhibitors used in the treatment of human-immunodeficiency virus type I (HIV-1) infection.

A signal of an interaction between lopinavir/ritonavir and quetiapine leading to major sedation was identified by France, based on one case described in a scientific conference[5] in France. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted the case report of major sedation leading to deep coma in a patient receiving quetiapine and treated with lopinavir / ritonavir and emtricitabine / tenofovir in the context of HIV post-exposure prophylaxis.

The concomitant administration of HIV protease inhibitors is explicitly contra-indicated in the product information of quetiapine-containing medicinal products due to the risk of increased quetiapine exposure. In contrast, the same contraindication is not reported in the product information of lopinavir/ritonavir-containing medicines although it is stated that medicinal products highly dependent on cytochrome P450 3A (CYP3A) for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events should not be co-administered with quetiapine.

Such drug-drug interaction is considered to be due to an increased exposure to quetiapine caused by inhibition of CYP3A4 by lopinavir and ritonavir.

The PRAC agreed that information on the interaction and a contraindication should be included in the product information for lopinavir/ritonavir-containing products, but should also be introduced in the product information of all other protease inhibitor-containing medicines.

Summary of recommendation(s)

- The MAH for Kaletra (lopinavir / ritonavir) should submit to the EMA, within 30 days, a variation with a proposal for amending the product information[6] to include a contraindication for the concomitant use of quetiapine.

[5] Peytavin G. Clinical case #1: drug interaction and post-exposure prophylaxis (PEP) for HIV. 7eme Workshop Nouvelles molecules et strategies antiretrovirales. 2013;NA:1-4
[6] SmPC; Section 4.3. Contraindications: Concomitant medicinal product levels increased – Antipsychotics; Quetiapine: increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contra-indicated (see section 4.5). Section 4.5 Interaction with other medicinal products and other forms of interaction:

- The MAHs of all other protease inhibitor-containing medicinal products (ATC code J05AE) should also introduce a contraindication in the product information for these medicines, by appropriate procedures, within 30 days[7].

4.1.3. Sitagliptin – **JANUVIA** (CAP), **RISTABEN** (CAP), **TESAVEL** (CAP), **XELEVIA** (CAP) **Sitagliptin**, **metformin – EFFICIB** (CAP), **JANUMET** (CAP), **RISTFOR** (CAP), **VELMETIA** (CAP) **Angiotensin-converting enzyme (ACE) inhibitors** (NAP)

- Signal of angioedema due to interaction between sitagliptin and angiotensin-converting enzyme (ACE) inhibitors

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Sitagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor used in the treatment of type-2 diabetes mellitus.

The exposure for centrally authorised medicines containing sitagliptin is estimated to have been more than 9 million patient-years worldwide, in the period from first authorisation in 2006 to 2011.

During routine signal detection activities, a signal of angioedema due to co-administration of sitagliptin and angiotensin-converting enzyme (ACE) inhibitors was identified by the EMA, based on 9 cases retrieved from EudraVigilance. A search of Eudravigilance was performed following the publication of an article on angioedema and DDP-4 inhibitors.[8] Five additional publications were found. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of angioedema reported in EudraVigilance and described in the literature. The PRAC noted that the product information for sitagliptin-containing medicines includes information on angioedema and hypersensitivity including anaphylaxis. Angioedema is also a known adverse reaction associated with ACE inhibitors. According to published research,[9] the co-administration of an ACE inhibitor and a DPP-4 inhibitor might potentially increase significantly the risk of angioedema.

An interference with the substance P metabolic pathway could be a possible mechanism for the development of angioedema following co-administration of DPP-4 and ACE inhibitors. Substance P is normally degraded by angiotensin-converting enzyme (ACE). When ACE is inhibited, however, substance P is inactivated by DPP-4. Substance P contributes to ACE inhibitor-associated tracheal oedema in animal models. Published data suggested that pharmacological inhibition of DPP-4 could increase the risk of angioedema in patients taking ACE inhibitors. The fact that sitagliptin is a substrate for p glycoprotein and organic anion transporter-3 (OAT3) and that ACE inhibitors, including quinapril and enalapril, inhibit OAT3, and the fact that quinapril and captopril are also transported by human

Antipsychotics; Quetiapine; Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase; Concomitant administration of Kaletra and quetiapine is contra-indicated as it may increase quetiapine-related toxicity.

[7] Post-meeting note: similar wordings applicable to the SmPCs of other protease inhibitor-containing medicinal products were adopted by PRAC and CHMP via written procedure on 14 August 2013.

[8] Millot et all. 'Treatment of a life-threatening laryngeal bradykinin angio-oedema precipitated by dipeptidylpeptidase-4 inhibitor and angiotensin-I converting enzyme inhibitor with prothrombin complex concentrates in Br J Anaesth. 2012 Nov; 109(5):827-9

[9] Waeber B, Buclin T, Grouzmann E. [Angioedema during ACE and DPP-4 inhibition]. Rev Med Suisse. 2010 Jan 13;6(231):28-31. French. PubMed PMID: 20196430.

OAT3 might suggest an association with a pharmacokinetic mechanism involved in the interaction with the organic anion transporter-3 (OAT3).

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

Summary of recommendation(s)

- The MAH for sitagliptin-containing medicines should submit to the EMA, within 60 days, a cumulative review of the signal including a discussion on the possible mechanism (i.e. pharmacodynamic and pharmacokinetic) of the interaction and propose amendments to the SmPC or other risk management activities.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.4. **Tamsulosin** (NAP)

- Signal of dry mouth syndrome

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background

Tamsulosin is an alpha 1-receptor antagonist used for the treatment of lower urinary tract symptoms related to benign prostate hyperplasia (BPH).
The exposure for medicines containing tamsulosin is estimated so far to have been more than 5 million patient-years worldwide.

During routine signal detection activities, a signal of dry mouth was identified by the NL, based on 15 cases retrieved from EudraVigilance. NL confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported and noted that a number of them described a positive dechallenge. A study published in the literature in 2012[10] studied the effects of alpha1-adrenoceptor antagonists on phenylephrine-induced salivary secretion and intraurethral pressure elevation in anesthetised rats. The authors showed that tamsulosin inhibited phenylephrine-induced salivary secretion in a dose-dependent fashion. These results suggested that tamsulosin inhibited not only urethral contraction but also salivary secretion, which may contribute to the incidence of dry mouth. In accordance with these findings, additional literature has reported an association between tamsulosin and the occurrence of dry mouth[11]. The PRAC also noted that this event is listed in the product information of medicines of the same therapeutic class containing doxazosin, silodosin, alfuzosin and terazosin. Based on this information the PRAC confirmed that an update of the product information for tamsulosin-containing medicines was warranted.

The PRAC appointed Sabine Straus (NL) as Rapporteur for this signal.

[10] Yanai-Inamura H, Ohtake A, Noguchi Y, Hatanaka T, Suzuki M, Ueshima K, Sato S, Sasamata M. Effects of α1-adrenoceptor antagonists on phenylephrine-induced salivary secretion and intraurethral pressure elevation in anesthetized rats. Eur J Pharmacol. 2012 Mar 15;679(1-3):127-31. doi: 10.1016/j.ejphar.2012.01.019. Epub 2012 Feb 1.

[11] Reference to be inserted

Summary of recommendation(s)

- The MAH(s) for tamsulosin-containing medicines should submit to the NCA of the MS, within 60 days, a variation for amending the product information to include 'dry mouth'[12].

4.1.5. **Thiopental** (NAP)

- Signal of hypokalaemia and rebound hyperkalaemia due to potassium imbalance

Regulatory details:
PRAC Rapporteur: Ruchika Sharma (IE)

Background

Thiopental is a barbiturate general anaesthetic which is given intravenously to induce short duration general anaesthesia. It is also used to control convulsive disorders and to reduce the intracranial pressure in patients with increased intracranial pressure, if controlled ventilation is provided.

The exposure for medicines containing thiopental in Ireland and the United Kingdom is estimated to have been more than 720,000 patient-days in the period from 2008 to 2011.

During routine signal detection activities, a signal of hypokalaemia during thiopental infusion and rebound hyperkalaemia after cessation of the thiopental infusion was identified by the EMA, based on 14 cases retrieved from EudraVigilance. Ireland confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of potassium imbalance reported in patients being treated for raised intracranial pressure. In addition, 3 literature articles described similar patterns of hypokalaemia and a rebound hyperkalaemia during and after thiopental infusion.

