11 April 2013
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Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 4-7 March 2013

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.

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

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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.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.

Corr. Amendments in Annex II

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1. Introduction

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

1.2. Adoption of agenda of the PRAC meeting on 4-7 March 2013

The agenda was adopted with the addition of the following topics upon request from the members of the Committee and the EMA secretariat: 2.1.1. flupirtine; 3.1.1. domperidone; 3.1.3. octocog alpha;3.2.3. diclofenac; 5.1.8. dimethyl fumarate; fenofibrate / simvastatin; and other issues under 'organisational matters' 12.4.2. ; 12.7.3. ; 12.7.4. .

1.3. Adoption of minutes of the previous PRAC meeting on 4-7 February 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 4-7 February 2013 were published on 15 March 2013 on the EMA website.

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

2.1. Newly triggered procedures

2.1.1. **Flupirtine** (NAPs)

- Review of the benefit-risk balance of flupirtine-containing medicines following notification by Germany of a referral under Article 107i of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)
PRAC Co-Rapporteur: Martin Huber (DE)

Background

The German medicines agency (Bfarm) sent a letter of notification on 28 February 2013 triggering a referral under Article 107i of Directive 2001/83/EC for a review of flupirtine-containing medicines, due to concerns about liver problems (ranging fromasymptomatic increase in liver enzymes to liver failure) associated with the use of these medicines for short and long-term pain relief.

Discussion

The PRAC noted the rationale evidence cited for the triggering of procedure provided by the German 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 also considered whether the safety concern was common to all products belonging to the same therapeutic class but was unable to conclude on this in the absence of currently available information on any such substances/products marketed in the EU.

This aspect will be further discussed at a later stage of the procedure. The PRAC appointed Margarida Guimarães (PT) as Rapporteur and Martin Huber (DE) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

- The procedure will follow the adopted timetable (EMA/PRAC/137732/2013).
- A list of questions should be addressed by the MAHs (published on the EMA website EMA/PRAC/137417/2013) and data will also be gathered from stakeholders (healthcare professionals, patients' organisations and the general public) by means of responses to a list of questions (EMA/PRAC/144072/2013).

2.2. Ongoing Procedures

2.2.1. Cyproterone, ethinylestradiol – DIANE 35 & other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms (NAPs)

- Review of the benefit-risk balance of Diane 35 & other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms following notification by France of a referral under Article 107i of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

A referral procedure under article 107i of Directive 2001/83/EC is ongoing for Diane 35 & other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms (see minutes of PRAC 4-7 February 2013).

Summary of recommendation(s)/conclusions

The PRAC noted a summary of cases reported in the Netherlands performed following a statement issued on 4 March 2013 by the Dutch Medicines Evaluation Board concerning reports of adverse events in women who have used Diane 35 or other medicines containing cyproterone acetate 2 mg with ethinylestradiol 35 micrograms.
The PRAC commented that the results of the summary did not justify any interim measures before the conclusion of the ongoing review, given that they did not change the current understanding of the known risk of venous thromboembolism with these medicines. Warnings to alert patients and prescribers to this risk are already included in their product information. The ongoing assessment will consider all available data and a recommendation will be agreed at the PRAC meeting on 13-16 May 2013.
The PRAC supported the organisation of an ad-hoc expert meeting to respond to a list of questions in the framework of the current procedure. The PRAC agreed on the expertise required and agreed a list of questions to be addressed by the ad-hoc expert group. Members were invited to propose candidates from the Member States. EMA clarified that the current provisions in terms of the handling of conflicts of interest will be applied.

2.2.2. Tetrazepam (NAP)

- Review of the benefit-risk balance of tetrazepam-containing medicines following notification by France of a referral under Article 107i of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)
PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

A referral procedure under Article 107i of Directive 2001/83/EC is ongoing for tetrazepam-containing medicines (see minutes of the PRAC 7-10 January 2013). A preliminary assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable for the procedure.

Summary of recommendation(s)/conclusions

Preliminary conclusions from both rapporteurs were presented to the PRAC, in preparation for the recommendations to be agreed at the April 2013 meeting. Some questions for the MAHs, to be addressed in an oral explanation to be held at the April 2013 meeting, were discussed.

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered Procedures

3.1.1. **Domperidone** (NAPs)

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

Regulatory details:

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

Background

The Belgian medicines agency (Federal Agency for Medicines and Health Products, FAMHP) sent a letter of notification dated 1 March 2013 triggering a referral under Article 31 of Directive 2001/83/EC for the review of all domperidone-containing medicines (for background, see minutes of the PRAC 4-7 February 2013 – Signals follow-up).

Discussion

The PRAC noted the notification letter from the Belgian 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 appointed Isabelle Robine (FR) as Rapporteur and Jean-Michel Dogné (BE) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/124198/2013) and a timetable for the procedure (EMA/PRAC/127280/2013).

3.1.2. Nicotinic acid and related substances – acipimox, xantinol nicotinate (NAPs)

- Review of the benefit-risk balance of medicinal products containing nicotinic acid and related substances indicated for treatment of lipid disorders, based on pharmacovigilance data following notification by Denmark of a referral under Article 31 of Directive 2001/83/EC

Regulatory details:

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

Background

For background, see minutes of the PRAC 4-7 February 2013.

The Danish medicines agency sent a letter of notification dated 27 February 2013 of a referral under Article 31 of Directive 2001/83/EC for the review of nicotinic acid-, acipimox- and xantinol nicotinate-containing medicines indicated for the treatment of lipid disorders.

Discussion

The PRAC noted the notification letter from the Danish 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 noted that all EU marketing authorisations for products containing nicotinic acid had been withdrawn.
The PRAC appointed Julia Pallos (HU) as Rapporteur and Line Micham (DK) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/138313/2013) and a timetable for the procedure (EMA/PRAC/138312/2013).

3.1.3. Octocog alfa – HELIXATE NEXGEN (CAP), KOGENATE BAYER (CAP)

- Review of the benefit-risk balance of Helixate Nexgen and Kogenate Bayer following notification of a referral by the European Commission under Article 20(8) of Regulation (EC) No 726/2004, following steps of Article 31 of Directive 2001/83/EC, resulting from pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
PRAC Co-Rapporteur: Ulla Wändel Liminga (SE)

Background

The European Commission initiated a referral under Article 20 of Regulation (EC) No 726/2004 for the review of Kogenate Bayer and Helixate Nexgen. These centrally authorised medicines contain octocog alpha and are indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). The need for a review was triggered by the results of the Rodin

Study[1] reporting increased development of inhibitory antibodies for the so-called 'second generation full-length recombinant factor VIII products', compared with third-generation ones.

