



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

29 November 2012  
EMA/PRAC/771924/2012  
Patient Health Protection

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the Meeting – 29-31 October 2012

### 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](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.

#### **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 8 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.europa.eu](http://www.europa.eu)

Chair: June Raine – Vice-Chair: Almath Spooner

## **1. Introduction**

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

The Chairperson opened the meeting and welcomed all participants to the 29-31 October 2012 meeting of the PRAC.

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 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 Scientific 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. 22 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

### ***1.2. Agenda of the meeting of 29-31 October 2012***

The agenda was adopted with the addition of the following topics upon request from the members of the Committee and the EMA secretariat: 4.1.3. fingolimod; 5.2.3. catumaxomab; 9.2.2. panitumumab.

### **1.3. Minutes of the previous PRAC meeting of the [1-3 October 2012](#)**

The minutes were adopted with some changes and will be published on the EMA website.

*Post-meeting note: the minutes were published on 7 November 2012 on the EMA website ([EMA/PRAC/635842/2012](#)).*

The EMA agreed to circulate a request for Non Urgent Information to the EU Member States to acquire data on interest of the public in the PRAC minutes at national level and on enquiries and feedback received by the Member States, in order to support the future development of the structure and readability of the document.

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

None

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

### **3.1. Newly triggered Procedures**

#### **3.1.1. Codeine (NAPs)**

- Risk of fatal or life-threatening drug toxicity in CYP2D6 ultra-rapid metabolisers - Article 31 of Directive 2001/83/EC for codeine-containing medicines used for pain in children

#### **Regulatory details:**

PRAC Rapporteur: Dolores Montero (ES)  
PRAC Co-Rapporteur: Julie Williams (UK)

#### **Background**

A referral procedure under Article 31 of Directive 2001/83/EC was triggered for codeine-containing medicines used for post-operative pain relief in children following the PRAC meeting of [1-3 October 2012](#) (see minutes for further background information).

#### **Discussion**

The PRAC noted an [amended notification letter dated 22 October 2012](#) from the UK's Medicines and Healthcare products Regulatory Agency (MHRA) reflecting a modification of the scope of the procedure to 'codeine-containing medicines used for pain in children'. This scope better reflected the safety signal.

#### **Recommendation(s)**

Having agreed on the revised scope of the referral, an amended timetable for the procedure was adopted and published on the EMA website (EMA/PRAC/688615/2012).

The references included in list of questions were revised to reflect the extended scope, however the content of the questions remained unchanged.

### **3.1.2. Diclofenac (NAPs)**

- Risk of thrombotic events - Article 31 of Directive 2001/83/EC for diclofenac-containing products for systemic use

#### **Regulatory details:**

PRAC Rapporteur: Doris Stenver (DK)  
PRAC Co-Rapporteur: Julie Williams (UK)

#### **Background**

On 19 October 2011, at the request of the UK's Medicines Agency (Medicines and Healthcare products Regulatory Agency - MHRA), the CHMP started a review under Article 5(3) of Regulation (EC) No 726/2004 of recently published data on the cardiovascular safety of NSAIDs (non-steroidal anti-inflammatory drugs). The review included nationally authorised NSAIDs and was concluded at the CHMP October 2012 meeting.

A [notification letter dated 17 October 2012](#) under Article 31 of Directive 2001/83/EC was sent by the MHRA requesting the PRAC to consider whether the risk of thrombotic events impacts the balance of benefits and risks for systemic diclofenac-containing products.

#### **Discussion**

The PRAC noted the notification letter from the MHRA triggering a procedure under Article 31 of Directive 2001/83/EC for diclofenac-containing products for systemic use, and discussed a list of questions to be addressed during the procedure as well as a timetable for conducting the review.

The Committee appointed Doris Stenver (DK) as PRAC Rapporteur and Julie Williams (UK) as PRAC co-Rapporteur.

#### **Recommendation(s)**

The Committee adopted a list of questions (published on the EMA website [EMA/PRAC/696495/2012](#)) and a timetable for the procedure ([EMA/PRAC/696496/2012](#)).

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

## **4. Signals assessment and prioritisation**

### **4.1. New signals detected from EU spontaneous reporting systems**

#### **4.1.1. Cetuximab - ERBITUX (CAP)**

- Signal of cytokine release syndrome (CRS)

#### **Regulatory details:**

PRAC Rapporteur: Ulla Wändel Liminga (SE)

#### **Background**

Cetuximab is an antineoplastic agent used in the treatment of metastatic colorectal cancer and squamous cell cancer of the head and neck.

Erbitux, a centrally authorised medicine containing cetuximab, is estimated to have been used by more than 400,000 patients worldwide, in the period from 2003 to 2011.

During routine signal detection activities, a signal of CRS was identified by the EMA, based on 20 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the information on the cases of CRS (a potentially fatal uncontrolled increased blood level of cytokines), which could result in multiple organ damage and which can be associated with monoclonal antibody therapy and cytokine therapy as well as infections.

The PRAC emphasized that in its early stages CRS could have a clinical appearance similar to an anaphylactic reaction and might be clinically indistinguishable from it. Nevertheless, CRS requires different clinical management. Given the known risk of misclassification and misdiagnosis between the two reactions and the possible adverse consequences for patients, the PRAC agreed that the signal warranted further investigation.

Given that an assessment of a PSUR was about to start for Erbitux the PRAC agreed that the PSUR procedure was an appropriate framework in which to further analyse the signal.

### **Recommendation(s)**

- The MAH for Erbitux (cetuximab) should submit a cumulative review consisting of a scientific assessment of all case reports of CRS, taking into account some recommended criteria, within the next PSUR with data lock point of 30 September 2012.
- This review will be assessed in the framework of the next PSUR assessment procedure; the timing of the PRAC recommendation on this review and the accompanying PSUR will be in accordance with the published EMA [PSUR timetable](#).

#### **4.1.2. Filgrastim, pegfilgrastim - NEULASTA, BIOGRASTIM, FILGRASTIM HEXAL FILGRASTIM RATIOPHARM, NIVESTIM, RATIOGRASTIM, TEVAGRASTIM, ZARZIO (CAPs and NAPs)**

- Signal of systemic capillary leak syndrome (SCLS) and cytokine release syndrome (CRS)

### **Regulatory details:**

PRAC Rapporteur (overall): Julie Williams (UK)

### **Background**

Filgrastim and pegfilgrastim are recombinant human granulocyte colony-stimulating factors (G-CSF) used to stimulate the proliferation and differentiation of granulocytes, especially polymorphonuclear granulocytes (PMNG) in various forms of neutropenia.

Neulasta, a centrally authorised medicine containing pegfilgrastim, is estimated to have been used by more than 2.7 million patients worldwide, in the period from its marketing authorisation in 2002 up to 2011. Products containing filgrastim are both centrally and nationally authorised and have been widely used.