Potassium imbalance may develop for a variety of reasons in patients being treated for raised intracranial pressure. In some but not all of the cases presented, concomitant medication included mannitol, which increases potassium excretion and could be considered a confounding factor. However, a strong temporal association was apparent in most cases and a consistent pattern of severe hypokalaemia and a rebound hyperkalaemia associated with thiopental administration suggested a causal relationship. Furthermore, thiopental has been shown to have functional effects on inward rectifying potassium channels[13], which could provide a plausible biological mechanism for the development of the reaction. In view of this information the PRAC agreed that the signal warranted further investigation.

The PRAC appointed Ruchika Sharma (IE) as Rapporteur for the follow-up of this signal.

Summary of recommendation(s)

- The MAH should provide to the Rapporteur, within 60 days, a review of cases of hypokalaemia and hyperkalaemia reported in relation to thiopental infusion and discuss potential mechanistic explanations.

[12] SmPCs section 4.8: SOC Gastrointestinal Disorders 'Dry Mouth'; frequency: 'unknown'
[13] López-Izquierdo A, Ponce-Balbuena D, Ferrer T, et al.; The development of hypokalaemia and rebound hyperkalaemia could lead to potentially life-threatening complications in this critically ill patient population; Eur J Pharmacol Jul 25; 638 (1-3): 33-41

- 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

4.2.1. 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)

- Signal of complex regional pain syndrome (CRPS) linked to the process of vaccination

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE), Jean-Michel Dogné (BE)

Background

Cervarix, Gardasil and Silgard are centrally authorised vaccines for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) types.

The exposure for Cervarix is calculated to have been between 12 and 36 million people worldwide.

Following a safety review in Japan, the Japanese pharmaceutical and medical devices agency published new safety information on Cervarix and Gardasil in June 2013, reporting 5 suspected cases of complex regional pain syndrome (CRPS) and 34 cases of extensive pain. As a result, and as a precautionary measure while they are gathering additional data, Japanese authorities temporarily suspended the recommendation to use these vaccines for routine immunisation. The vaccines remain available on the Japanese market for people who want to complete or start their vaccination.

Following a review of the data available from Eudravigilance and WHO database and since several articles have been published relating to cases of CRPS after vaccination[14] and/or venepuncture and the Rapporteurs confirmed that the signal needed further analysis and prioritisation by the PRAC.

Discussion

Reflex sympathetic dystrophy (RSD), also known as CRPS type I, is a chronic condition characterised by burning pain and abnormalities in the sensory, motor and autonomic nervous systems. The PRAC acknowledged that the syndrome seems to be triggered by trauma, typically appears after an acute injury to a joint or limb without nerve lesions, though it may occur with no obvious precipitating event. Mechanisms suggested to cause RSD/CRPS are elusive. It is possible that several mechanisms interact to cause RSD/CRPS. The PRAC noted that, in particular early CRPS symptoms may overlap with other diagnoses as CRPS has a wide range of symptoms involving different physiological functions. Criteria

[14] Arch Dis Child. 2012 Oct;97(10):913-5. doi: 10.1136/archdischild-2011-301307. Epub 2012 Aug. Complex regional pain syndrome following immunisation. Richards S, Chalkiadis G, Lakshman R, Buttery JP, Crawford NW.
Pediatr Int. 2012 Jun;54(3):e4-6. doi: 10.1111/j.1442-200X.2011.03526.x. Complex regional pain syndrome by vaccination: a case of complex regional painsyndrome after vaccination of influenza A(H1N1). Kwun BS, Park JW, Lee HJ, Kim AS, Ryu GH.
Eur J Pain. 2005 Oct;9(5):517-20. Epub 2004 Dec 18. Complex regional pain syndrome type-I after rubella vaccine. Genc H, Karagoz A, Saracoglu M, Sert E, Erdem HR.
J Pediatr. 2003 Dec;143(6):802-4.Complex regional pain syndrome after hepatitis B vaccine.Jastaniah WA, Dobson S, Lugsdin JG, Petty RE.
Sem Hop. 1977 Oct 23;53(36):1965-6.[A case of algodystrophic syndrome of the upper limb following tetanus vaccination].[Article in French]Bensasson M, Lanoe R, Assan R. PMID: 208165 [PubMed - indexed for MEDLINE]

for diagnosis of CRPS exist[15]. The PRAC agreed that further information should be requested from the MAHs in order to better evaluate the signal using an international case definition.

Summary of recommendation(s)

- The MAH for Gardasil, Cervarix and Silgard (human papillomavirus vaccines) should submit to the EMA, within 60 days, a cumulative review of the signal of complex regional pain syndrome (CRPS).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Levetiracetam – KEPPRA (CAP)

- Signal of syndrome of inappropriate antidiuretic hormones secretion (SIADH)

Regulatory details:
PRAC Rapporteur: Jean-Michel Dogné (BE)

Background

For background information see PRAC minutes 10-13 May 2013.

The MAH replied to the request for information on the signal and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the medically confirmed reports compatible with the 'preferred term' SIADH included in the safety database of the MAH. The analysis of these case reports did not show convincing evidence of a causal relationship between the use of levetiracetam and the onset of SIADH, as most of the cases were insufficiently documented or confounded by the patient's medical history or by concomitant drugs for which SIADH is a known related adverse drug reaction.

Furthermore, currently available data did not reveal any pattern of drug-drug interaction between levetiracetam and other antiepileptic drugs with regards to SIADH. As a consequence, the analysis of the currently available information was considered not sufficient by the PRAC to show a causal relationship between levetiracetam and SIADH.

Nevertheless the PRAC noted two published case reports[16] documenting a probable causal relationship between the use of levetiracetam and hyponatraemia. Since this aspect was not covered by the MAH review, the PRAC agreed that more information should be requested on this before concluding the evaluation of the signal.

Summary of recommendation(s)

- The MAH for Keppra should submit within 60 days a new cumulative review, including all cases of hyponatraemia to the EMA.

[15] Harden RN et al: Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007; 8:326-31
[16] Nasrallah K, Silver B. Hyponatremia associated with repeated use of levetiracetam. Epilepsia. 2005 Jun;46(6):972-3. Belcastro V, Costa C, Striano P. Levetiracetam-associated hyponatremia. Seizure. 2008 Jun;17(4):389-90

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

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the CHMP on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation.

Full information relating to PRAC discussions on products in the pre-authorisation phase will be released once the CHMP has reached an opinion for such medicines.

Please refer to the CHMP pages for upcoming information (http://www.ema.europa.eu/ Home>About Us>Committees>CHMP Meetings).

5.1.1. Afatinib

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.2. Albiglutide

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.3. Aripiprazole

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.4. Budesonide, formoterol

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.5. Cabozantinib

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.6. Canagliflozin, metformin

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.7. Cobicistat

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.8. Delamanid

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.9. Empagliflozin

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.10. Ex-vivo expanded autologous human corneal epithelial cells containing stem cells

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.11. Filgrastim

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.12. Fluticasone furoate, vilanterol

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.13. Follitropin alfa

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.14. Imatinib

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.15. Indacaterol, glycopyrronium bromide

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.16. Influenza vaccine (tetravalent, live attenuated, nasal)

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.17. Laquinimod

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.18. Lurasidone

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.19. Macitentan

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.20. Masitinib

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.21. Memantine

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.22. Nalfurafine

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.23. Ospemifene

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.24. Propranolol

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.25. Radium-223

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.26. Turoctocog alfa

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.1.27. Vedolizumab

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

5.2. Medicines already authorised

RMP in the context of a PSUR procedure

5.2.1. Abatacept – ORENCIA (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 15 of the RMP for the above mentioned medicine.

See also 6.1.1.

5.2.2. 5-aminolevulinic acid hydrochloride – AMELUZ (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 7 of the RMP for the above mentioned medicine.

See also 6.1.5.

5.2.3. Belatacept – NULOJIX (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 10.1 of the RMP for the above mentioned medicine.

See also 6.1.6.

5.2.4. Besilesomab – SCINTIMUN (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 10 of the RMP for the above mentioned medicine.

See also 6.1.7.

5.2.5. Cabazitaxel – JEVTANA (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 5 of the RMP for the above mentioned medicine.

See also 6.1.10.

5.2.6. Caffeine – PEYONA (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 12 of the RMP for the above mentioned medicine.

See also 6.1.11.

5.2.7. Omalizumab – XOLAIR (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 8 of the RMP for the above mentioned medicine.

See also ***Error! Reference source not found.***

5.2.8. Plerixafor – MOZOBIL (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 8 of the RMP for the above mentioned medicine.

See also 6.1.25.

5.2.9. Roflumilast – **DALIRESP** (CAP), **DAXAS** (CAP), **LIBERTEK** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Miguel-Angel Macia (ES)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 11 of the RMP for the above mentioned medicine.