Discussion

The PRAC noted the notification letter from the European Commission and discussed a list of questions to be addressed during the procedure as well as a timetable for conducting the review. The PRAC noted that the PRAC Rapporteur for the procedure will be Brigitte Keller-Stanislawski (DE) and Ulla Wändel Liminga (SE) as PRAC Co-Rapporteur.

Summary of recommendation(s) / conclusions

The Committee adopted a list of questions (EMA/PRAC/142800/2013) and a timetable for the procedure (EMA/PRAC/142799/2013).

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 of combined hormonal contraceptives based on pharmacovigilance data following notification by France of a referral under Article 31 of Directive 2001/83/EC

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 minutes of the PRAC 4-7 February 2013).
An extension of the timetable for submitting responses to the PRAC list of questions had been requested by one of the MAHs concerned. The PRAC agreed with the request for an extension based on the rationale provided.

Summary of recommendation(s) / conclusions

Following the extension agreed for the MAHs, in the light of the expected volume of data to be analysed and the need for a thorough evaluation, the Rapporteurs for the procedure proposed to extend the assessment phase of the timetable, leading to agreement of recommendations or a List of Outstanding Issues (LoOI) in July 2013.

EMA secretariat highlighted that, notwithstanding such an extension, the procedure will have to be concluded within the legal timeframe set by the current legal provisions. The PRAC noted the impact that such extension could have on the latter phase of the procedure, and adopted a revised timetable for the procedure (EMA/PRAC/122032/2013 - Rev 2).

[1] Gouw SC, et al; PedNet and RODIN Study Group. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med 2013; 368: 231-9.

3.2.2. **Diacerein** (NAPs)

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

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 is ongoing (see PRAC minutes 26-29 November 2012). The PRAC was informed of a clarification requested on the adopted list of questions by one of the MAHs concerned.

Summary of recommendation(s) / conclusions

The PRAC noted the request for clarification received and adopted a revised list of questions to address this request (EMA/PRAC/759123/2012 Rev.1). The PRAC also noted an extension of the timetable for the procedure, which was previously requested by the one of the MAHs and was considered appropriate by the Rapporteur (EMA/PRAC/747322/2012).

3.2.3. **Diclofenac** (NAPs)

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for diclofenac-containing medicines is ongoing (see minutes of the PRAC 29-31 October 2012). The PRAC adopted a revised timetable following a request for extension by the Rapporteur, in order to allow full assessment of all data of interest for the review of the benefit-risk balance.

Summary of recommendation(s) / conclusions

The PRAC noted the request for extension and adopted a revised timetable (EMA/PRAC/146068/2013).

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

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for HES-containing products (see minutes of the PRAC 4-7 February 2013).

An updated Cochrane systematic review[2] as well as a review in JAMA[3] and in the BMJ[4] had been published on this topic since the referral procedure had started.

Summary of recommendation(s)/conclusions

The PRAC noted the new publications concerning HES solutions for infusion and agreed that these reviews should be considered in the assessment by the Rapporteurs. The EMA will inform the MAHs. The current timetable for review was considered appropriate, but the PRAC recommended that a preliminary discussion takes place in April 2013 before a list of outstanding issues or PRAC recommendation is agreed at the May 2013 PRAC.

The PRAC supported the organisation of an ad-hoc expert meeting in the framework of the current procedure. The PRAC agreed on the expertise required. Members were invited to propose candidates from the Member States. EMA clarified that the current provisions in terms of conflicts of interest will be applied. A list of questions for the experts will be discussed at the April 2013 meeting.

3.3. Procedures for finalisation

None

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

None

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Clopidogrel – ISCOVER** (CAP), **PLAVIX** (CAP) **& generics** (CAPS and NAPs)

- Signal of acquired haemophilia A

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

[2] Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD000567. DOI: 10.1002/14651858.CD000567.pub6 .Perel P, Roberts I, Ker K.Published Online: February 28, 2013pPublished Online: February 28, 2013

[3] Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA. 2013 Feb 20;309(7):678-88. doi: 10.1001/jama.2013.430

[4] Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, Wetterslev J. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis - BMJ 2013;346:f839

Background

Clopidogrel is an antithrombotic agent used in the prevention of atherothrombotic events in peripheral vascular diseases, stroke, acute coronary syndrome, myocardial infarction and atrial fibrillation. Medicines containing clopidogrel are estimated to have been used by more than 174 million patients worldwide since the initial marketing authorisation in 1997.

During routine signal detection activities, a signal of acquired haemophilia was identified by the EMA, triggered by a total of 11 cases retrieved from EudraVigilance or published in the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the reported cases and noted that the cases involved both males and females, unlike congenital haemophilia A and B. In most of the cases other alternative causes were excluded. Resolution was observed within 2-3 months in all patients after withdrawal of clopidogrel and additional treatment with immunosuppressants. In light of the strength of the evidence the PRAC agreed that the signal warranted prompt further investigation.

Summary of recommendation(s)

- The MAH for Plavix/Iscover (clopidogrel) should submit to the EMA, within 30 days, a cumulative review of the cases of acquired haemophilia associated with clopidogrel, and a proposal for amending the product information as well as a proposal for a Direct Healthcare Professional Communication (DHPC) and a communication plan.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Clopidogrel – ISCOVER (CAP), **PLAVIX** (CAP) **& generics** (CAPs and NAPs)

- Signal of cross-reactivity between clopidogrel and ticlopidine among patients with previous allergic and/or haematological reactions to one of these products.

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Background

Clopidogrel is an antithrombotic agent used in the prevention of atherothrombotic events in peripheral vascular diseases, stroke, acute coronary syndrome, myocardial infarction and atrial fibrillation. Medicines containing cloidogrel are estimated to have been used by more than 174 million patients worldwide since the initial marketing authorisation in 1997.