During routine signal detection activities, a signal of disproportionate reporting of systemic capillary leak syndrome (SCLS) and cytokine release syndrome (CRS) was identified by the EMA based on 15

cases retrieved from EudraVigilance for filgrastim and pegfilgrastim. The Rapporteur for Neulasta confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the information on the cases of SCLS and CRS with filgrastim and pegfilgrastim.

Regarding the specific characteristics of the syndromes, the PRAC emphasised that they are likely to be part of the same cascade of pathophysiological events and that there could be a risk of misclassification between the two conditions. The potential for misdiagnosis or under-recognition due to misclassification (i.e end-organ damage is more likely to be reported) was discussed and should be taken into account in the analysis of spontaneously reported data.

In conclusion, the PRAC agreed that the signal warranted further investigation and that a review should focus on both syndromes.

The PRAC appointed Julie Williams (UK) as overall PRAC Rapporteur.

### **Recommendation(s)**

- The MAH for the reference products should submit within 60 days a systematic review of the literature and a cumulative review of all case reports of CLS and CRS and their analysis.
- A 60 day-timetable was supported to assess the results of this review, which will lead to a further PRAC recommendation.

#### **4.1.3. Fingolimod – GILENYA (CAP)**

- Signal of haemophagocytic syndrome

#### **Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

#### **Background**

Fingolimod is an immunosuppressant used in the treatment of multiple sclerosis.

The exposure for Gilenya, a centrally authorised medicine containing fingolimod, is estimated to have been more than 34,000 patient-years worldwide from the time of first authorisation in 2011 to 2012, including patients exposed during clinical trials.

A signal of haemophagocytic syndrome was identified by the French Medicines Agency (Agence nationale de sécurité du médicament et des produits de santé (ANSM)), triggered by 2 cases with a fatal outcome. The Rapporteur also confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the information on the cases of haemophagocytic syndrome. This is a rare and potentially life-threatening syndrome that seems to be caused by dysregulation in cytokine secretion, and activation, frequently associated with infections particularly viral ones in an immunocompromised patient. Given the rarity of the condition and the non-specificity of clinical symptoms, the diagnosis is challenging and misclassification could occur.

The PRAC noted that a consistent definition of the condition is lacking and some scientific literature refers to it as macrophage activation syndrome (MAS) or as histiocytic medullary reticulosis.

The PRAC concurred that, given the serious nature of the reaction and the existence of a plausible biological mechanism, the signal warranted further investigation to clarify a possible role of fingolimod in the genesis of the reaction. The review should take into account expert advice. A further search of spontaneously reported cases should be performed using an extended list of preferred terms, to take into account possible limits arising from misclassification of the diagnosis. This review should also include information arising from other data sources such as disease registries.

### **Recommendation(s)**

- The MAH for Gilenya (fingolimod) should submit within 90 days a cumulative review and analysis of all case reports of haemophagocytic syndrome arising from a search using an extended list of preferred terms, and take into account expert advice.
- A 60-day timetable was supported for the assessment, which will lead to a further PRAC recommendation.

*Post meeting note: following the meeting, the MAH for Gilenya proposed alternative search criteria for taking the review further. The PRAC considered this proposal acceptable.*

#### **4.1.4. Nomegestrol acetate / estradiol – ZOELY (CAP)**

- Signal of deep vein thrombosis

### **Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

### **Background**

Nomegestrol acetate / estradiol, is a combination of a progestin and an oestrogen used as an oral contraceptive.

Zoely, a centrally authorised medicine containing nomegestrol acetate / estradiol, is estimated to have been used by more than 150,000 women worldwide, from its marketing authorisation until 2011.

For the class of combined oral contraceptive (COCs), thromboembolic side effects are known, serious adverse reactions but very rare. During routine signal detection activities, a signal of deep vein thrombosis was identified by the Swedish Medicines Agency, based on a case reported in Sweden with the combination nomegestrol acetate / estradiol. Additional reports of thromboembolism from the EEA were identified in EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the information on the cases reported and agreed that the information was in line with the already identified risk for Zoely. However, the PRAC considered that an update of the product information based on the more recent cases could be beneficial for patients and prescribers.

The PRAC noted that for Zoely a post authorisation safety study (PASS) to clarify further aspects of the incidence of venous thromboembolism is expected to start in 2013, following some refinements of the study protocol proposed by the CHMP.

### **Recommendation(s)**

- The MAH for Zoely (norgestrel acetate / estradiol) should submit a review of all reported cases of thromboembolism within the ongoing PSUR procedure with data lock point of 26 July 2012, which started on 11 October 2012 and will lead to a further PRAC recommendation at the February 2013 PRAC meeting.
- Regarding the protocol of the PASS, which is still under assessment at the CHMP, the MAH should take all the necessary measures to ensure a prompt start of the study.

#### **4.1.5. Sugammadex – BRIDION (CAP)**

- Signal of bradycardia and cardiac arrest

#### **Regulatory details:**

PRAC Rapporteur: Kirsti Villikka (FI)

#### **Background**

Sugammadex is a selective relaxant binding agent used in reversal of neuromuscular blockade induced by rocuronium or vecuronium.

Bridion, a centrally authorised medicine containing sugammadex, is estimated to have been used by more than 2.5 million patients worldwide, in the period from 2008 to 2012.

During routine signal detection activities, a signal was identified by the EMA based on 14 cases of bradycardia and 10 cases of cardiac arrest (including 3 of the cases of bradycardia) retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### **Discussion**

The PRAC discussed the information on the cases from EudraVigilance and noted that cardiac arrhythmias and QT prolongation have been kept under close surveillance and reviews of these events have been included in recent PSURs assessed. It was also noted that the results of a QT study were reassuring but that there were cases of QT prolongation with concomitant medications that deserved further investigation. The PRAC noted how some cases were reported in the context of a hypersensitivity reaction and commented that this aspect should be further clarified. Therefore the PRAC recommended that the signal warranted further investigation.

### **Recommendation(s)**

- The MAH for Bridion (sugammadex) should submit within 30 days a cumulative review and analysis of reported cases of bradycardia and cardiac arrest.
- A 60 day-timetable was supported to assess the results of this review, which will lead to a further PRAC recommendation.

#### **4.1.6. Tolvaptan – SAMSCA (CAP)**

- Signal of dehydration involving a possible interaction with diuretics.

#### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

## **Background**

Tolvaptan is a vasopressin antagonist used in the treatment of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

The exposure for Samsca, a centrally authorised medicine containing tolvaptan, is estimated to have been around 1,800 patient-years worldwide, in the period from 2011 to 2012.

During routine signal detection activities, a signal of dehydration, involving a possible interaction with diuretics, was identified by the EMA based on 16 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

## **Discussion**

The PRAC discussed the information on the cases and emphasised that the number of reports of severe dehydration received, considering the relatively low post-marketing exposure to tolvaptan in the EU, was considerable. Amongst other factors, the PRAC considered that the reaction was biologically plausible and that there was a pattern suggesting a temporal relationship with tolvaptan treatment. The PRAC noted that in the context of the ongoing PSUR review, consideration had been given of the need for updates to the product information to reflect an increased risk of more severe dehydration leading to renal dysfunction, particularly when tolvaptan was administered concomitantly with a diuretic.