See also 6.1.27.

5.2.10. Ticagrelor – **BRILIQUE** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Background

Ticagrelor is a selective adenosine diphosphate (ADP) receptor antagonist used with acetylsalicylic acid (ASA). It is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndromes in selected patients.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR for Brilique, a centrally authorised product containing ticagrelor.

Summary of advice

- The updated RMPs version 7 for Brilique (ticagrelor) was considered acceptable.

See also 6.1.29.

5.2.11. Ustekinumab – **STELARA** (CAP)

- Evaluation of an RMP in the context of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 9 of the RMP for the above mentioned medicine.

See also 0

RMP in the context of a variation

5.2.12. Aflibercept – EYLEA (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

Background

Eylea is an antineovascularisation agent, used for the treatment of neovascular (wet) age-related macular degeneration (AMD).

The CHMP is evaluating an application for an extension of the therapeutic indication for Eylea, a centrally authorised product containing aflibercept, to include the treatment of macular oedema following central retinal vein occlusion (CRVO). 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 RMP version 10 for Eylea (aflibercept) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable.
- The next update of the RMP should take into account some minor amendments suggested by the PRAC.

5.2.13. Anakinra – KINERET (CAP)

- Evaluation of an RMP in the context of a variation, line extension

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

Anakinra is an immunosuppressant used in the treatment of signs and symptoms of rheumatoid arthritis in combination with methotrexate (MTX), in adults with inadequate response to MTX alone.

The CHMP is evaluating an application for a line extension for Kineret, a centrally authorised product containing anakinra, to introduce a graduated syringe to allow dosing by bodyweight for the treatment of cryopyrin-associated periodic syndromes (CAPS) in adult and paediatric patients. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation for a line extension.

Summary of advice

- The updated RMP version 3 for Kineret (anakinra) in the context of the line extension under evaluation by the CHMP was not yet considered acceptable and the MAH was requested to submit an update to address some outstanding issues raised by the PRAC, including patient populations not studied, infection rate in CAPS, and some aspects to be clarified on pharmacovigilance and risk minimisation activities.

5.2.14. Atanazavir – REYATAZ (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 7 of the RMP for the above mentioned medicine.

5.2.15. Canakinumab – ILARIS (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 7 of the RMP for the above mentioned medicine in support of the CHMP's evaluation of an application for an extension of the indication for the treatment of active systemic juvenile idiopathic arthritis (SJIA) in selected patients.

5.2.16. Certolizumab pegol – CIMZIA (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 9 of the RMP for the above mentioned medicine in support the CHMP's evaluation of an application for an extension of indication for the treatment of active psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

5.2.17. Darunavir – PREZISTA (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 17.1 of the RMP for the above mentioned medicine in support of the CHMP's evaluation of an application for an extension of indication to include treatment of HIV-infected naive patients aged 12 to 18 years.

5.2.18. Eptacog alfa – NOVOSEVEN (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 4 of the RMP for the above mentioned medicine to include dosing recommendations for the prevention of bleeding in factor VIII-deficient children in the product information.

5.2.19. Insulin human – **INSUMAN** (CAP)

- Evaluation of an RMP in the context of a variation, line extension

Regulatory details:
PRAC Rapporteur: Jean-Michel Dogné (BE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 1.2 of the RMP for the above mentioned medicine in support of the CHMP's evaluation of an application to introduce a solution for intraperitoneal use with an implantable intraperitoneal insulin pump.

5.2.20. Insulin lispro – **HUMALOG** (CAP), **LIPROLOG** (CAP)

- Evaluation of an RMP in the context of a worksharing variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Insulin lispro is an insulin used in the treatment of diabetes mellitus. The CHMP is evaluating a variation application for centrally authorised products containing insulin lispro to include a change in the manufacturing process. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 1 for Humalog and Liprolog (insulin lispro) in the context of the variation under evaluation by the CHMP could be acceptable provided that an updated RMP and satisfactory responses to list of questions are submitted before finalisation of the variation procedure by the CHMP.
- The PRAC agreed list of questions included the need for some further risk minimisation measures to manage the switching of patients between differently manufactured insulin lispro-containing products that will be available as a result of the change in manufacturing process. It was recommended that a communication highlighting the new manufacturing process and any potentially associated risk of hypersensitivity or anaphylactic reactions should be issued by the MAH. The MAH will also need to consider whether communication alone is sufficient to manage patients switching from one product to another and will also need to consider how the effectiveness of any risk minimisation measures proposed can be measured.

5.2.21. Ipilimumab – **YERVOY** (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 8.1 of the RMP for the above mentioned medicine to support the CHMP's evaluation of an application for an extension of indication to include treatment naïve adult patients with advanced (unresectable or metastatic) melanoma.

5.2.22. Paclitaxel – ABRAXANE (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 12 of the RMP for the above mentioned medicine in support of the CHMP's evaluation of an application for an extension of indication to include first-line treatment of adult patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas in combination with gemcitabine.

5.2.23. Pandemic influenza vaccine (N5N1) (whole virion, vero cell derived, inactivated) – PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 1 of the RMP for the above mentioned medicine in support of the CHMP's evaluation of an application for an extension of indication to include use in the paediatric population from 6 months of age onwards.

5.2.24. Pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) – PANDEMRIX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 16 of the RMP for the above mentioned medicine in support of the CHMP's evaluation of an application for the inclusion of the adverse drug reaction angioedema as a result of a cumulative review.

5.2.25. Posaconazole – NOXAFIL (CAP)

- Evaluation of an RMP in the context of a variation, line extension

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 10 of the RMP for the above mentioned medicine in support of the CHMP's evaluation of an application for a line extension.

5.2.26. Prepandemic influenza vaccine (H5N1) (whole virion, vero cell, non-adjuvanted) – VEPACEL (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Jean-Michel Dogné (BE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 1 of the RMP for the above mentioned medicine in support of the CHMP's evaluation of an application for an extension of indication to include use in the paediatric population from 6 months of age onwards.

5.2.27. Ranibizumab – LUCENTIS (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Ranibizumab is a monoclonal antibody used in the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME) and visual impairment due to macular oedema secondary to retinal vein occlusion (RVO) (branch RVO or central RVO).

The CHMP is evaluating an application for a variation for Lucentis, a centrally authorised product containing ranimizumab, to include a pre-filled syringe presentation for Lucentis, and other associated changes. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 12 for Lucentis (ranimizumab) in the context of the variation under evaluation by the CHMP was considered acceptable provided that some amendments are included on the risk of medication errors and the text of the RMP summary is further refined before finalisation of the variation procedure by the CHMP.

5.2.28. Rivastigmine – EXELON (CAP), PROMETAX (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details
PRAC Rapporteur: Evelyne Falip (FR)

Background

Rivastigmine is a cholinesterase inhibitor used in the treatment of mild to moderately severe Alzheimer's dementia.

The CHMP is evaluating an application for Exelon/Prometax, centrally authorised products containing rivastigmine, to extend the use of the transdermal patch to the symptomatic treatment of severe Alzheimer's dementia.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the proposed RMP to support this variation.

Summary of advice

- The RMP Version 7.1 for Exelon/Prometax (rivastigmine) in the context of the variation under evaluation by the CHMP was considered acceptable.
- The next update of the RMP should include some amendments requested by the PRAC concerning the description of the study ENA713D2409 'Exelon Transdermal Patch: A Drug Utilization Study'.

5.2.29. Ustekinumab – STELARA (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 10 of the RMP for the above mentioned medicine in support of the CHMP's evaluation of an application for an extension of indication to include psoriatic arthritis.

RMP in the context of a renewal of the marketing authorisation, conditional renewal or annual reassessment

See also Agomelatine (Thymanax, Valdoxan) under 8.1.1. , Eptotermin (Opgenra) 8.1.2. , Octocog alfa (Advate) 8.1.4. , Romiplostim (Nplate) 8.1.5.

RMP in the context of a stand-alone RMP procedure

5.2.30. Abacavir – ZIAGEN (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 6 of the RMP for the above mentioned medicine.

5.2.31. Aripiprazole – ABILIFY (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 8 of the RMP for the above mentioned medicine.

5.2.32. Fentanyl – INSTANYL (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 18.02 of the RMP for the above mentioned medicine.

5.2.33. Fesoterodine – TOVIAZ (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Miguel-Angel Macia (ES)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 8 of the RMP for the above mentioned medicine.