A retrospective study[5] conducted on 76 patients who developed allergy to clopidogrel or ticlopidine had shown that approximately a third of the patients developed the same reaction when subsequently treated with the other product. More recently, during routine signal detection activities, 20 relevant spontaneous case reports were retrieved from EudraVigilance which further supported a signal of

[5] Frequency of allergic or hematologic adverse reactions to ticlopidine among patients with allergic or hematologic adverse reactions to clopidogrel. Lokhandwala JO, Best PJ, Butterfield JH, Skelding KA, Scott T, Blankenship JC, Buckley JW, Berger PB. Department of Cardiology, Geisinger Medical Center, Danville, PA 17822-3003, USA. Circ Cardiovasc Interv. 2009 Aug;2(4):348-51. Epub 2009 Jul 22.

potential cross-reactivity between ticlopidine and clopidogrel. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reviewed and agreed that the evidence suggesting cross-reactivity between clopidogrel, ticlopidine and between the thienopyridines in general warranted an update of the product information to inform prescribers of these findings.

Summary of recommendation(s)

- The MAHs for Plavix/Iscover (clopidogrel) should be requested to submit to the EMA within 30 days a variation to update the product information to include the information on cross-reactivity between thienopyridines[6].

4.1.3. Levetiracetam – KEPPRA (CAP)

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

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Background

Levetiracetam is an antiepileptic medicine. The worldwide exposure for Keppra, a centrally authorised medicine containing levetiracetam, is estimated to have been more than 796,000 patient-years in the period from 2010 to 2011.

During routine signal detection activities, a signal of syndrome of inappropriate antidiuretic hormone secretion (SIADH) was identified by the EMA, based on 13 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 SIADH as well as other reported cases of hyponatraemia and noted that the available information on the temporal relationship, dechallenge and rechallenge seemed to suggest a probable association between the reaction and treatment with levetiracetam. The potential role of concomitant treatments in sensitising the patient to levetiracetam-associated SIADH and hyponatraemia should be further investigated.

Summary of recommendation(s)

- The MAH for Keppra (levetiracetam) should submit to the EMA within 60 days a cumulative review of all cases reported (within the Standardised MedDRA Query 'Hyponatraemia and SIADH'), including a scientific discussion on putative drug-drug interactions between

[6] Section 4.4 of the Summary of Product Characteristics (SmPC): "Thienopyridines (clopidogrel, prasugrel and ticlopidine) may cause mild to severe allergic reactions such as: rash, angioedema, thrombocytopenia and neutropenia. Observational studies and post-marketing surveillance data highlighted the possibility of occurrence of a cross reactivity between thienopyridines. Patients who develop an allergic reaction (e.g. haematological or cutaneous reaction) to clopidogrel may have an increased risk of developing the same or another allergic reaction to another drug of the same pharmacological class, ticlopidine or prasugrel. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised (see section 4.8)."

levetiracetam and other antiepileptic drugs emphasising the potential role of these interactions in the onset of SIADH and hyponatraemia.

- 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. **Cinacalcet – MIMPARA** (CAP)

- Signal of a fatal case with severe hypocalcaemia in a paediatric clinical study

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Cinacalcet is a calcimimetic agent used in the treatment of hyperparathyroidism (HPT) of different origins. Mimpara, a centrally authorised medicine which contains cinacalcet, has been used by an estimated number of more than 700,000 patients worldwide in the period from 2004 until 2010.

The EMA was informed of the temporary suspension of all paediatric clinical trials of cinacalcet after the death of a 14-year-old patient who had severe hypocalcaemia was reported in a trial. This information was also reported by the FDA in a 'Drug safety communication'.

Discussion

The PRAC noted the information on the reported case and confirmed that the current product information addresses the risk of hypocalcaemia. The PRAC noted that a Type II variation will be submitted to the EMA to give further information on this signal, as well as a review of "hypocalcaemia" across clinical trials and post-marketing databases in both paediatric and adult populations. It was also noted that a DHPC was to be circulated to inform prescribers of this event, to highlight that Mimpara is not indicated for use in paediatric subjects and that, as adressed in the product information, patients should be carefully monitored for the occurrence of hypocalcaemia.

Summary of recommendation(s)

- No further regulatory action is currently recommended further to the dissemination of the DHPC.
- Further PRAC recommendations could be provided before finalisation of the assessment of the variation submitted by the MAH at CHMP level, as applicable.

4.3. Signals follow-up

4.3.1. **Filgrastim -** NAP **and BIOGRASTIM** (CAP), **FILGRASTIM HEXAL** (CAP), **NIVESTIM** (CAP), **RATIOGRASTIM** (CAP), **TEVAGRASTIM (CAP), ZARZIO** (CAP)
Pegfilgrastim - NEULASTA (CAP)

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

Regulatory details:

PRAC Rapporteur (overall): Julie Williams (UK)

Background

For background information see PRAC minutes 29-31 October 2012.

The MAH for the reference filgrastim and pegfilgrastim-containing medicines submitted a systematic review of the literature and a cumulative review of all case reports of CLS and CRS and their analysis as requested. The results were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the review and concluded that the post-marketing reports provide fairly strong evidence of a temporal and causal association between filgrastim treatment and CLS. In light of the available evidence from case reports of CLS in EudraVigilance and the scientific literature, and given the seriousness of the syndrome and its potentially life-threatening nature, the PRAC agreed that the product information should be updated to inform prescribers of this risk.
The PRAC also discussed the need for a DHPC to inform relevant healthcare professionals of these changes.

The post-marketing evidence for CRS in association with filgrastim/pegfilgrastim was considered limited at present but it was recommended that this issue should be kept under review.

Summary of recommendation(s)

- The MAH for the reference filgrastim and pegfilgrastim-containing medicines Neupogen (filgrastim) and Neulasta (pegfilgrastim) should submit within 30 days (to the NCAs[7] and to the EMA as appropriate), a proposal for amending the product information[8], including a DHPC and a communication plan.
- The same MAH is also requested to submit an updated Risk Management Plan within 90 days to include the important identified risk of “capillary leak syndrome” and the potential risk of “cytokine release syndrome” and proposed pharmacovigilance activities, as appropriate.
- Follow-up to the remaining biosimilar products will be in accordance to current procedures.

4.3.2. Fluoroquinolones: ciprofloxacin - enoxacin - flumequine - lomefloxacin - levofloxacin - moxifloxacin - ofloxacin - pefloxacin - prulifloxacin – rufloxacin - norfloxacin (NAPs)

- Signal of retinal detachment

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

[7] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to.