The PRAC noted that the product information already contained warnings on the risk of dehydration and noted the ongoing PSUR review; nevertheless, it was judged that an update to product information, especially regarding the possible interaction between tolvaptan and ACE-inhibitors or angiotensin II receptor blockers (ARBs) and the risk of renal dysfunction, may also be necessary and could be beneficial for patients and prescribers.

## **Recommendation(s)**

- The MAH for Samsca (tolvaptan) should submit a review of the possible interaction between tolvaptan and ACE-inhibitors or ARBs and risk of renal dysfunction, including a proposal for updating the product information.
- A 60 day-timetable was supported to assess the results of this review, which will lead to a further PRAC recommendation.

### **4.1.7. Vitamin K antagonists: warfarin, phenprocoumon (NAPs)**

- Signal of interaction with Goji berries (*Lycium barbarum*)

## **Regulatory details:**

PRAC Rapporteur: Doris Stenver (DK)

## **Background**

Warfarin and phenprocoumon are two anticoagulants used for the prophylaxis and treatment of thromboembolic disorders.

The exposure for Marcumar, a nationally authorised product containing phenprocoumon, is estimated to have been more than 2,200,000 patients-years worldwide, in the period from 2008 to 2010. Products containing warfarin have also been widely used worldwide since their approval in the 1950s.

A signal of interaction of phenprocoumon with Goji berries leading to bleeding was identified by the German Medicines Agency (BfArM), triggered by a case reported in Germany and by 3 cases identified by a literature search. DK as lead Member State for the signal detection activities for warfarin confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the information arising from the case reported in Germany and from the published cases<sup>1</sup> related to phenprocoumon and warfarin. No cases were identified with other vitamin K antagonists. The Committee considered that there is existing evidence that a number of herbal, vitamin and food products might have a pharmacokinetic or direct pharmacodynamic interaction with anticoagulants, possibly leading to an increased bleeding time. Therefore, with the aim of assessing whether Goji berries should be added to the list of drug-food interaction reported in the product information, the PRAC agreed that the signal be further investigated and appointed Doris Stenver (DK) as PRAC Rapporteur.

### **Recommendation(s)**

- The MAHs for warfarin and phenprocoumon should submit within 60 days a cumulative review and analysis of drug-food interactions between Goji berries (*Lycium barbarum*) and warfarin/phenprocoumon, including data from the literature, and discuss the findings and the underlying mechanism(s).
- A 60-day timetable for the assessment of the MAH's responses to the list of questions was agreed, leading to a further PRAC recommendation.
- A NUI request should be circulated to the Member States to investigate the extent of the information on drug-food interaction provided in the product information of warfarin- and phenprocoumon-containing medicines across the EU.
- The Committee on Herbal Medicinal Products (HMPC) should be informed of the NUI request.

## **4.2. New signals detected from other sources**

None

## **4.3. Signals follow-up and prioritisation**

### **4.3.1. Fluoroquinolones: ciprofloxacin - enoxacin - flumequin - lomefloxacin - levofloxacin - moxifloxacin - ofloxacin - pefloxacin - prulifloxacin - rufloxacin - norfloxacin (NAPs)**

- Signal of retinal detachment

### **Regulatory details:**

PRAC Rapporteur: Martin Huber (DE)

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<sup>1</sup> Lam AY, Elmer GW, Mohutsky MA: Possible interaction between warfarin and *Lycium barbarum* - Ann Pharmacother. 35, 1199-1201 (2001)

Leung H, Hung A, Hui ACF, Chan TYK: Warfarin overdose due to the possible effects of *Lycium barbarum* - Food Chem Toxicol. 46, 1860-1862 (2008)

Rivera CA, Ferro CL, Bursua AJ, Gerber BS: Probable interaction between *Lycium barbarum* (goji) and warfarin - Pharmacotherapy. 32 (3), e50-3 (2012 Mar)

## **Background**

Fluoroquinolones are a class of antibiotics used to treat infections caused by susceptible microorganisms.

Fluoroquinolones have been authorised since the 1980s and are widely used worldwide.

In 2012, the Pharmacovigilance Working Party (PhVWP) was informed of the publication of an article by Etminan *et al.*<sup>2</sup> reporting retinal detachment in ophthalmologic patients treated with oral fluoroquinolones. The PhVWP agreed to investigate the signal further and that further review should include an analysis of spontaneously reported cases, obtaining more data on non-clinical aspects and specifically to invite the authors of the study to provide some clarification on the results. DE as lead Member State for this assessment confirmed that the signal needed follow-up discussion at the PRAC.

## **Discussion**

The PRAC discussed the study by Etminan *et al.*, as well as the reviewed spontaneous and non-clinical data. The PRAC considered that the study's limitations made the interpretation of the results challenging, despite the clarifications provided by the authors. The number of spontaneous reports of retinal detachment retrieved for fluoroquinolones was considered small in the context of the high patient exposure. Regarding the non-clinical data, the PRAC questioned to what extent these data could be extrapolated to humans. Overall, the available evidence was not considered robust enough to warrant any regulatory action at this stage. However, the PRAC considered that ocular toxicity with fluoroquinolones should be closely monitored. The PRAC noted that lead Member States for signal management had been appointed for the various fluoroquinolones as recorded in the '[List of active substances subject to worksharing for signal management](#)', and appointed Martin Huber (DE) as overall PRAC Rapporteur for follow-up.

## **Recommendation(s)**

- The limited available data do not currently justify recommending any regulatory action. However, general ocular toxicity with fluoroquinolones should be kept under close monitoring.

The EMA will assess the feasibility of performing a study on fluoroquinolones and retinal detachment in databases of electronic records, in collaboration with the PRAC Rapporteur, and will provide timely feedback to the PRAC for further discussion.

### **4.3.2. Human albumin solutions (NAPs)**

- Signal of increased risk of mortality in patients with severe traumatic brain injury and in patients with burns.

## **Regulatory details:**

PRAC Rapporteur: Martin Huber (DE)

## **Background**

Human albumin solutions are used in various clinical conditions where restoration and maintenance of circulating blood volume are necessary.

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<sup>2</sup> Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. JAMA. 2012 Apr 4;307(13):1414-9.

In 2012, in the framework of the preparation of the [Draft Guideline on core SmPC \(Summary of Product Characteristics\) for human albumin solutions](#), the PhVWP provided input on a signal of increased risk of mortality in patients with severe traumatic brain injury and in patients with burns, and recommended an addition to the product information with regards to this risk. Comments on the Draft Guideline had been received from some MAHs pointing out new relevant data to be considered.