5.2.34. Lamivudine, zidovudine – COMBIVIR (CAP), LAMIVUDINE / ZIDOVUDINE VIIV (Art 58)

- Evaluation of an RMP in the context of a stand-alone RMP procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 4 of the RMP for the above mentioned medicine.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[17]

6.1.1. Abatacept – ORENCIA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Orencia, a centrally authorised medicine containing abatacept, remains favourable in the approved indication(s)

[17] Where a regulatory action is recommended (variation, suspension or revocation of the terms of Marketing Authorisation(s)), the assessment report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion. Where PRAC recommends the maintenance of the terms of the marketing authorisation(s), the procedure finishes at the PRAC level.
For each PRAC recommendation, in cases where other medicinal products containing the same substance are currently authorised in the EU, or subject to future authorisation procedures in the EU, the PRAC recommends that the concerned Member States and Marketing Authorisation Holders take due consideration of it.

and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

See also 5.2.1.

6.1.2. Aliskiren / amlodipine / hydrochlorothiazide – RASITRIO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Rasitrio, a centrally authorised medicine containing aliskiren/amlodipine/hydrochlorothiazide, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.3. Ambrisentan – VOLIBRIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Dolores Montero Corominas (ES)

Background

Ambrisentan is an endothelin receptor antagonist (ERA) selective for the endothelin A (ETA) receptor. It is used for the treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Volibris, a centrally authorised medicine containing ambrisentan, 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 benefit-risk balance of Volibris (ambrisentan) in the approved indication(s) remains favourable. The current terms of the marketing authorisation should be maintained.
- In the next PSUR, the MAH should provide an updated cumulative review of visual disturbances potentially associated with ambrisentan.
- The Rapporteur underlined unexpected findings of a study in neonate and juvenile rats included in the approved Paediatric Investigation Plan (PIP) (EMEA-000434-PIP01-08-M01)

currently on hold. The results are under review by CHMP in collaboration with the PDCO. PRAC will be involved in the review as applicable. Volibris (ambrisentan) is currently not authorised in paediatric patients.

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 and published on the EMA website.

6.1.4. Amifampridine – FIRDAPSE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Firdapse, a centrally authorised medicine containing amifampridine, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.5. 5-aminolevulinic acid hydrochloride – AMELUZ (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Ameluz, a centrally authorised medicine containing 5-aminolevulinic acid hydrochloride, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website. 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.

6.1.6. Belatacept – NULOJIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Nulojix, a centrally authorised medicine containing belatacept, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

See also 5.2.3.

6.1.7. Besilesomab – SCINTIMUN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Scintimun, a centrally authorised medicine containing besilesomab, 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, this procedure was finalised at the PRAC level without further plenary discussion.

The frequency of submission of PSURs should be changed from 6-monthly to yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point at 10 January 2014. The list of Union reference dates (EURD list) is updated accordingly.

See also 5.2.4.

6.1.8. Bimatoprost, timolol – GANFORT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Background

Bimatoprost/timolol is used to reduce intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ganfort, a centrally authorised medicine containing bimatoprost/timolol, 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 benefit-risk balance of Ganfort (bimatoprost/timolol) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to better reflect the fact that bronchospasm, dyspnoea, eyelid retraction and dizziness were reported with the combination and not only with bimatoprost or timolol alone. In addition and in line with the recent EMA/CHMP review of the use of phosphate buffers in medicinal products given as eye drops,

the product information should be updated to reflect the occurrence of corneal calcification as an undesirable effect with a very rare frequency in patients with significantly damaged corneas. Therefore the current terms of the marketing authorisation should be varied[18].

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 and published on the EMA website.

6.1.9. C1 inhibitor, human – CINRYZE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Cinryze, a centrally authorised medicine containing active C1 esterase inhibitor (human), 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.10. Cabazitaxel – JEVTANA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Jevtana, a centrally authorised medicine containing cabazitaxel, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

See also 5.2.5.

6.1.11. Caffeine – PEYONA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

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

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Peyona, a centrally authorised medicine containing caffeine, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

See also 5.2.6.

6.1.12. Canakinumab – ILARIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Ilaris, a centrally authorised medicine containing canakinumab, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.13. Darunavir – PREZISTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background

Darunavir is a protease inhibitor. It is used with low dose of ritonavir and other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients as well as antiretroviral therapy (ART)-experienced paediatric patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prezista, a centrally authorised medicine containing darunavir, 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 benefit-risk balance of Prezista (darunavir) in the approved indication(s) remains favourable.

- Nevertheless, the product information should be updated to include 'drug reaction with eosinophilia and systemic symptoms' (DRESS) as a warning and an undesirable effect with rare frequency. Therefore the current terms of the marketing authorisation should be varied[19].

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 and published on the EMA website.

6.1.14. Eptacog alfa – NOVOSEVEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of NovoSeven, a centrally authorised medicine containing eptacog alfa, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.15. Ferumoxytol – RIENSO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Rienso, a centrally authorised medicine containing ferumoxytol, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.16. Fondaparinux – ARIXTRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

[19] 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.

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Arixtra, a centrally authorised medicine containing fondaparinux, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.17. Hydroxocobalamin – CYANOKIT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Cyanokit, a centrally authorised medicine containing hydroxocobalamin, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.18. Influenza vaccine (trivalent, live attenuated, nasal) – FLUENZ (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Fluenz, a centrally authorised influenza vaccine (trivalent, live attenuated, nasal), 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.19. Lamivudine – EPIVIR (CAP), LAMIVUDINE VIIV (Art 58)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Epivir and Lamivudine ViiV, centrally authorised and scientific opinion medicines containing lamivudine, remains

favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) for Evipir, as well as the CHMP's scientific opinion(s)[20] for Lamivudine ViiV, together with the assessment report. As per agreed criteria, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.20. **Lamivudine**, **zidovudine – COMBIVIR** (CAP), **LAMIVUDINE / ZIDOVUDINE VIIV** (Art 58)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Combivir and Lamivudine/zidovudine ViiV, centrally authorised and scientific opinion medicines containing lamivudine/zidovudine, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s), as well as the CHMP's scientific opinion(s), together with the assessment report. As per agreed criteria, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.21. **Nitric oxide – INOMAX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of INOmax, a centrally authorised medicine containing nitric acid, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.22. **Omalizumab – XOLAIR** (CAP)

- Evaluation of a PSUR procedure

[20] Opinion(s) given in accordance with Article 58 of Regulation (EC) No 726/2004 (see also Opinions on medicines for use outside the EU)

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Xolair, a centrally authorised medicine containing omalizumab, 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, this procedure was finalised at the PRAC level without further plenary discussion.

The frequency of submission of PSURs should be changed from yearly to 6-monthly and the next PSUR is to be submitted to the EMA within 70 days of the data lock point set at 30 June 2013 as per the conclusion of the recently finalised variation updating the product information dosing table (see variation II/37: Xolair EPAR Procedures after authorisation). The list of Union reference dates (EURD list) is updated accordingly.

See also 5.2.7.

6.1.23. Paliperidone – **INVEGA** (CAP), **XEPLION** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Invega and Xeplion, centrally authorised medicines containing paliperidone, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.24. Perflutren – **LUMINITY** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Luminity, a centrally authorised medicine containing perflutren, remains unaltered in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This medicine is currently suspended for use in the European Union.

This recommendation is without prejudice to any measure that has been taken by competent authorities to ensure the continuous quality of the medicinal products concerned[21]. The continued

[21] http://ec.europa.eu/health/documents/community-register/2012/20120525120689/dec_120689_en.pdf

suspension of the marketing authorisation due to issues in the quality management system, particularly in relation to the sterile filling process and possible particle contamination during the manufacturing process, remains in place until the MAH obtains approval for an alternative GMP-compliant manufacturing site. As per agreed criteria, this procedure was finalised at the PRAC level without further plenary discussion.

The frequency of submission of PSURs for this specific perflutren-containing product should be changed from yearly to 3-yearly with a data lock point set at 27 December 2015 and the next PSUR should be submitted to the EMA within 90 days of the data lock point. This frequency is subject to revision, should there be lifting of the suspension of the marketing authorisation(s) in the interim period. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.25. Plerixafor – MOZOBIL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Mozobil, a centrally authorised medicine containing plerixafor, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

See also 5.2.8.