[8] Section 4.8 of the SmPC (Undesirable effects) as a post-marketing life-threatening ADR in cancer patients and healthy donors. Section 4.4 of the SmPC (Special warnings and precautions for use) ‘Capillary leak syndrome is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care’. Additionally, the section 4 of the PIL (Possible side effects) should be updated to contain an appropriate description of symptoms indicative of CLS which may need medical attention.

Background

For background, see PRAC minutes 29-31 October 2012.

EMA performed a feasibility analysis of using The Health Improvement Network (THIN) database to examine retinal detachment associated with prescription of (fluoro)quinolones and the results were assessed by the Rapporteur.

Discussion

The PRAC agreed that based on data analysed on exposure to systemic (fluoro)quinolones and the incidence of retinal detachment, and in light of the number of patients that were prescribed a systemic (fluoro)quinolone on or before their first record of retinal detachment, further detailed consideration was warranted of appropriate methodologies for further analyses in THIN to assess the signal.

Summary of recommendation(s)

- EMA, in collaboration with the PRAC Rapporteur, should further explore possible designs for a study in the THIN database and provide feedback to the PRAC at the 8-11 April 2013 meeting.

4.3.3. Temozolomide - TEMODAL (CAP)

- Signal of hepatic failure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

For background information see PRAC Minutes 1-3 October 2012.

The MAH for Temodal (temozolomide) submitted a cumulative review of the signal of hepatic failure and related terms as requested by the PRAC, which was assessed by the Rapporteur.

Discussion

The PRAC discussed the information assessed and concluded that the strength of the evidence analysed warranted an amendment to the product information. However, some of the data to support risk minimisation measures should be further clarified. Further information is needed on the potential dose-dependent effect of temozolomide-related liver toxicity and the relevance of monitoring liver function in patients treated and in those who have to be treated with temozolomide.

Summary of recommendation(s)

- The MAH for Temodal (temozolomide) should be requested to submit to the EMA, within 60 days, a variation proposing appropriate amendments to the product information, including a proposal for a communication plan and provision of supplementary information as requested by the PRAC.
- The MAHs should also be requested to submit an updated Risk Management Plan within the next regulatory procedure to reclassify the 'important potential risk' of 'hepatobiliary disorders' to an 'important identified risk' and include information on 'severe liver injuries' including those with fatal outcome.

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

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. Afamelanotide

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.2. Ataluren

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.3. Sipuleucel-T

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.4. Bosentan Monohydrate

- 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. Alemtuzumab

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.7. Delamanid

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.8. Dimethyl Fumarate

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.9. Enzalutamide

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.10. Etarfolatide

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.11. Fenofibrate /simvastatin

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.12. Folic acid

- 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. Macitentan

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.15. Mercaptine bitartrate

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.16. Para-aminosalicylic acid

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.17. Pomalidomide

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.18. Ponatinib

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.19. Recombinant human follicle-stimulating hormone, follitropin alfa

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.20. Regorafenib

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.21. Turoctocog alfa

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.22. Vintafolide

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.23. Voriconazole

- Evaluation of an RMP in the context of an initial Marketing Authorisation Application procedure

5.1.24. Zoledronic acid

- 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. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (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 3 of the RMP for the above mentioned medicine.

See also 0

5.2.2. Epoetin alfa – **ABSEAMED** (CAP), **BINOCRIT** (CAP), **EPOETIN ALFA HEXAL** (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

See also 6.1.10.
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 14 of the RMP for the above mentioned medicine.

The PRAC recommended that the Rapporteurs for epoetin-containing CAPs discuss and present to the PRAC a list of questions to be transmitted to the MAHs to address any outstanding issues relating to the risk management system in relation to risk of tumour progression and increased morbidity in cancer patients.

EMA secretariat will provide support as appropriate, including regulatory advice on the most suitable procedures to take forward any advice. The EMA will also be exchanging information with the lead researchers of the project funded by the EC under the 7th framework programme EpoCan to provide an update on research projects being conducted.

5.2.3. Fentanyl – **PECFENT** (CAP)

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

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
See also 6.1.12.

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.

5.2.4. Influenza vaccine – **IDFLU** (CAP), **INTANZA** (CAP)

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

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)
See also 6.1.14.

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.

5.2.5. Maraviroc – CELSENTRI (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
See also 6.1.17.

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.

5.2.6. Moroctocog alfa – REFACTO AF (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)
See also 5.2.6.

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.

5.2.7. Nonacog alfa – BENEFIX (CAP)

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
See also 6.1.20.

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.

5.2.8. Prifenidone – ESBRIET (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
See also 6.1.25.

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 3 of the RMP for the above mentioned medicine.

5.2.9. Pandemic influenza vaccine – PUMARIX (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
See also 6.1.22.

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.

5.2.10. Silodosin – **SILODYX** (CAP), **UROREC** (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
See also 6.1.27.

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.

5.2.11. Ulipristal – **ESMYA** (CAP)

- Evaluation of an RMP in the context a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)
See also 6.1.29.

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.

5.2.12. Vernakalant – **BRINAVESS** (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)
See also 6.1.32.

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 3.3 of the RMP for the above mentioned medicine.

5.2.13. Zoledronic acid – **ZOMETA** (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)
See also 6.1.33.

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 via written procedure on the 12th of March 2013.

RMP in the context of a variation of the marketing authorisation

5.2.14. Aflibercept – EYLEA (CAP)

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

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Aflibercept is a recombinant fusion protein that binds to vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF), used for the treatment of treatment of neovascular (wet) age-related macular degeneration (AMD) in adults.

The CHMP is evaluating an extension of the therapeutic indication for Eylea, a centrally authorised medicine 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 8 for Eylea (aflibercept) submitted in the context of the extension of indication under evaluation by the CHMP was considered acceptable provided an updated risk management plan and satisfactory responses addressing some questions raised by the PRAC are submitted.
- Additional pharmacovigilance activities are needed. In particular the 'post-authorisation randomised study with the primary objective of comparing the standard regime of injections every 8 weeks with a reactive regimen based on visual and anatomic outcomes, based on a CHMP approved protocol' – included as a condition of the MAs - should be extended to include the new target population of adult patients with macular oedema following CRVO, to analyse relevant aspects.