### **Discussion**

The PRAC considered that, in the light of the additional information submitted by the MAHs which was previously not included in the review, the signal should be further assessed. This should be done in the context of a widened review of the benefit-risk of human albumin solutions in traumatic brain injury and in patients with burns, which would be necessary before maintaining or revising the current recommendation included in the Draft Guideline on the Core SmPC for these products. In addition, the PRAC emphasised the need to have more information on current use of human albumin solutions at the level of the Member States and on whether there are specific scientific recommendations available at national level. The PRAC appointed Martin Huber as Rapporteur for follow-up.

### **Recommendation(s)**

- A NUI request should be sent to Member States to gather further information on the use of albumin solutions in traumatic brain injury and burns according to the licensed indication and scientific guidelines.
- Based on the responses received, the PRAC will consider whether a formal benefit-risk review is warranted in the indication of traumatic brain injury and burns.

#### **4.3.3. Hydroxyethyl starch (NAPs)**

- Signal of increased risk of mortality in patients with severe sepsis

#### **Regulatory details:**

PRAC Rapporteur: *Martin Huber (DE)*

#### **Background**

Hydroxyethyl starch (HES) is a colloid used in various clinical conditions for plasma volume replacement.

In 2012, the PhVWP was informed of a publication by the 6S Trial Group - Scandinavian Critical Care Trials Group<sup>3</sup> - which concluded that patients with severe sepsis assigned to fluid resuscitation with hydroxyethyl starch (HES) 130/0.42 had an increased risk of death at day 90 and were more likely to require renal-replacement therapy, compared with patients receiving Ringer's acetate. DE as lead Member State for further assessment reviewed the article together with other published data and confirmed that the signal needed follow-up discussion at the PRAC.

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<sup>3</sup> N Engl J Med. 2012 Jul 12;367(2):124-34. Epub 2012 Jun 27. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søre-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J; 6S Trial Group; Scandinavian Critical Care Trials Group.

## **Discussion**

The PRAC discussed the studies reviewed by DE. The risk of death at day 90 found in the 6S trial was not confirmed by the results of the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) trial<sup>4</sup> although the CHEST trial did show that renal replacement therapy was significantly more frequent in the HES group than in the saline group. The PRAC agreed that the evidence supporting this signal was robust and agreed on the need of a full assessment of the benefits and risks of all HES-containing products within an appropriate regulatory framework.

The need for amendments to the product information was discussed, and the PRAC was informed of ongoing variation procedures for nationally authorised products. The PRAC proposed to circulate a NUI request within a short timeframe to clarify the ongoing actions at the level of the individual Member States and support setting the most appropriate scope of the review. The PRAC appointed Martin Huber as Rapporteur for follow-up.

## **Recommendation(s)**

- The benefit-risk balance of HES should be re-assessed.
- The terms of a full benefit-risk review will be discussed at the 26-29 November 2012 meeting.
- A NUI request should be transmitted to Member States to clarify the ongoing actions taken at the level of the individual Member States and to compile a list of questions for the review.

### **4.3.4. Olmesartan (NAPs)**

- Signal of increased risk of fatal events from cardiovascular causes in patients with type 2 diabetes with additional cardiovascular risks

## **Regulatory details:**

PRAC Rapporteur: Martin Huber (DE)

See also 9.1.1.

## **Background**

Olmesartan is an angiotensin receptor II blocker (ARB) used in the treatment of hypertension.

In 2011, the PhVWP started a review of a signal arising from the findings of the Randomized Olmesartan and Diabetes Microalbuminuria Prevention Study (ROADMAP<sup>5</sup>) study, describing an increased risk of cardiovascular mortality observed with olmesartan treatment for prevention of worsening of renal function in patients with type 2 diabetes at increased cardiovascular risk as compared with placebo. Follow-up discussion took into consideration additional analyses of the ROADMAP and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT<sup>6</sup>) studies and additional information from further studies performed to evaluate the

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4 October 17, 2012 DOI: 10.1056/NEJMoa1209759 Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D., Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D., and Steven A.R. Webb, M.D., Ph.D. for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group October 17, 2012  
<sup>5</sup> N Engl J Med 2011; 364:907-917 March 10, 2011 DOI: 10.1056/NEJMoa1007994

Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes Hermann Haller, M.D., Sadayoshi Ito, M.D., Ph.D., Joseph L. Izzo, Jr., M.D., Andrzej Januszewicz, M.D., Shigehiro Katayama, M.D., Ph.D., Jan Menne, M.D., Albert Mimran, M.D., Ton J. Rabelink, M.D., Ph.D., Eberhard Ritz, M.D., Luis M. Ruilope, M.D., Lars C. Rump, M.D., and Giancarlo Viberti, M.D. for the ROADMAP Trial Investigators

<sup>6</sup> Diabetologia. 2011 Dec;54(12):2978-86. Epub 2011 Oct 13.

safety concern. The review also involved data for the ARB telmisartan (see also 9.1.1. telmisartan). DE, who had been in the lead in assessing the signal, confirmed that the issue needed follow-up discussion at the PRAC.

### **Discussion**

The PRAC discussed the findings from the ROADMAP and ORIENT studies as well as data from additional studies and analyses in the context of the responses of the MAH to a further list of questions. The PRAC agreed that at this stage the evidence did not support the conclusion of an increased risk of cardiovascular mortality in patients with type 2 diabetes at increased cardiovascular risk. However, the PRAC agreed that it was appropriate for the main findings of the studies to be included in the product information for olmesartan-containing medicines.

Furthermore, the need for a large individual patient data meta-analysis comprising trial data from all ARBs was discussed for further evaluation of the signal at therapeutic class level – see 9.1.1. telmisartan.

### **Recommendation(s)**

- The MAH for the originator of olmesartan-containing products should submit a variation in order to update the product information to address the signal and provide additional clarification on some data included in their responses.
- A 60-day timetable was agreed for the assessment of this variation, which will lead to a further PRAC recommendation.

#### **4.3.5. Pandemic influenza vaccine – PANDEMRIX (CAP)**

- Signal of narcolepsy: further information following conclusion of the review of Pandemrix and narcolepsy under Article 20 of Regulation (EC) No 726/2004

### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

### **Background**

For background information see PRAC Minutes 3-5 September 2012 (published on the EMA website [EMA/PRAC/571481/2012 Final](https://www.ema.europa.eu/en/PRAC/571481/2012_Final)).

### **Discussion**

The PRAC discussed the available data and recommended a revision of the wording included the product information regarding the “very rare risk of narcolepsy”, to reflect the totality of the epidemiological evidence in children and adolescents under 20 years of age.

The PRAC was informed of the final data from a French study which raised a signal for the adult population. The Vaccine Adverse Event Surveillance & Communication ([VAESCO](#)) study contains the French data and thus reported the same signal. The PRAC was also informed that additional data from ongoing studies are expected in the next few months and agreed that further discussions on whether

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Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. Imai E, Chan JC, Ito S, Yamasaki T, Kobayashi F, Haneda M, Makino H; ORIENT study investigators.

there is a need to amend the product information regarding narcolepsy in adults should await evaluation of these new data.

#### **Recommendation(s)**

- The MAH for Pandemrix should submit a type II variation in order to update the product information.
- A 60-day timetable for this variation was agreed; an additional PRAC recommendation will be provided if requested by the CHMP.