6.1.26. Pneumococcal polysaccharide conjugate vaccine (adsorbed) – SYNFLORIX (CAP)

- Evaluation of a PSUR procedure

Status: *for discussion and agreement of recommendation to CHMP*

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Synflorix, a centrally authorised pneumococcal polysaccharide conjugate vaccine (adsorbed), is indicated for the active immunisation against invasive disease and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 5 years of age.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Synflorix 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 benefit-risk balance of Synflorix (pneumococcal polysaccharide conjugate vaccine (adsorbed)) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- Nevertheless, the MAH should submit to the EMA within 60 days a detailed meta-analysis of individual cases for Kawasaki's disease reported in clinical trials, including a comparison between cases reported with Synflorix and control cases. Moreover, the MAH should conduct an observed vs. expected rate analysis for the spontaneous cases and the cases reported in observational studies. In addition, the MAH should discuss the recent increased reporting rate of hypotonic hyporesponsive episode (HEE).
- In the next PSUR, the MAH should include a cumulative review of cases of sudden death/sudden infant death syndrome (SIDS) reported from clinical trials and post-marketing sources. Finally, the MAH should keep under close monitoring cases of immune thrombocytopenic purpura (TTP) and vasculitis.

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 and published on the EMA website.

6.1.27. Roflumilast – **DALIRESP** (CAP), **DAXAS** (CAP), **LIBERTEK** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Miguel-Angel Macia (ES)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Daliresp, Daxas and Libertek, centrally authorised medicines containing roflumilast, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

See also 5.2.9.

6.1.28. Thyrotropin alfa – **THYROGEN** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Thyrogen, a centrally authorised medicine containing thyrotropin alfa, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.29. Ticagrelor – BRILIQUE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Background

Ticagrelor is a platelet aggregation inhibitor used with acetylsalicylic acid (ASA) for the treatment of atherothrombotic events in adult patients with acute coronary syndrome, including patients managed medically and those who are managed with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brilique, a centrally authorised medicine containing ticagrelor, 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 benefit-risk balance of Brilique (ticagrelor) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- Nevertheless, the MAH should submit to EMA within 60 days a variation to reflect in the product information the results of the study by *Holmberg et a.l*[22] on the risk of interaction with grapefruit juice resulting in an increased patient exposure to ticagrelor leading to a risk of dizziness (see also PRAC Minutes February 2013). In addition the product information should be updated to reflect cases of intracranial bleeding as an 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 and published on the EMA website.

See also 5.2.10.

6.1.30. Tobramycin – TOBI PODHALER (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

[22] Holmberg et al. (2012). Grapefruit juice markedly increases the plasma concentrations and antiplatelet effects of ticagrelor in healthy subjects. Br J Clin Pharmacol.

Background

Tobramycin is an aminoglycoside antibiotic indicated for the suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tobi Podhaler, a centrally authorised medicine containing tobramycin inhalation powder, 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 benefit-risk balance of Tobi Podhaler (tobramycin, inhalation powder) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add aphonia with a frequency category unknown. Therefore the current terms of the marketing authorisation should be varied[23].
- In the next PSUR, the MAH should include a cumulative review of cases of dizziness due to its relationship with the potential risk of ototoxicity.

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 and published on the EMA website.

6.1.31. Ustekinumab – STELARA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Stelara, a centrally authorised medicine containing ustekinumab, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

See also 5.2.11.

6.1.32. Verteporfin – VISUDYNE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

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

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Visudyne, a centrally authorised medicine containing verteporfin, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.1.33. Ziconotide – PRIALT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Jean-Michel Dogné (BE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Prialt, a centrally authorised medicine containing ziconotide, 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, this procedure was finalised at the PRAC level without further plenary discussion.

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 and published on the EMA website.

6.2. Follow-up to PSUR procedures[24]

6.2.1. Aripiprazole – ABILIFY (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Background

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine, the PRAC requested the MAH to submit further data (see PRAC Minutes February 2013). The responses were assessed by the Rapporteur for further PRAC advice.

As per agreed criteria, the Committee endorsed the conclusions of the Rapporteur without further plenary discussion.

Summary of recommendation(s)/conclusions

- In the next PSUR, the MAH for Abilify (aripiprazole) should continue to monitor adverse drug reactions associated with the use of aripiprazole during pregnancy and lactation.

[24] Follow up as per the conclusions of the previous PSUR procedure, assessed outside next PSUR procedure.

6.2.2. Asenapine – SYCREST (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine, the PRAC requested the MAH to submit further data (see PRAC Minutes March 2013). The responses were assessed by the Rapporteur for further PRAC advice.

As per agreed criteria, the Committee endorsed the conclusions of the Rapporteur without further plenary discussion.

Summary of recommendation(s)/conclusions

- In the next PSUR, the MAH for Sycrest (asenapine) should closely monitor cases of neutropenia and medication errors and further evaluate the reasons or medication errors.

6.2.3. Orlistat – XENICAL (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

Background

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine, the PRAC assessed further data from the MAH (see PRAC Minutes April 2013) regarding patient exposure in India. The responses were assessed by the Rapporteur for further PRAC advice.

As per agreed criteria, the Committee endorsed the conclusions of the Rapporteur without further plenary discussion.

Summary of recommendation(s)/conclusions

- The issue is resolved, no further follow-up is deemed necessary.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of post-authorisation safety studies

7.1.1. Aclidinium bromide – BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP)

- Evaluation of a PASS protocol pursuant to an obligation imposed in accordance with Article 21a and 22a of Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

For background see PRAC minutes 8-11 April 2013. The MAH provided an amended protocol as per previous request of the PRAC.

Endorsement/refusal of the protocol

Having considered the updated protocol for Eklira/Bretaris Genuair (aclinidium bromide), in accordance with Article 107n of Directive 2001/83/EC, the PRAC considered that the study design was acceptable.

7.1.2. Alipogene tiparvovec – GLYBERA (CAP)

- Evaluation of a PASS protocol pursuant to an obligation imposed in accordance with Article 21a and 22a of Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

The Rapporteur assessed the study protocol for PASS 'SOB001', a longitudinal observational registry study involving lipoprotein lipase-deficient (LPLD) patients, who have either been treated or not with alipogene tiparvovec. Since all comments received on the assessment of the study protocol were addressed before the plenary, the PRAC endorsed the conclusion of the Rapporteurs and, having considered that the draft protocol was in accordance with Article 107n of Directive 2001/83/EC, endorsed the draft protocol for Glybera.

7.1.3. Colistimethate sodium – COLOBREATHE (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

The Rapporteur assessed the PASS protocol for a long-term observational safety study of Colobreathe (dry powder colistin) in cystic fibrosis patients using cystic fibrosis registries. Since all comments received on the assessment of the study protocol were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteur on the assessment of the protocol requesting some amendments to be submitted to the EMA.

7.1.4. Dapagliflozin – FORXIGA (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

The Rapporteur assessed the study protocols for four pharmaco-epidemiological PASSs (a study on the risk of severe complications of urinary tract infections (UTI); a study on the risk of acute renal failure; a study on the risk of acute hepatic failure; and a study on the risk of cancer). Since all comments received on the assessment of the study protocols were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteur on the assessment of the protocols and endorsed a request for supplementary information to be submitted to the EMA.

7.1.5. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

The Rapporteur assessed the study protocol for the PASS 'Post-licensure observational safety study of specific outcomes after Optaflu vaccination among adults in The Health Improvement Network (THIN) database of routine UK primary care records'. Since all comments received on the assessment of the study protocol were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs, and having considered the draft protocol endorsed a request for some amendments.

7.1.6. Lixisenatide – LYXUMIA (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Comments were received on the assessment of the study protocol for two PASSs. The first PASS was a retrospective database study using existing databases and registries in Sweden, Denmark, and Norway to estimate the incidence rates of acute pancreatitis, pancreatic and thyroid cancer among adult type diabetes mellitus (2T2DM) patients treated with glucagon-like peptide-1 (GLP-1) receptor agonists compared with other anti-diabetics. This study also aims to evaluate the potential association between acute pancreatitis, pancreatic cancer and thyroid cancer and the use of GLP-1 receptor agonists compared with the use of other anti-diabetics among adult T2DM patients.

The second PASS was a patient registry involving adult T2DM patients treated with lixisenatide after launch in Sweden, Denmark, and Norway and aiming to monitor the occurrence of events of interest including acute pancreatitis, pancreatic and thyroid cancer among adult T2DM patients treated with lixisenatide after launch).

Since all comments received on the assessment of the study protocols were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteur without further discussion at the meeting, and having considered the draft protocols, endorsed a request for supplementary information and amendments to be submitted to the EMA.

7.1.7. Maraviroc – CELSENTRI (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

The Rapporteur assessed an updated PASS protocol for a prospective observational epidemiological study on the safety of maraviroc. Since all comments received on the assessment of the study protocol were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteur who considered the draft protocol acceptable.