5.2.15. 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 a recombinant human interleukin-1 inhibitor used in selected patients for the treatment of signs and symptoms of rheumatoid arthritis, in combination with methotrexate.
The CHMP is evaluating an extension of the therapeutic indication for Kineret, a centrally authorised medicine containing anakinra, to include treatment of adult and paediatric patients with cryopyrin-associated periodic syndromes. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of the indication.

Summary of advice

- The updated RMP version 2 for Kineret (anakinra) in the context of the extension of indication under evaluation by the CHMP was considered acceptable provided that an updated version is submitted in response to a Request for Supplementary Information to be adopted by CHMP.
- The updated version should take into account some additions proposed by the PRAC regarding the safety concerns and the pharmacovigilance plan, and address some remaining editorial comments.

5.2.16. Boceprevir – VICTRELIS (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 5 of the RMP for the above mentioned medicine.

5.2.17. 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 version 1 of the RMP for the above mentioned medicine.

5.2.18. Certolizumab pegol – CIMZIA (CAP)

- Evaluation of an RMP in the context of a variation

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 8.1 of the RMP for the above mentioned medicine.

5.2.19. Denosumab – XGEVA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Denosumab is a bisphosphonate, used for the prevention of skeletal-related events in patients with bone metastases from solid tumours.

The CHMP is evaluating an extension of the therapeutic indication for Xgeva, a centrally authorised medicine containing denosumab, to include the treatment of giant cell tumour of bone (GTCB) in adults or skeletally mature adolescents. 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 3.1 for Xgeva (denosumab) submitted in the context of the variation under evaluation by the CHMP was considered acceptable provided that some outstanding issues are addressed before finalisation of the variation procedure by the CHMP.
- These include, among others, long term treatment to be added as 'missing information'; potential malignant transformation to be added as 'potential risk' as well as off label use in giant-cell bone tumours, primarily curable by surgery. Additional pharmacovigilance activities to follow up on long term safety with adequate duration should be discussed.

5.2.20. Eculizumab – SOLIRIS (CAP)

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

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

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.

5.2.21. 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.

5.2.22. Icatibant – FIRAZYR (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Icatibant is a selective competitive antagonist at the bradykinin type 2 (B2) receptor and is used for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase-inhibitor deficiency.
The CHMP is evaluating an extension of the therapeutic indication for Firazyr, a centrally authorised medicine containing icatibant, to include the treatment of acute angiotensin converting enzyme inhibitor-induced angioedema. 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 5 for Firazyr (icatibant) submitted in the context of the extension of indication under evaluation by the CHMP could be considered acceptable provided an updated risk management plan including satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA. This includes a clarification on the potential risk of 'deterioration of cardiac function under ischaemic conditions', which should be elaborated upon, given the new indication applied for and the likely higher risk in this population.

5.2.23. Omalizumab – XOLAIR (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Omalizumab is a monoclonal antibody, used for the treatment of severe allergic asthma in selected patients.

The CHMP is evaluating a variation of the product information for Xolair, a centrally authorised medicine containing omalizumab, to update the product information with the final results from the Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS) study and the results of two pooled clinical trial analyses on malignancies and arterial thromboembolic events. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the current RMP to support this variation.

Summary of advice

- Regarding malignancies, the PRAC noted that the final results of the EXCELS study, consistent with the results of the pooled clinical trial analyses, did not indicate that Xolair treatment is associated with an overall increased risk of malignancies. A list of questions (LoQs) to be addressed by the MAH – subject to further discussion at the CHMP – was agreed to seek clarification on the new proposed text for the SmPC.
- A new version of the RMP should be submitted in the context of the variation under evaluation by the CHMP to support the proposed changes to the product information. Further PRAC advice will be provided upon provision of an updated version of the RMP.

5.2.24. Ranibizumab – LUCENTIS (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 11.1 of the RMP for the above mentioned medicine.

5.2.25. Rituximab – MABTHERA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Rituximab is a monoclonal antibody, used for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis in selected patients.
The CHMP is evaluating a variation of the product information for Mabthera, a centrally authorised medicine containing rituximab, to update the product information regarding the occurrence of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients receiving rituximab for the treatment of autoimmune indications. 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 9.2 for Mabthera (rituximab) submitted in the context of the variation under evaluation by the CHMP could be considered acceptable.

5.2.26. 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 for the symptomatic treatment of mild to moderately severe Alzheimer's dementia and mild to moderately severe dementia in patients with idiopathic Parkinson's disease.
The CHMP is evaluating an extension of the therapeutic indication for Exelon and Prometax, centrally authorised medicines containing rivastigmine, to include the symptomatic treatment of severe Alzheimer's dementia. 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 7 for Exelon and Prometax (rivastigmine) submitted in the context of the extension of indication under evaluation by the CHMP was considered acceptable provided an updated version is submitted to the EMA to address minor additions requested by the PRAC.

5.2.27. 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 9 of the RMP for the above mentioned medicine.

5.2.28. Vildagliptin –GALVUS (CAP), **JALRA** (CAP), **XILIARX** (CAP); **vildagliptin, metformin** – **EUCREAS** (CAP), **ICANDRA** (CAP), **ZOMARIST** (CAP)

- Evaluation of an RMP in the context of a variation

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 11 of the RMP for the above mentioned medicines.

5.2.29. Voriconazole – VFEND (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

The PRAC noted that the assessment of this RMP will be carried out for the 8-11 April PRAC.

5.2.30. Voriconazole – VFEND (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

The PRAC noted that the assessment of this RMP will be carried out on the 8-11 April PRAC.

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

5.2.31. Iloprost – VENTAVIS (CAP)

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

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

See also 8.1.6.

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 3 of the RMP for the above mentioned medicine, submitted within the renewal of the marketing authorisation.

5.2.32. Lacosamide – VIMPAT (CAP)

- Evaluation of an RMP in the context of a renewal 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 10 of the RMP for the above mentioned medicine.

See also 8.1.7.

5.2.33. Methylnaltrexone Bromide – RELISTOR (CAP)

- Evaluation of an RMP in the context of a renewal 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 2 of the RMP for the above mentioned medicine.

See also 8.1.8.

RMPs in the context of a stand-alone RMP procedure or measures of the RMP

5.2.34. Azacitidine – VIDAZA (CAP)

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

5.2.35. Catridecacog – NOVOTHIRTEEN (CAP)

- Evaluation of a risk minimisation activity of the RMP

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

The PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the final readability report of the patient educational material and physician brochure for the above mentioned medicine since no comments were raised during the consultation phase preceding the meeting.