#### **4.3.6. Short-acting beta agonists: hexoprenaline - fenoterol - ritodrine - salbutamol - terbutaline (NAPs)**

- Signal of maternal cardiovascular adverse drug reactions following use in tocolysis

#### **Regulatory details:**

PRAC Rapporteur: n/a

#### **Background**

Short-acting beta ( $\beta_2$ -adrenoceptor) agonists (SABAs) are used as sympathomimetic agents for the management of asthma, bronchospasm and/or reversible airways obstruction. Some are also indicated in obstetric conditions such as the management of premature labour.

In 2009 the PhVWP reviewed the risk of myocardial ischemia associated with the use of SABAs in respiratory and obstetric indications (see October 2009 PhVWP Monthly Report [EMEA/666243/2009](http://www.emea.europa.eu/pressroom/media/attach/pdf/HM0900009.pdf)). The product information for salbutamol and terbutaline, as with all SABAs, had already been updated to state that SABAs should not be used to inhibit uterine contractions in pregnant women with or at increased risk for heart disease. More recently the PhVWP further reviewed the issue following a communication from the US Food and Drug Administration (FDA) on terbutaline (<http://www.fda.gov/Drugs/DrugSafety/ucm243539.htm>). UK the lead Member State for the further assessment of the signal, confirmed that it needed follow-up discussion at the PRAC.

#### **Discussion**

The PRAC discussed the latest data reviewed by the UK. Regarding parenteral formulations in obstetric use, a clear risk of serious adverse reactions including cardiovascular reactions appeared to be confirmed for the class of SABAs, and the PRAC concluded that there is a need for strengthened warnings on cardiovascular risks and increased patient monitoring in the product information of the relevant products. The PRAC also concluded that the obstetric indications of the oral and suppository formulations should also be re-assessed in light of the cardiovascular risk and lack of data to support efficacy in obstetric use. The PRAC considered that there was a need to have clarity on the currently authorised obstetric indication in the various Member States and on their therapeutic benefit. The UK will collect more information on these details.

#### **Recommendation(s):**

- The benefit-risk balance of oral or suppository formulations of SABAs for the obstetric indication of tocolysis, should be re-assessed and the product information for the parenteral formulations should be updated.

- A NUI request should be addressed to the Member States and based on the responses received a list of questions will be compiled to define the grounds for the more appropriate regulatory framework to conduct such a review.

The PRAC will appoint Rapporteurs in the framework of the regulatory procedure to follow.

## **5. Risk management plans**

### **5.1. Medicines in the pre-authorisation phase**

None

### **5.2. Medicines already authorised**

#### **5.2.1. Anidulafungin - ECALTA (CAP)**

- Evaluation of the updated RMP in the context of a stand-alone RMP

##### **Regulatory details:**

PRAC Rapporteur: Sabine Straus (NL)  
PRAC Co-Rapporteur: Doris Stenver (DK)

##### **Background**

Anidulafungin is an antifungal agent used in the treatment of invasive candidiasis.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following the assessment of the latest PSUR for Ecalta, a centrally authorised medicine containing anidulafungin.

##### **Advice**

- The RMP for Ecalta (anidulafungin) was considered acceptable.
- The next routine update of the RMP should take into account some additions proposed by the PRAC including results from a PASS conducted to clarify the hepatic safety profile of anidulafungin and to provide milestone dates for all pharmacovigilance activities.

#### **5.2.2. Bortezomib – VELCADE (CAP)**

- Evaluation of the updated RMP in the context of a 60- day type II variation

##### **Regulatory details:**

PRAC Rapporteur: Carmela Macchiarulo (IT)  
PRAC Co-Rapporteur: Kirsti Villika (FI)

##### **Background**

Bortezomib is an antineoplastic agent used in the treatment of multiple myeloma.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in relation to an ongoing type II variation to add safety information to the product information for Velcade, a centrally authorised product containing bortezomib.

### **Advice**

- The RMP for Velcade (bortezomib), in the context of the type II variation under evaluation, was not yet considered acceptable and supplementary information on the updates of the RMP should be submitted by the MAH.

Additional PRAC advice on a revised RMP may be provided following further discussions at the CHMP.

### **5.2.3. Catumaxomab – REMOVAB (CAP)**

- Evaluation of the updated RMP in the context of a 60-day type II variation

#### **Regulatory details:**

PRAC Rapporteur: Ulla Wändel Liminga (SE)

#### **Background**

Catumaxomab is a monoclonal antibody used in the treatment of malignant ascites.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in relation to a type II variation to add safety information to the product information for Removab, a centrally authorised product containing catumaxomab.

### **Advice**

- The RMP for Removab (catumaxomab), in the context of the type II variation under evaluation, was considered acceptable.

### **5.2.4. Dabigatran – PRADAXA (CAP)**

- Evaluation of the updated RMP in the context of a 60-day type II variation

#### **Regulatory details:**

PRAC Rapporteur: Doris Stenver (DK)

PRAC Co-Rapporteur: Isabelle Robine (FR)

#### **Background**

Dabigatran is antithrombotic agent used in the prevention of venous thromboembolic events, in specific clinical conditions.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in relation to a type II variation to include additional safety information in the product information for Pradaxa, a centrally authorised medicine containing dabigatran, and to propose revision of the educational material.

### **Advice**

- The RMP for Pradaxa (dabigatran), in the context of the type II variation under evaluation, was considered acceptable provided that an updated version of the RMP including some additions, such as information on studies to evaluate the effectiveness of risk minimisation measures that have already been completed or are being conducted, is submitted.
- The final content and format of the educational materials, together with a communication plan, should be agreed with the national competent authorities prior to distribution.

### 5.2.5. Darunavir – PREZISTA (CAP)

- Evaluation of the updated RMP in the context of a 60-day type II variation

#### **Regulatory details:**

PRAC Rapporteur: Menno van der Elst (NL)  
PRAC Co-Rapporteur: Julie Williams (UK)

#### **Background**

Darunavir is a protease inhibitor used in the treatment of HIV infection.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in relation to a type II variation to include additional safety and interaction information in the product information for Prezista, a centrally authorised medicine containing darunavir.

#### **Advice**

- The RMP for Prezista (darunavir), in the context of the type II variation under evaluation, was considered acceptable.
- The next routine update of the RMP should take into account some additions and clarifications proposed by the PRAC such as the inclusion of the interaction between darunavir and raltegravir as an 'important potential risk'.

### 5.2.6. Fampridine – FAMPYRA (CAP)

- Evaluation of the updated RMP in the context of a 60-day type II variation

#### **Regulatory details:**

PRAC Rapporteur: Sabine Straus (NL)  
PRAC Co-Rapporteur: Martin Huber (DE)

#### **Background**

Fampridine is a potassium channel blocker used in the treatment of multiple sclerosis.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in relation to a type II variation to include additional safety information in the product information for Fampyra, a centrally authorised medicine containing fampridine.