7.1.8. **Nomegestrol, estradiol – ZOELY** (CAP), **IOA** (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

Background

For background, see PRAC Minutes April 2013. The CHMP had discussed the advice of the PRAC recommending that a post-authorisation safety study for Zoely/Ioa in accordance with Article 10a of Regulation (EC) No 726/2004 should be imposed as a condition in ANNEX II of the marketing authorisation. The MAH provided comments on the proposal and these comments were assessed by the Rapporteur for further PRAC advice.

Summary of advice

The PRAC had previously advised that the MAH should be requested to carry out a PASS with the primary objective of evaluating the risk of VTE in healthy women initiating or restarting use of the fixed combination products containing nomegestrol acetate and 17beta-estradiol (NOMAC-E2) compared with the risk in women initiating or restarting use of combined oral contraceptives (COCs) containing levonorgestrel. The PRAC confirmed that the conduct of the PASS should be included as an obligation on the concerned marketing authorisation holder in accordance with Article 10a of Regulation (EC) No 726/2004

The PRAC agreed on some key aspects of the design of the study which could be implemented as amendments to the ongoing PASS called CELINA.

7.1.9. **Ocriplasmin – JETREA** (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

The Rapporteur assessed an updated PASS protocol for a prospective drug utilisation study (TG MV 017) on the use of intravitreal Jetrea (ocriplasmin) in clinical practice. Since all comments received on the assessment of the study protocol were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteur.

7.1.10. **Pertuzumab – PERJETA** (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

Perjeta is a centrally authorised medicine containing pertuzumab, an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody indicated for use in combination with trastuzumab and

docetaxel in selected adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer.

As part of the RMP for Perjeta (pertuzumab), the MAH submitted a protocol for a study on the 'MotHER' pregnancy registry in the EU to monitor the pregnancy period which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC agreed that an updated protocol should be submitted to the EMA taking into account a number of points and questions raised by the PRAC on the study design, including feasibility, sample size and timelines of the study. Further PRAC advice will be provided upon submission of a revised protocol.

7.1.11. Teduglutide – REVESTIVE (CAP)

- PRAC consultation on PASS protocol conducted pursuant to an obligation imposed in accordance with Article 21a and 22a of Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Background

Revestive is a centrally authorised medicine containing teduglutide, a recombinant GLP-2 analogue, indicated for the treatment of adult patients with short bowel syndrome (SBS). Following PRAC advice in February 2013 the MAH submitted a revised protocol that was assessed by the Rapporteur.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 2.0 in accordance with Article 107n of Directive 2001/83/EC, endorsed the draft protocol for the above listed medicinal product.

7.1.12. Ulipristal acetate – ELLAONE (CAP)

- PRAC consultation on a PASS protocol included in the pharmacovigilance plan of the RMP in accordance to Article 107m Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Measures to strengthen awareness of a pregnancy registry collecting data on exposed pregnancies, available in all European countries where the product is launched and accessible to all EllaOne prescribers, were previously discussed by the PRAC at the April 2013 meeting. Since all comments received on the assessment of these measures were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs that the measures were acceptable pending some modifications to the pregnancy registry specification.

7.2. Results of post-authorisation safety studies

7.2.1. Aflibercept – ZALTRAP (CAP)

- PRAC consultation on PASS study results

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

The Rapporteur assessed the protocol of a Drug Utilisation Study (DUS) to address the potential for off-label use, particularly intravitreal off-label use. Since all comments received on the assessment of the study protocol were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs that the protocol of the DUS was acceptable.

7.2.2. Betaine – CYSTADANE (CAP)

- PRAC consultation on PASS study results

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

The Rapporteur assessed the third update report from the re-started ROCH (Registry for Cystadane – Homocystinuria) registry aimed at better establishing clinical knowledge on the use of betaine in patients affected by homocystinuria. Since all comments received on the assessment of this third update report were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs to request further clarifications on the findings to be submitted to the EMA.

7.2.3. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study

- PRAC evaluation of D:A:D data merger results

Regulatory details:

PRAC Representatives: Filip Josephson (SE), Deborah Ashby (UK)

The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) was initiated in 1999 following a request from the CHMP and is a prospective multi-cohort study of HIV-infected persons under active follow-up. The initial purpose of the study was to assess the incidence of myocardial infarction (MI), cardiovascular disease (CVD) and other clinical markers of severe organ dysfunction amongst HIV/AIDS patients and to investigate whether treatment with antiretroviral drugs (ARVs) as part of a current or past combination antiretroviral therapy (cART) regimen is associated with the development of these adverse events. In 2008, the scope was broadened to include analyses of the incidence of further serious non-AIDS events (liver and renal failure and non-AIDS malignancies).

At the current meeting, the EMA representatives on the highly active antiretroviral therapy (HAART) Oversight Committee (see PRAC Minutes March 2013) presented the assessment of the D:A:D study's 13th data merger relating mainly to the relative safety of antiretroviral therapy. Data showed that not only has the rate of death in AIDS decreased within the cohort over time, but this also applies to liver-related deaths, death due to non-AIDS defining malignancies and death due to cardiovascular disease. Present findings on renal safety are reassuring, as they indicate the appropriate management of known risks, and do not give a signal of an association between any drugs and advanced kidney disease. Results describing an impact on renal function are difficult to interpret and not fully consistent with other available data. Data on the protease inhibitors (PI) class and the possible risk of malignancy due to xenobiotic exposure secondary to profound CYP3A blockade are not indicative of a heightened level of concern, given the present extent of use and duration of exposure within the study. The particular finding of an association between cumulative PI use and an increased risk of anal cancer remains very

difficult to interpret as to its potentially causal nature, and may possibly be due to residual confounding factors.

The PRAC concluded that the 13th data merger does not contain any data that would require further questions to be put to the D:A:D study investigators, or any other regulatory action.

See also 12.14.1.

7.2.4. Fentanyl – INSTANYL (CAP)

- PRAC consultation on PASS study results

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

Background

Instanyl is a centrally authorised fentanyl-containing intranasal spray indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain.

As part of the RMP for Instanyl, the MAH was requested to conduct a PASS study investigating possible misuse, abuse and overdose in patients treated with Instanyl nasal spray (PIUS study). The MAH provided an interim clinical study report of this study, which was assessed by the Rapporteur. The PRAC would provide advice to CHMP following assessment of the study results.

Summary of advice

The PRAC noted that the overall rate of misuse (presence of at least one misuse criterion) in the PIUS study was about 95%. However these findings should be interpreted with caution. This rate was derived from combination of several criteria and was likely to overestimate the misuse of Instanyl.

The level of misuse assessed through the PIUS study is difficult to quantify further because of some limitations since the representativeness of the sample of participating patients was questionable. In addition the PIUS study, for feasibility reasons, is being conducted in France and the results cannot be automatically extrapolated to other European countries.

The PRAC noted that an EU-wide study (LINUS) will provide further results son the same matter; the study results are expected with the next PSUR submission.

The PRAC therefore recommended that the results of both studies are fully analysed in the context of the next PSUR procedure (due for submission in July 2013, DLP: 30/04/2013).

7.2.5. Octocog alfa – ADVATE (CAP)

- PRAC consultation on PASS study results

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

The Rapporteur assessed the study results of a PASS (PISA) on ADVATE rAHF-PFM in Haemophilia A (TW-BS-09001) and a post marketing Italian surveillance study on ADVATE rAHF-PMF in the treatment of Haemophilia A evaluating its efficacy, safety and immunogenicity. Since all comments received on the assessment of the study protocol were addressed before the plenary, the PRAC endorsed the conclusion of the Rapporteurs that the results of the studies do not raise any new safety concern and no regulatory action was necessary at this time.

8. Renewals of the Marketing Authorisation, Conditional Renewals and Annual Reassessments

8.1.1. Agomelatine – **THYMANAX** (CAP), **VALDOXAN** (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Agomelatine is a melatonergic (MT_1 and MT_2 receptors) agonist and 5-HT_{2C} antagonist indicated for the treatment of major depressive episodes in adults. Thymanax and Valdoxan, centrally authorised medicines containing agomelatine, were authorised in 2009.

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

Based on the review of the risk management system for Thymanax/Valdoxan (agomelatine), and the CHMP Rapporteur's assessment report, the PRAC considered that an additional renewal after five years should be required because of issues relating to the risks of QT prolongation* and hepatotoxicity. The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated RMP version 15 and considered that the renewal procedure could be finalised if satisfactory clarification is given on some pending issues relating to the RMP. The PRAC noted that the ongoing PSUR procedure for agomelatine-containing products is due for PRAC recommendation in September 2013.

*post-meeting note: this refers to an ongoing signal evaluation on the potential association between agomelatine and QT prolongation (see PRAC minutes 13-16 May 2013). Follow-up discussion on this signal is expected at the PRAC October 2013 meeting.