5.2.36. Doripenem – DORIBAX (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP 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 the Final Clinical Study Report for Study DORINOS4001 included in the RMP for the above mentioned medicine.

5.2.37. Ferumoxitol – RIENSO (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP 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 2.1 of the RMP for the above mentioned medicine.

5.2.38. Mecasermin – INCRELEX (CAP)

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

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Background

Mecasermin is an a human insulin-like growth factor used for the long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary insulin-like growth factor-1 deficiency (primary IGFD).

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Increlex, a centrally authorised medicine containing mecasermin, to align it with the GVP module V format and include results of 'Study 1419'.

Summary of advice

- The updated RMP version 6 for Increlex (mecasermin) was considered acceptable.
- The next update of the RMP should take into account some minor changes proposed by the PRAC, including a request to include off-label use as a 'potential risk' in the RMP; relevant pharmacovigilance and risk minimisation measures should be proposed with regards to this.

5.2.39. Tenofovir disoproxil fumarate – VIREAD (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 14 of the RMP for the above mentioned medicine.

See also 7.1.4. .

5.2.40. Vemurafenib – ZELBORAF (CAP)

- Evaluation of an RMP in the context of a stand-alone RMP 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 6 of the RMP for the above mentioned medicine.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1.1. A/H5N1 pre-pandemic influenza vaccine – VEPACEL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogne (BE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Vepacel, a centrally authorised pre-pandemic influenza vaccine containing antigen A/Vietnam/1203/2004 (H5N1), remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.2. **Aliskiren**, **amlodipine** – **RASILAMLO** (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 Rasilamlo, a centrally authorised medicine containing aliskiren/amlodipine, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain once yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.3. **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, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.4. **Asenapine – SYCREST** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Asenapine is an atypical antipsychotic used for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sycrest, a centrally authorised medicine containing asenapine, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Sycrest (asenapine) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The PRAC noted deficiencies in the way data were presented in the PSUR. Therefore the MAH should submit within two months to the EMA a cumulative review of all cases of neutropenia and agranulocytosis as well as a cumulative review of medication errors and related terms.
- In the next PSUR, the MAH should provide a cumulative review of cases of angioedema (including information on time to onset, rechallenge/dechallenge) as well as a cumulative review of cases of agitation. In addition, the MAH should closely monitor cases of Stevens Johnson syndrome, the use of asenapine during pregnancy, cerebrovascular accident, seizures and suicide-related events.

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.

6.1.5. Azilsartan medoxomil – **EDARBI** (CAP), **IPREZIV** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Azilsartan medoxomil is an angiotensin II antagonist used in the treatment of essential hypertension in adults. Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Edarbi and Ipreziv, centrally authorised medicines containing azilsartan medoxomil, and discussed recommendations on their marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Edarbi and Ipreziv (azilsartan medoxomil) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- However, a variation to update the product information to reflect relevant contraindications and warnings regarding concomitant use of azilsartan and aliskiren should be submitted to the EMA within 2 months. Reference should be made to the recently approved Product Information of Rasilez (aliskiren) accessible on the EMA website (EPAR Rasilez)
- The MAH should also provide further information within one month on the number of fatal cases that were reported during the review period and cumulatively, and should discuss the need for inclusion of several non-serious events in the product information. In addition, the MAH should discuss any new reports of anaphylaxis and related events.

The frequency of submission of PSURs should remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.6. Colistimethate – COLOBREATHE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Colobreathe, a centrally authorised medicine containing colistimethate, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.7. Collagenase clostridium histolyticum – XIAPEX (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 Xiapex, a centrally authorised medicine containing collagenase clostridium histolyticum, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.8. Eflornithine – VANIQA (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 Vaniqa, a centrally authorised medicine containing eflornithine, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain once every 3 years and the next PSUR should be submitted to the EMA within 90 days of the data lock point.

6.1.9. **Emtricitabine**, **rilpivirine**, **tenofovir disoproxil – EVIPLERA** (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 Eviplera, a centrally authorised medicine containing emtricitabine/rilpivirine/tenofovir disoproxil, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.10. **Epoetin alfa – ABSEAMED** (CAP), **BINOCRIT** (CAP), **EPOETIN ALFA HEXAL** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Epoetin alfa is used in the treatment of various conditions including symptomatic anaemia associated with chronic renal failure (CRF) in selected patients and anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Abseamed, Binocrit and Epoetin Alfa Hexal, centrally authorised medicines containing epoetin alfa, and issued a recommendation on their marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Abseamed, Binocrit, Epoetin Alfa Hexal (epoetin alfa) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSUR, the MAHs should closely monitor cases of pure rare cell aplasia (PRCA) after recombinant erythropoietin (rhEPO) therapy by the intravenous route. In addition, the MAHs should provide cumulative reporting rate of thrombotic and embolic vascular events and off-label use regarding intravenous application in renal anaemia, as recommended in the RMP.

The frequency of submission of PSURs should be changed from yearly to once every 3 years to be in accordance with the EURD list and the next PSUR should be submitted to the EMA within 90 days of the data lock point.

6.1.11. Eptotermin alfa – OPGENRA (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 Opgenra, a centrally authorised medicine containing eptotermin alfa, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 maintained to once every 3 years and the next PSUR should be submitted to the EMA within 90 days of the data lock point.

6.1.12. Fentanyl – PECFENT (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 PecFent, a centrally authorised medicine containing fentanyl citrate, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.13. Human protein C – CEPROTIN (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 Ceprotin, a centrally authorised medicine containing human protein C, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.14. Influenza vaccine – **IDFLU** (CAP), **INTANZA** (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 IDflu and Intanza, centrally authorised influenza vaccines, remained favourable in the approved indications(s) and adopted a recommendation to maintain the current terms of the marketing authorisations 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 to 8 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.15. Influenza vaccine – **OPTAFLU** (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 the centrally authorised influenza vaccine Optaflu (surface antigen, inactivated, prepared in cell cultures) remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 8 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.16. Lapatinib – **TYVERB** (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 Tyverb, a centrally authorised medicine containing lapatinib, remained favourable in the approved indication(s). As per agreed criteria, the PRAC adopted without further plenary discussion a recommendation to maintain the current terms of the marketing authorisation together with the assessment report on the PSUR for Tyverb (lapatinib).