#### **Advice**

- The RMP for Fampyra (fampridine), in the context of the type II variation under evaluation, was considered acceptable provided that an updated version of the RMP including satisfactory responses to an agreed list of questions is submitted.

### 5.2.7. Imatinib – GLIVEC (CAP)

- Evaluation of the updated RMP in the context of a 60-day type II variation

#### **Regulatory details:**

PRAC Rapporteur: Dolores Montero (ES)  
PRAC co-Rapporteur: Isabelle Robine (FR)

## **Background**

Imatinib is an antineoplastic agent used in the treatment of bcr-abl positive chronic myelogenous leukaemia, gastrointestinal stromal tumours (GIST), myelodysplastic-myeloproliferative diseases, dermatofibrosarcoma, precursor cell lymphoblastic leukaemia-lymphoma and hypereosinophilic syndrome.

The PRAC is responsible for providing advice to the CHMP on the necessary amendments to the RMP in relation to a type II variation to update the product information for Glivec, a centrally authorised product containing imatinib, with additional information on its use in paediatric rare diseases.

## **Advice**

- The RMP for Glivec (imatinib), in the context of the type II variation under evaluation, was considered acceptable.

### **5.2.8. Ipilimumab – YERVOY (CAP)**

- Evaluation of the updated RMP in the context of a 90-day type II variation, extension of indication

## **Regulatory details:**

PRAC Rapporteur: Sabine Straus (NL)  
PRAC Co-Rapporteur: Dolores Montero (ES)

## **Background**

Ipilimumab is a monoclonal antibody used in the treatment of melanoma in adults who have received prior therapy.

The CHMP is evaluating an extension of the therapeutic indication for Yervoy, a centrally authorised product containing ipilimumab, for the treatment of melanoma in treatment-naïve adults. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of the indication.

## **Advice**

- The RMP for Yervoy (ipilimumab), in the context of the extension of indication under evaluation by the CHMP, was considered acceptable provided that an update of the RMP, to be submitted in response to a Request of Supplementary Information to be adopted by CHMP, is submitted.
- The update should take into account some additions and clarifications proposed by the PRAC such as the inclusion of the monitoring of case reports with the use of higher doses of ipilimumab and close monitoring of those cases in which severe hepatic adverse reactions are reported for patients receiving the higher doses in combination with dacarbazine.

### **5.2.9. Raltegravir – ISENTRESS (CAP)**

- Evaluation of the updated RMP in the context of 60-day type II variation

## **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)  
PRAC Co-Rapporteur: Isabelle Robine (FR)

## **Background**

Raltegravir is an integrase inhibitor used in the treatment of HIV infection.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in relation to a type II variation to include additional safety and interactions information in the product information for Isentress, a centrally authorised medicine containing raltegravir.

## **Advice**

- The RMP for Isentress (raltegravir), in the context of the type II variation under evaluation, was considered acceptable provided that an updated version of the RMP is submitted, including the interaction between darunavir and raltegravir as an 'important potential risk'.

### **5.2.10. Sunitinib – SUTENT (CAP)**

- Evaluation of the updated RMP in the context of a 60-day type II variation

## **Regulatory details:**

PRAC Rapporteur: Carmela Macchiarulo (IT)

PRAC Co-Rapporteur: Doris Stenver (DK)

## **Background**

Sunitinib is an antineoplastic agent used in the treatment of pancreatic neuroendocrine tumours, gastrointestinal stromal tumors (GIST) and metastatic renal cell carcinoma.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in relation to a type II variation to include additional safety information in the product information for Sutent, a centrally authorised medicine containing sunitinib.

## **Advice**

- The RMP for Sutent (sunitinib), in the context of the type II variation under evaluation, was considered acceptable.
- The next planned update of the RMP should take into account some additions and clarifications proposed by the PRAC to better characterise the risk of oesophagitis.

## **6. Assessment of periodic safety update reports (PSURs)**

None

## **7. Post-authorisation safety studies (PASS)**

### **7.1. Post-authorisation safety studies protocols**

None

### **7.2. Results of post-authorisation safety studies**

None

## 8. Product related pharmacovigilance inspections

### 8.1. List of planned pharmacovigilance inspections

None

### 8.2. 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 protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the published minutes.

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

### 9.1. Safety related variations of the Marketing Authorisation (MA)

**9.1.1. Telmisartan - KINZALMONO, MICARDIS, PRITOR (CAP)**  
**Telmisartan/HCT - KINZALKOMB, MICARDISPLUS, PRITORPLUS (CAP)**  
**Telmisartan/amlodipine - ONDUARP, TWYNSTA (CAP)**

- Safety-related type II variation upon CHMP request

#### **Regulatory details:**

PRAC Rapporteur (lead for worksharing variation): Carmela Macchiarulo (IT)  
PRAC Rapporteurs: Carmela Macchiarulo (IT) (Kinzalmono, Micardis, Pritor, Kinzalkomb, MicardisPlus, PritorPlus); Martin Huber (DE) (Onduarp, Twynsta)

#### **Background**

Telmisartan is an angiotensin receptor II blocker used in the treatment of hypertension.

For further background see also 4.3.4. The PRAC was requested to provide advice to the CHMP on a type II variation application by the MAH to include in the product information for telmisartan-containing centrally authorised medicines a precautionary statement for diabetic patients with an additional cardiovascular risk. Centrally authorised medicines containing telmisartan are also indicated – among other conditions – for cardiovascular prevention, for the reduction of cardiovascular morbidity in patients with type 2 diabetes mellitus with documented target organ damage.

#### **Advice**

- The proposed variation to update the product information of the telmisartan-containing medicines included in the work-sharing procedure under evaluation at the CHMP was not considered justified based on the available evidence.
- However, the signal of a possible increase of cardiovascular risk in the diabetic population with additional cardiovascular risk factors should be further reviewed at therapeutic class level (see also olmesartan 4.3.4. ). Therefore, the need for an ad-hoc study (such as a patient-level meta-analysis) using data concerning all ARBs should be discussed. A further PRAC discussion will take place to address the terms and the regulatory framework of such a review at the next meetings.

## **9.2. Renewals of the Marketing Authorisation**

### **9.2.1. Ambrisentan - VOLIBRIS (CAP)**

- Renewal of the marketing authorisation after first 5 years

#### **Regulatory details:**

PRAC Rapporteur: Dolores Montero (ES)

PRAC Co-Rapporteur: Jana Mlada (CZ)

#### **Background**

Ambrisentan is an endothelin receptor antagonist (ERA) used in the treatment of pulmonary arterial hypertension (PAH).

Volibris, a centrally authorised product containing ambrisentan, was authorised in 2008. Since the period of validity of the first marketing authorisation expires after 5 years, a renewal of the marketing authorisation was submitted by the MAH 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.

#### **Advice**

Based on the review of the risk management system for Volibris (ambrisentan) in the treatment of patients with pulmonary arterial hypertension, and the CHMP Rapporteur assessment report, the PRAC provided advice on the PSUR submission frequency and advised, on an indefinite renewal of the marketing authorisation.