See also under 5.2

8.1.2. Eptotermin alfa – **OPGENRA** (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Background

Eptotermin alfa is a bone morphogenetic protein indicated for the treatment for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed or is contra-indicated. Opgenra, a centrally authorised medicine containing eptotermin alfa, was authorised in2009.

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

Based on the review of the available pharmacovigilance data for Opgenra (eptotermin alfa) and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could be concluded. However, the PRAC considered that an additional 5-year renewal should be required because of the limited experience on safety and efficacy and that evaluation of the PASS study protocol entitled *'Prospective observational registry study in subjects treated with Opgenra (eptotermin alfa) in the European Union'* included in the conditions of marketing authorisation (Annex II) is ongoing and the study has not yet started. The PRAC endorsed the conclusions of the Rapporteur on the assessment of the updated RMP version 6.

See also under 5.2

8.1.3. Influenza vaccine (split virion, inactivated) – IDFLU (CAP), INTANZA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Miguel-Angel Macia (ES)

Based on the review of the available pharmacovigilance data for IDflu and Intanza (influenza vaccine (split virion, inactivated)) and the CHMP Rapporteur's assessment report, the PRAC considered that these first five year renewal procedures could be concluded and supported the renewal of the marketing authorisations for an unlimited period. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.4. Octocog alfa – ADVATE (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Based on the review of the available pharmacovigilance data for Advate (octocog alfa) and the CHMP Rapporteur's assessment report, the PRAC considered that this second five year renewal procedure could be concluded and supported the renewal of the marketing authorisation for an unlimited period. The PRAC also endorsed the conclusions of the Rapporteur on the assessment of the updated RMP version 14. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

See also under 5.2

8.1.5. Romiplostim – NPLATE (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Dolores Montero Corominas (ES)

Based on the review of the available pharmacovigilance data for Nplate (romiplostim) and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could

be concluded and supported the renewal of the marketing authorisation for an unlimited period. The PRAC also endorsed the conclusions of the Rapporteur on the assessment of the updated RMP version 13. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

See also under 5.2

8.1.6. Tafamidis – VYNDAQEL (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Based on the review of the available information on the status of fulfilment of specific obligations and the safety data submitted, the MAH's response to the CHMP's request for supplementary information and the recent PSUR procedure (see PRAC Minutes June 2013), the PRAC considered that this annual re-assessment procedure for Vyndaqel (tafamidis) could be concluded. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.7. Tocilizumab – ROACTEMRA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Based on the review of the available pharmacovigilance data for RoActemra (tocilizumab) and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could be concluded and supported renewal of the marketing authorisation for an unlimited period. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

8.1.8. Ustekinumab – STELARA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Based on the review of the available pharmacovigilance data for Stelara (ustekinumab) and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could be concluded and supported the renewal of the marketing authorisation for an unlimited period. As per agreed criteria, the procedure was finalised at the PRAC level without further plenary discussion.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. On-going or concluded pharmacovigilance inspection

The PRAC discussed the results of some inspections conducted in the EU. Disclosure of information on results of pharmacovigilance inspections could undermine the purpose of these inspections, investigations and audits. Therefore such information is not reported in the published minutes.

9.3. Others

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

10.1. Safety-related variations of the marketing authorisation (MA)

10.1.1. **Filgrastim** (NAP), **pegfilgrastim – NEULASTA** (CAP)

- PRAC consultation on a safety-related variation, upon CHMP request

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Neupogen is a nationally authorised medicine (via mutual recognition procedure) containing filgrastim, a human granulocyte-colony stimulating factor (G-CSF). Neulasta is a centrally authorised medicine containing pegfilgrastim, a covalent conjugate of recombinant methionyl human G-CSF and monomthoxypolyethylene glycol.

Both filgrastim and pegfilgrastim are indicated for reducing the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). Filgrastim (Neupogen) is also indicated for the mobilisation of peripheral blood progenitor cells in patients and normal donors

In October 2012, PRAC started a review of 15 case reports of capillary leak syndrome associated with pegfilgrastim or filgrastim reported to EudraVigilance and asked the MAH to provide a cumulative review of all available data with a view to updating the product information (for background see PRAC Minutes November 2012). A variation was triggered by the PRAC following assessment of the MAH's response in March 2013 and PRAC advice to CHMP was requested.

Summary of advice

The PRAC agreed some proposed changes to the product information on capillary leak syndrome, the content of a DHPC to inform prescribers of these changes and a communication plan.

10.1.2. **Paliperidone – INVEGA** (CAP), **XEPLION** (CAP); **risperidone** (NAP)

- PRAC consultation on a safety-related variation, upon CHMP request

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)
PRAC Co-Rapporteur (lead): Martin Huber (DE)

Background

Risperdal is a nationally authorised medicine containing risperidone, an antipsychotic, indicated for the treatment of schizophrenia, manic episodes associated with bipolar disorders, persistent aggression in patients with moderate to severe Alzheimer's dementia and treatment of persistent aggression in conduct disorder in children. Invega is a centrally authorised medicine containing paliperidone, the major metabolite of risperidone, which is also indicated for treatment of schizophrenia.

A worksharing variation is under evaluation by the CHMP to update the product information of paliperidone and risperidone-containing medicinal products with the addition of new post-marketing adverse drug reactions for intraoperative floppy iris syndrome (IFIS). PRAC advice was requested on this variation by CHMP.

Summary of advice

The PRAC discussed the content of a DHPC to inform surgeons and other healthcare professionals of IFIS and recommended amendments to improve the readability of the overall message as well as of the detailed recommendation and background information. The PRAC also reviewed the communication plan and made some suggestion for improvement.

10.2. Timing and message content in relation to MS safety announcements

None

10.3. Other requests

10.3.1. Tofacitinib

- PRAC consultation on a re-examination procedure of an initial marketing authorisation upon CHMP request

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

On 25 April 2013, the CHMP adopted a negative opinion, recommending the refusal of a marketing authorisation for the medicinal product Xeljanz (EMEA/H/C/002542), intended for the treatment of rheumatoid arthritis. The applicant requested a re-examination of the opinion. Upon CHMP request the PRAC provided advice on the re-examination procedure relating to risk management aspects.

Summary of advice

Based on the PRAC review of the RMP version 1.3, the PRAC provided advice on the risk management system for Tofacitinib citrate (Xeljanz) in the proposed indication.

Post-meeting note: after considering the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 21 February 2013 (see EMA Q&A EMA/109958/2013).

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

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Pharmacovigilance audits and inspections

None

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

12.3.1. Union Reference Date List

12.3.1.1. Consultation on the draft List, version July 2013

In April 2013, the CMDh requested the harmonisation of the PSUR frequency and submission dates for all seasonal influenza vaccines. Considering the seasonality of influenza, the CMDh proposed that PSURs should be submitted twice a year, once after 8 months (DLP: 30 April 2013), followed by another submission 4 months later (DLP: 31 August). In addition to this harmonisation, it was proposed that all seasonal influenza vaccines be grouped together in a single PSUR assessment procedure. These proposals were sent to the PRAC/CHMP in May 2013 in the framework of the EURD list monthly update. In the absence of objections, a new entry covering all seasonal influenza vaccines (CAPs and NAPs) had been included in the EURD list with the "8+4 months" PSUR frequency scheme.

In July 2013, concerns were raised about the relevance of single PSUR assessments for CAP/NAP vaccines on the grounds of product-specific safety issues and benefit/risk assessments. Although all seasonal vaccines contain the same strains, products could differ in terms of manufacturing process and safety profile. As a consequence, only PSURs for CAPs will be assessed by the PRAC. The EURD list entry 'seasonal influenza' was therefore deleted in favour of single entries for each CAP (i.e. Optaflu, IDflu/Intanza). PSURs for NAPs are to be assessed at national level in parallel with the assessment of the CAPs PSURs and following the same PSUR frequency supported by the PRAC. To avoid duplication of assessment for these products, a PSUR Work Sharing procedure should be considered where relevant.

The topic will be raised at the CMDh PSUR Work Sharing Working Party for further discussion. Should a NCA identify specific concerns during the assessment of these PSURs for which the view of the PRAC could be useful, each NCA is encouraged to seek PRAC advice as relevant. This was considered a temporary solution until single PSUR assessments, covering products relating to individual substances contained in NAPs only, will be assessed by the PRAC as per the full implementation of the legal provisions of the EU pharmacovigilance legislation.