As long as the marketing authorisation remains under exceptional circumstances, the frequency of submission of PSURs should remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.17. Maraviroc – CELSENTRI (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 Celsentri, a centrally authorised medicine containing maraviroc, remained favourable in the approved indication(s). As per agreed criteria, the PRAC adopted without further plenary discussion a recommendation to maintain the current terms of the marketing authorisation together with the assessment report on the PSUR for Celsentri (maraviroc).

The frequency of submission of PSURs should be changed from yearly to once every 3 years and the next PSUR should be submitted to the EMA within 90 days of the data lock point.

6.1.18. Mecasermin – INCRELEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Kirsti Villika (FI)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Increlex, a centrally authorised medicine containing mecasermin, remained favourable in the approved indication(s). As per agreed criteria, the PRAC adopted without further plenary discussion a recommendation to maintain the current terms of the marketing authorisation together with the assessment report on the PSUR for Increlex (mecasermin).

The frequency of submission of PSURs should remain yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.19. Moroctocog alfa – REFACTO AF (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Refacto AF, a centrally authorised medicine containing moroctocog alfa, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.20. Nonacog alfa – BENEFIX (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 BeneFIX, a centrally authorised medicine containing nonacog alfa, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.21. Octocog alfa – ADVATE (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 Advate, a centrally authorised medicine containing octacog alfa, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.22. Pandemic influenza vaccine – PUMARIX (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 Pumarix, a centrally authorised medicine containing pandemic influenza vaccine (H5N1) split virion, inactivated, adjuvanted, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 5 monthly to yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.23. Pantoprazole – **CONTROLOC CONTROL** (CAP), **PANTECA CONTROL** (CAP), **PANTOLOC CONTROL** (CAP), **PANTOZOL CONTROL** (CAP), **SOMAC CONTROL** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Controloc Control, Panteca Control, Pantoloc Control, Pantozol Control and Somac Control - centrally authorised medicines-containing pantoprazole - remained favourable in their approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisations 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 once every 3 years and the next PSUR should be submitted to the EMA within 90 days of the data lock point.

6.1.24. Prasugrel – **EFIENT** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Prasugrel is used for the prevention of atherothrombotic events in selected patients with acute coronary syndrome.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Efient, a centrally authorised medicine containing prasugrel, and discussed a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Efient (prasugrel) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- In the next PSURs, the MAH should discuss data examining a previously described non-significant increase in non-benign neoplasms from the TRILOGY-ACS[9] study as soon as they become available. In addition, the MAH should put these data from TRILOGY-ACS in context with findings from the TRITON-TIMI 38[10] study. The PRAC noted that the CHMP had been also evaluating the data from the TRILOGY-ACS study and considered the MAH should also comment on the CHMP outcome in the next PSUR.

[9] A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects With Unstable Angina/Non-ST-Elevation Myocardial Infarction Who Are Medically Managed
[10] Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38

The frequency of submission of PSURs should remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.25. Prifenidone – **ESBRIET** (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 Esbriet, a centrally authorised medicine containing prifenidone, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.26. Rotigotine – **LEGANTO** (CAP), **NEUPRO** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Maria-Alexandra Pego (PT)

Background

Rotigotine is used for the symptomatic treatment of moderate to severe idiopathic restless-legs syndrome in adults and for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease, as monotherapy or in combination with levodopa.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Leganto and Neupro, centrally authorised medicines containing rotigotine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Leganto and Neupro (rotigotine) in the approved indication(s) remains favourable.
- The PRAC recommended that the product information should be updated to add angioedema, tongue oedema and lip oedema as adverse drug reactions with unknown frequency and disorientation as an uncommon adverse reaction. In addition, the PRAC recommended broadening the warning on hallucinations to abnormal thinking and behaviour[11]. Therefore, the current terms of the marketing authorisation should be varied[12].

[11] In SmPC sections 4.4 and 4.8. The package leaflet should be updated accordingly as agreed by the PRAC.
[12] The PRAC Assessment Report and PRAC recommendation have been transmitted to the CHMP for adoption of an opinion.

- In the next PSURs the MAH should continue to monitor all fatal cases as well as the adverse events related to the fatal cases. In addition, the MAH should provide in the next PSUR details relating to several planned, ongoing and finalised studies.

The frequency of submission of PSURs should remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.27. Silodosin – **SILODYX** (CAP), **UROREC** (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 Silodyx and Urorec, centrally authorised medicines containing silodosin, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisations 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

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

- Evaluation of a PSUR procedure

Status: *for discussion*

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Strontium ranelate is used in the treatment of osteoporosis in postmenopausal women and in men.

The PRAC is currently reviewing the benefit-risk balance of Osseor and Protelos (strontium ranelate), centrally authorised medicines, in the framework of a single assessment PSUR procedure due for PRAC recommendation in April 2013.

Summary of conclusions

The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUR procedure. The assessment has identified some risks that potentially impact on the overall benefit-risk balance of the products. In line with GVP module VII on PSURs, an oral explanation will be held at the April 2013 PRAC meeting.

6.1.29. **Ulipristal – ESMYA** (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 Esmya, a centrally authorised medicine containing ulipristal, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.30. **Velaglucerase alfa – VPRIV** (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 Vpriv, a centrally authorised medicine containing velaglucerase alfa, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.31. **Vemurafenib – ZELBORAF** (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 Zelboraf, a centrally authorised medicine containing vemurafenib, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation 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 remain 6 monthly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

6.1.32. Vernakalant – BRINAVESS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Vernakalant is used for the rapid conversion of recent onset atrial fibrillation to sinus rhythm in selected patients. Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brinavess, a centrally authorised medicine containing vernakalant, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Brinavess (vernakalant) in the approved indication(s) remains favourable.
- The PRAC recommended the maintenance of the current terms of the marketing authorisation.
- The MAH should clarify, in the interim results of the ongoing non-interventional registry study to be submitted within the next PSUR, the relative effectiveness of individual risk minimisation activity components.

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.