### **9.2.2. Panitimumab – VECTIBIX (CAP)**

- Renewal of conditional marketing authorisation

#### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

PRAC Co-Rapporteur:

#### **Background**

Panitimumab is an antineoplastic medicine used in the treatment of colorectal cancer.

Vectibix, a centrally authorised product containing panitimumab, was authorised under a conditional marketing authorisation in 2007. Since the period of validity of the conditional marketing authorisation needs to be renewed on a yearly basis, a renewal of the marketing authorisation was submitted by the MAH 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.

#### **Advice**

Based on the review of the risk management system for Vectibix (panitimumab) and the CHMP Rapporteur assessment report, the PRAC advised on a renewal of the conditional marketing authorisation.

However, PRAC advised that some amendments to the 'specific obligations to complete post-authorisation measures for the conditional marketing authorisation' should be implemented.

### **9.2.3. Prepandemic Influenza Vaccine (H5N1) (split virion, inactivated, adjuvanted) - PREPANDRIX (CAP)**

- Renewal of the marketing authorisation after the first 5 years

#### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)  
PRAC Co-Rapporteur: Sabine Straus (NL)

#### **Background**

Prepandrix, a centrally authorised prepandemic influenza vaccine, was authorised in 2008 for active immunisation against the H5N1 subtype of influenza A virus.

A renewal of the marketing authorisation was submitted by the MAH 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.

#### **Advice**

Based on the review of the risk management system for Prepandrix (influenza vaccine (H5N1)) and the CHMP Rapporteur assessment report, and having considered some 'potential risks' (as included in the RMP) still need to be kept under close monitoring, the PRAC recommended an additional renewal period of 5 years of the marketing authorisation.

### **9.3. Timing and message content in relation to MS safety announcements**

None

### **9.4. Other requests**

#### **9.4.1. Acclidinium bromide – EKLIRA GENUAIR, BRETARIS GENUAIR (CAP)**

- Drug utilisation study protocol requested as a RMP measure by the CHMP

#### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)  
PRAC Co-Rapporteur: Adam Przybylkowski (PL)

#### **Background**

Acclidinium bromide is an anticholinergic used in the treatment of chronic obstructive pulmonary disease (COPD).

At the time of the marketing authorisation for the centrally authorised products containing acclidinium bromide, Eklira/Bretaris Genuair, the CHMP requested the MAH to perform a drug utilisation study (DUS) and a post-authorisation safety study (PASS) to examine the risk of selected cardiovascular events.

A protocol for a drug utilisation study (DUS) had been submitted and the CHMP requested advice from the PRAC on the study protocol.

## **Advice**

- The drug utilisation study protocol for Eklira Genuair and Bretaris Genuair (acridinium bromide) was considered acceptable provided that an updated version taking into account some additional amendments to the study design proposed by the PRAC is submitted before the start of the study.

### **9.4.2. Epoetins: Darbepoetin-alfa - ARANESP (CAP), Epoetin-beta - NEORECORMON (CAP), Epoetin-zeta - RETACRIT SILAPO (CAP), Epoetin alfa – BINOCRIT (CAP), ABSEAMED (CAP), EPOETIN ALFA HEXAL (CAP), Epoetin theta – EPORATIO (CAP), Methoxy polyethylene glycol-epoetin beta – MIRCERA (CAP)**

- Evaluation of a proposal for a joint post-authorisation safety study on target haemoglobin levels in chronic kidney disease patients

## **Regulatory details:**

PRAC Rapporteur (overall): Martin Huber (DE)  
PRAC Co-Rapporteur (overall): Isabelle Robine (FR)

## **Background**

Epoetins are used to treat – among other conditions - anaemia caused by chronic kidney disease

Epoetin products authorised in the EU are indicated to achieve haemoglobin levels at a range of 10 to 12 g/dl in chronic kidney disease patients, including both patients who are on dialysis and those who are not. Despite their therapeutic benefits, some aspects of the risk of cardiovascular and cerebrovascular events associated with the higher haemoglobin levels obtained with epoetins were discussed earlier in 2012 by the PhVWP and by the CHMP, and it was considered that further evidence was needed to better clarify these risks.

The CHMP is evaluating a draft of key elements protocol for a PASS proposed jointly by the MAHs of several epoetin-containing medicines, involving re-analysis of clinical trial data on the haemoglobin target levels in chronic kidney disease patients.

## **Advice**

- The study protocol elements for a PASS to investigate the risk of cardiovascular and cerebrovascular events associated with higher haemoglobin levels involving all epoetin-containing medicines were considered acceptable provided that a detailed statistical analysis plan taking into account some comments proposed by the PRAC is submitted before the start of the study.
- After the CHMP evaluation of the protocol elements is concluded, the PRAC may consider further measures in order to ascertain that the requests and timetables for this PASS are duly adhered to in order to continue to address the impact of cardio-and cerebrovascular outcomes and mortality associated with epoetins treatment.

## **10. Other Safety issues for discussion requested by the Member States**

### **10.1. Renewals of the Mas**

None

## **10.2. Safety related variations of the marketing authorisation**

### **10.2.1. Granisetron (NAPs)**

- Risk of QT prolongation and Torsade de Pointes

#### **Regulatory details:**

PRAC Rapporteur: *to be appointed*

#### **Background**

Earlier in 2012 the PhVWP discussed the risk of QT prolongation and Torsade de Pointes for ondansetron and for all 5-HT<sub>3</sub> receptor antagonists and reviewed the available evidence. The results of an ongoing QT study in line with ICH E14 guidance were awaited for ondansetron. It was agreed that a similar study was also required for granisetron. SK, in light of the withdrawal of the marketing authorisation for Kytril, a granisetron-containing product nationally authorised in Slovakia, for which Slovakia was the PSUR - Reference Member State, requested the advice of the PRAC on the need for and modalities for conducting a study.

#### **Advice**

- In order to take an informed decision on further risk minimisation strategies, new data on the safest dose of granisetron are essential. A QT study (ICH E14 compliant) is the most suitable option to obtain such data.
- Therefore the request to perform a study should be reiterated. Given the withdrawal of the product in Slovakia, the Lead MS (DK) for signal management activities for granisetron will take forward this proposal.

### **10.2.2. Ondansetron (NAPs)**

- Risk of QT prolongation and Torsade de Pointes

#### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

#### **Background**

For further background on this topic please refer to the [1-3 October PRAC minutes](#).

#### **Advice**

- The proposed variation to update the product information for Zofran (ondansetron), under evaluation by UK, could be acceptable on the basis of the results of additional pharmacokinetic modelling using the results of a QT study. However, PRAC considered that the MAH should submit additional information taking into account some points proposed by the PRAC and propose an updated wording for the product information.
- An appropriate risk management plan should be submitted for Zofran (ondansetron) taking into account the discussed risk of QT prolongation and Torsade de Pointes.