Post-meeting note: following the PRAC meeting in July 2013, the updated EURD list was adopted by the CHMP at its July 2013 meeting and was published on the EMA website on 8 August 2013 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission)

12.4. Signal Management

12.4.1. Signal Management

- Feedback from Signal Management Review Technical (SMART) Working Group

The PRAC was informed that the SMART Working Group will present an update on its achievements for the first year of activities at the September 2013 PRAC meeting.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. List of Product under Additional Monitoring

12.5.1.1. Consultation on the draft List, version July 2013

The PRAC was updated on the changes made to the list of products under additional monitoring (version July 2013).

The PRAC agreed that further discussion was needed on the process of adding medicines to the list. The EMA secretariat will promote further discussion with the relevant project team in the framework of the implementation of the new pharmacovigilance legislation and update the PRAC as appropriate.

Post-meeting note: the list of products under Additional Monitoring, version July 2013, was published on the EMA website on 15 July 2013 (EMA list of Additional Monitoring).

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of risk Minimisations

12.7.1. Progressive multifocal leukoencephalopathy (PML): possibilities for monitoring and labelling

- Development of an evidence-based strategy

Following discussion at the PRAC meeting of February 2013 (see: PRAC Minutes February 2013), the EMA secretariat presented the conclusion of a preliminary review performed jointly with some PRAC members of the PML labelling for various products and the level of related evidence supporting such labelling. It was acknowledged that an evaluation of available evidence, including case validation based on an accepted case definition, is needed for the assessment of causality before labelling decisions are taken.

The PRAC supported the strategy to promote consistent labelling and endorsed the proposed next steps that include the integration of case validation analysis to the dataset, analysis of evidence in consideration of what is currently included in current product information and RMPs, as well as the testing of the correlation between the proposal for an evidence-based strategy and the actual pharmacovigilance activities included in the individual RMPs. A further update will be presented to PRAC last quarter of 2013. A proposal for consultation with patient organisations and other stakeholders was supported.

12.8. Post-authorisation Safety Studies (PASS)

12.8.1. Patient Registries

- Proposal to initiate the process of encouraging collaborative disease based-registries

As a follow-up to the PRAC Minutes June 2013, the call to PRAC delegates to volunteer to participate in the development of a strategy paper for promoting cooperation amongst MAH in the development and running disease registries was extended until 16 August 2013.

12.8.2. Handling of PASS protocols and results

- Revised procedural aspects relating to the handling of PASS protocols and results by EMA Committees

The EMA secretariat gave a presentation to the PRAC on revised procedures relating to the handling of applications for the evaluation of PASS protocols and results by the CHMP and PRAC, depending on whether the study is a clinical trial, a non-interventional study, imposed according to Article 107n of Directive 2001/83/EU or non-imposed, as part of the pharmacovigilance plan of RMP. Further information and guidance will be published in due course.

12.9. Community Procedures

None

12.10. Risk communication and Transparency

None

12.11. Continuous pharmacovigilance

None

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Committees

None

12.12.2. Working Parties

12.12.2.1. Vaccine Working Party (VWP)

- Explanatory note on the withdrawal of the 'Note for Guidance on Harmonisation of Requirements for Influenza Vaccines' (CPMP/BWP/214/96) and of the Core SmPC/PIL for inactivated seasonal influenza vaccines (CMDh/128/2003/Rev5 and CMDh/129/2008/Rev3)

Following adoption by the Vaccine Working Party (VWP) and Biological Working Party (BWP), the explanatory note justifying the withdrawal of the guideline on annual strain change and of the core SmPC and PIL for seasonal influenza vaccines was shared with PRAC for written comments. The main change introduced is the removal of requirements for the small clinical trials so far requested for annual strain updates, in favour of a strengthened monitoring system of vaccine performance over the years focusing on effectiveness studies. The purpose of the explanatory note is to provide guidance in the interim period until the revised influenza guideline is finalised. Following implementation of comments, the explanatory note was endorsed by the CMDh and CHMP. The document (see EMA/CHMP/VWP/232674/2013, public consultation) is open for public consultation until 31 October 2013.

12.13. Interaction within the EU regulatory network

None

12.14. Contacts of the PRAC with external parties and interaction of the EMA with interested parties

12.14.1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study

- PRAC evaluation of D:A:D data merger results

See 7.2.3.

12.14.2. Medication errors

- Workshop outcome: implementation plan and deliverables

As a follow-up to the PRAC Minutes June 2013, a call to PRAC delegates for expression of interest in participating on the development of Good Practice Guidance (technical and scientific) was launched for response to EMA by 16 July 2013.

13. Any other business

13.1.1. Implementation of the revised variations guidelines

The PRAC was updated on the revised variations guidelines, on the details of the various categories of variations and on the operation of the procedures laid down in Chapters II, IIa, III and IV of Variations Regulation adopted by the EC on 16 May 2013, which apply to all variation applications submitted as of 4 August 2013. The guidelines were reviewed to reflect changes introduced to the variations Regulation (EC) No 1234/2008 and the Pharmacovigilance legislation and experience acquired with the application of existing guidelines, including Article 5 recommendations. This guideline replaces the current 'procedural guideline' and 'classification guideline' in force since 1 January 2010.

The major changes (EC Guidelines on the details of the various categories of variations[25]) and the main consequences regarding PRAC and CHMP involvement in those procedures as applicable were presented. Further information will be provided at the September 2013 PRAC meeting.

Post-meeting note: A dedicated news item and Practical Questions and Answers to support the implementation of the Variations Guidelines in the centralised procedure were published on 26 July 2013 on the EMA website.

[25] Guidelines of 16 May 2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures

ANNEX I – List of abbreviations

For a List of the abbreviation used in the PRAC minutes, see:

www.ema.europa.eu

Home>About Us>Committees>PRAC Agendas, minutes and highlights

ANNEX II – List of participants: *including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 8-11 July 2013 meeeting.*

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance
Bettina Schade	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	Combined hormonal contraceptives, radium-223, aflibercept
Yuliyan Eftimov	Bulgaria	Full involvement	
Marin Banovac	Croatia	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Jana Mladá	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer-reviewer for:	Fesoterodine, tafamidis, tofacitinib
Julia Pallos	Hungary	Full involvement	
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Pernille Harg	Norway	Full involvement	
Kamila Czajkowska	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance
Daniela Pomponiu	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Milena Radoha-Bergoč	Slovenia	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Julia Dunne	United Kingdom	Full involvement	
June Munro Raine	United Kingdom	Full involvement	
Julie Williams	United kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product / substance
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise (Marieke) De Bruin		Full involvement	
Stephen J. W. Evans		Cannot act as Rapporteur or Peer-reviewer for:	Human papillomavirus vaccine, albiglutide, pneumococcal polysaccharide conjugate vaccine
Birgitte Keller-Stanislawski		Full involvement	
Hervé Le Louet		Full involvement	
Lennart Waldenlind		Full involvement	

Health care professionals and patients observers	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product / substance
Flip Babylon		Full involvement	
Kirsten Myhr		Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (2013-05-30) http://www.ema.europa.eu/docs/en_GB/document_library/contacts/avanderzeijden_DI.pdf	

Additional European experts participating at the meeting for specific Agenda items	Country	
Laurence de Fays	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Rikke Jensen	Denmark	
Gedske Thomsen	Denmark	
Kim Bouillon	France	
Gaelle Guyander	France	
Corinne Kiger	France	
Beatrice Porokhov	France	
Camille Thomassin	France	
Violaine Vermillard	France	
Fabio Facchinetti	Italy	
Elisabeth Rook	Netherlands	
Lies can Vlijmen	Netherlands	
Charlotte Backman	Sweden	
Filip Josephson	Sweden	
Deborah Ashby	United Kingdom	
Elena Elliot-Smith	United Kingdom	
Sarah Mee	United Kingdom	
Nicola Parkinson	United Kingdom	
Raquel Rogers	United Kingdom	
Catherine Tregunno	United Kingdom	
Jane Woolley	United Kingdom	

Observer from the European Commission
Helen Lee - DG Health and Consumers

European Medicines Agency
Peter Arlett – Sector Head, Pharmacovigilance and Risk Management
Roberto De Lisa - Scientific Administrator, PRAC Secretariat

European Medicines Agency
Zaide Frias - Section Head, Regulatory Affairs
Georgy Genov – Section Head, Signal Detection and Data Analysis
Grace Hernandez – Assistant, CHMP/PRAC Secretariat
Ana Hidalgo-Simon – Section Head, Risk Management
Kasia Kmiecik – Assistant, PRAC Secretariat
Sheila Kennedy – Section Head, Scientific Committee Support
Anabela Marcal – Section Head, Community Procedures
Geraldine Portier - Scientific Administrator, PRAC Secretariat
Tanya Sepehr – Assistant, PRAC Secretariat