### **10.3. Timing and message content in relation to MS safety announcements**

None

## **11. Organisational, regulatory and methodological matters**

### **11.1. Mandate and organisation of the PRAC**

#### **11.1.1. PRAC Rapporteurship**

The topic was deferred to the next meeting.

#### **11.1.2. Rules of Procedure of the PRAC**

The PRAC Rules of Procedures were discussed at the [77th meeting](#) of the EMA Management Board on 4 October 2012. A proposal for some revisions had been put forward and the updated PRAC Rules of Procedure will be discussed at the 26-29 November 2012 PRAC meeting for adoption.

### **11.2. Pharmacovigilance audits and inspections**

#### **11.2.1. Pharmacovigilance Systems and their Quality Systems**

#### **11.2.2. Pharmacovigilance System Master File**

#### **11.2.3. Pharmacovigilance Inspections**

The PRAC was presented with an overview of the Draft Guideline for Good Pharmacovigilance Practices (GVP) Module III to be published in December 2012.

### **11.3. Periodic Safety Update Reports & Union Reference Date (EURD) List**

#### **11.3.1. Periodic Safety Update Reports**

#### **11.3.2. PSURs Repository**

#### **11.3.3. Union Reference Date List**

##### **11.3.3.1. Consultation on the draft List, version November 2012**

The PRAC was consulted on the EURD list version November 2012. Considering the number of requests received from the MAHs since the last publication on 1 October 2012, it was agreed that a deadline should be set to Friday 9 October 2012 for the PRAC members to give additional input on the few outstanding issues.

The responses received will be integrated into the list which will then be provided to the CMDh and CHMP as an updated version for adoption at their November 2012 meetings. Any unresolved issues will be brought back to the PRAC at its 26-28 November 2012 meeting.

## **11.4. Signal Management**

### **11.4.1. Signal Management**

## **11.5. Adverse Drug Reactions reporting and additional reporting**

### **11.5.1. Management and Reporting of Adverse Reactions to Medicinal Products**

### **11.5.2. Additional Monitoring**

#### **11.5.2.1. Standardised statements for medicinal products under additional monitoring and for the encouragement of Adverse Drug Reactions (ADR) reporting for all medicinal products**

The wording on additional monitoring and adverse drug reactions reporting to be included in the product information template (SmPC and package leaflet) was presented to the PRAC.

These statements went through external consultation (involving industry, user testing specialists, patients and HCP organisations) in July-August 2012. Comments were analysed and discussed with interested parties on 9 October and at the Quality Review of Documents Working Group (QRD) plenary meeting on 10 October 2012.

The final version following the external consultation was circulated to PRAC members for comments and was discussed during the plenary meeting. The final wording will be circulated to the PRAC in due course.

*Post meeting note: EMA circulated to the PRAC the final wording of the QRD product information template on 6 November 2012.*

### **11.5.3. List of Product under Additional Monitoring**

#### **11.5.3.1. Creation and maintenance of the List**

EMA presented the current status and the next steps for the creation of the list in line with the amendments of the legal framework (i.e. extension of the mandatory scope criteria). EMA will follow-up by transmitting an NUI to the Member States for comments.

## **11.6. EudraVigilance Database**

None

## **11.7. Risk Management Plans and Effectiveness of risk Minimisations**

### **11.7.1. Implementation of summary of Risk Management Plan**

The EMA presented a proposal for the development of summaries of the risk management plan and their publication. The proposal took into account the feedback received during a Stakeholders Workshop including patients and healthcare professionals as well as experience in some Member States.

The EMA proposed for discussion that basic information is reported in the Summary of the (European) Public Assessment Report to complement the already tabulated information included in the Scientific Discussion of the (European) Public Assessment Report and that more comprehensive information is included in a stand-alone RMP Summary.

For the time being the implementation will follow a stepwise approach. The EMA will take forward the implementation for centrally authorised products and, in parallel, a gradual implementation will take place in MSs taking into consideration the availability of summaries of the assessment reports published.

The PRAC noted the proposal and offered some comments.

### ***11.8. Community Procedures***

None

### ***11.9. Risk communication and Transparency***

None

### ***11.10. Continuous pharmacovigilance***

None

### ***11.11. Inter Status with EMA Committees and Working Parties***

None

### ***11.12. Inter Status within the EU regulatory network***

None

### ***11.13. Contacts of the PRAC with external parties and inter Status of the EMA with interested parties***

None

## **12. Any other business**

None

## **ANNEX I – List of Abbreviations**

For a [List of the abbreviation used in the PRAC minutes](#), see:

[www.ema.europa.eu](http://www.ema.europa.eu)

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**ANNEX II – List of Participants:** *including any restrictions with respect to involvement of members / alternates / experts following evaluation of Declared interests for the 29-31 October 2012 meeting.*

<b>PRAC member PRAC alternate</b>	<b>Country</b>	<b>Outcome restriction following evaluation of e-DoI for the meeting</b>	<b>Topics on the current Committee Agenda for which restriction applies</b>  <b>Product/ substance</b>
Jean-Michel Dogne	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	Codeine, diclofenac; Vitamin K antagonists; fluoroquinolones; human albumin; olmesartan, telmisartan; granisetron, ondansetron
Virginie Chartier	Belgium	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Yuliyani Eftimov	Bulgaria	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Jana Mlada	Czech Republic	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uuskula	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Terhi Lehtinen	Finland	Cannot act as Rapporteur for:	Tolvaptan, olmesartan, short-acting beta agonists; dabigatran; telmisartan
Isabelle Robine	France	Full involvement	
Evelyne Falip	France	Full involvement	
Martin Huber	Germany	Full involvement	
George Aislaitner	Greece	Full involvement	
Julia Pallos	Hungary	Full involvement	
Gudrun Kristin Steingrimsdottir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Fernanda Ferrazin	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	
Ingebjorg Buajordet	Norway	Full involvement	
Pernille Harg	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida	Portugal	Full involvement	

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

<b>Independent scientific experts nominated by the European Commission</b>	<b>Country</b>	<b>Outcome restriction following evaluation of e- DoI for the meeting:</b>	<b>Topics on the current Committee Agenda for which restriction applies</b>
			<b>Product/ substance</b>
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise (Marieke) De Bruin		No restriction with regard to agenda items	
Birgitte Keller-Stanislawski		Full involvement	
Lennart Waldenlind		Full involvement	

<b>Additional European experts participating at the meeting for specific Agenda items</b>	<b>Country</b>	
Rikke Jensen	Denmark	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Diane Halle	France	
Christine Diesinger	Germany	
Thomas Grueger	Germany	
Jutta Krappweis	Germany	
Valerie Strassmann	Germany	
Maria Grazia Evandri	Italy	
Daniela Melchiorri	Italy	
Giuseppe Rosano	Italy	
Charlotte Backman	Sweden	
Phillip Bryan	United Kingdom	
Kathryn Ord	United Kingdom	
Karen Slevin	United Kingdom	
Jane Woolley	United Kingdom	