6.1.33. Zoledronic acid – ZOMETA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Zometa is a centrally authorised medicine containing zoledronic acid (4mg) indicated for the prevention of skeletal related events in patients with advanced malignancies involving bone and for the treatment of tumour-induced hypercalcaemia.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zometa, (zoledronic acid 4mg) and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Zometa (zoledronic acid 4 mg) in the approved indication(s) remains favourable.
- The PRAC recommended that the product information should be updated to reflect interaction with anti-angiogenic medicinal products when used concomitantly. It also recommended reflecting cardiac arrhythmia, seizures, numbness and tetany with a “very rare” frequency as

secondary events related to hypocalcaemia[13]. Therefore, the current terms of the marketing authorisation should be varied[14].

- In the next PSUR the MAH should closely monitor cases of vascular calcification in women under the age of 65 years and should perform a safety review of all cases of hepatobiliary disorders, including any relevant literature cases and scientific publications. In addition, the MAH should provide a cumulative review of all cases of osteonecrosis of the jaw (ONJ) from all available sources. Finally the MAH should consider in the next RMP update whether the current risk minimisation measures are still appropriate and effective to prevent the occurrence or minimise the severity of ONJ (see **Error! Reference source not found.**) and propose any amendments as appropriate.

The frequency of submission of PSURs should remain yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of post-authorisation safety studies

7.1.1. Dapagliflozin – FORXIGA (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Forxiga is a centrally authorised medicine containing dapagliflozin, a sodium-dependent glucose cotransporter (SGLT)-2 inhibitor indicated for the treatment of type 2 diabetes mellitus under certain circumstances.
As part of the RMP for Forxiga (dapagliflozin), the MAH for was required to conduct a PASS in order to analyse the risk of an event (deriving from severe complications to UTI/acute renal failure/acute liver injury/cancer) in patients with type 2 diabetes mellitus starting dapagliflozin compared with those starting other antidiabetic treatments.
The MAH submitted a protocol for a study (as part of the RMP) which was assessed by the Rapporteur. The PRAC was to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PASS protocol was considered satisfactory as regards the objectives, intended population and variables. However certain issues need still to be addressed by the MAH, who should be requested to expand the geographical scope of the study (e.g. include additional databases) and/or extend the observation time in order to gain statistical precision for the study results. Some additional questions to be addressed by the MAH were agreed.
- The MAH should submit a revised protocol within 60 days leading to further PRAC advice to CHMP, as applicable.

[13] In SmPC sections 4.4, 4.5 and 4.8. The package leaflet should be updated accordingly as agreed by the PRAC.
[14] The PRAC Assessment Report and PRAC recommendation have been transmitted to the CHMP for adoption of an opinion.

7.1.2. Ivacaftor – KALYDECO (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: Miguel-Angel Macia (ES)
PRAC Co-Rapporteur: Melinda Palfi (HU)

Background

For background, see minutes of the meeting of PRAC 26-29 November 2013.

The MAH submitted a revised protocol, as recommended by the PRAC, which was assessed by the Rapporteur. Some outstanding amendments and additions to the protocol were identified by the Rapporteur for discussion.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.2, submitted in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product, as the Committee considered that the design of the study did not fulfil the requirements.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 30-day assessment timetable will be applied.

7.1.3. Mifamurtide – MEPACT (CAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Mepact is a centrally authorised medicine containing mifamurtide, indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection.

As part of the RMP for Mepact, the MAH for was required to conduct a PASS in order to provide further data on the various safety issues. Due to slow patient recruitment a proposal to lengthen the study duration was proposed by the MAH. Cumulatively, approximately 1,200 patients have now been treated with mifamurtide. The PRAC was to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- In order to provide detailed argumentation for the slow recruitment of the PASS, the MAH should submit to the EMA a cumulative overview of all currently available retrospective safety data as well as follow-up data of all patients recruited in all studies (including at time of licensing and post-marketing) within 90 days.

- Further PRAC advice to CHMP on the appropriateness of the extended timeline will be provided upon provision of these data, as applicable.

7.1.4. **Tenofovir disoproxil fumarate – VIREAD** (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
The PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment protocol synopses for a PASS of HIV-1 and HBV infected paediatric patients included in the version 14 of the RMP since all comments were addressed in the consultation phase.

7.2. Results of post-authorisation safety studies

7.2.1. **Finasteride** (NAP)

- PRAC consultation on PASS results, upon Member State's request

Regulatory details:

PRAC Rapporteur: n/a advice provided upon MS request

Background

Finasteride is a type II 5α-reductase inhibitor contained in nationally authorised medicines, available in the EU as 1 mg and 5 mg tablets (Propecia and Proscar) for the treatment of male pattern hair loss and benign prostate hyperplasia, respectively.

Following the outcome of a review of data pertaining to the potential risk of male breast cancer performed by the RMS (Sweden), in 2009 the Pharmacovigilance Working Party (PhVWP) concluded a review on the same risk (see EMEA/666243/2009) and the MAH was requested to investigate a possible association.
Information regarding use of finasteride and male breast cancer is included in the current SmPCs and patient leaflets for Propecia and Proscar.

In November 2012, the MAH submitted to the Swedish Medicines Agency (MPA) results from a Nordic register-based cohort study, performed during 1995-2010, which was performed to evaluate the potential association between finasteride use and male breast cancer. This study was assessed by the Swedish Medicines Agency which requested the advice of the PRAC.

Summary of advice

- The PRAC endorsed the overall assessment made by the RMS.
- The MAH should be requested to provide supplementary information to the Swedish Medicines Agency. It was pointed out that, if feasible to undertake, analyses for the different doses (1 and 5 mg, respectively), should be asked for. A justification for excluding data from Norway and Sweden should be provided by the MAH, as these data can provide valuable information. For stage 2 of the study, in addition to analyses of dose and duration, intensity of treatment should also be addressed.

- Further PRAC advice will be provided as applicable upon request of the MSs.

7.2.2. Stavudine – ZERIT (CAP)

- PRAC consultation on results of a Drug Utilisation Study (DUS) included in the pharmacovigilance plan of the RMP in accordance with Article 107m of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Zerit is a centrally authorised medicine containing stavudine, indicated in combination with other antiretroviral medicinal products for the treatment of HIV, when other antiretrovirals cannot be used. The duration of therapy with stavudine should be limited to shortest time possible.

A drug utilisation study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) was requested by the CHMP when restrictions on the use of stavudine were recommended after the renewal procedure concluded in February 2011 (EMEA/H/C/000110/R/0079).

The MAH submitted the results of a study performed on the EuroSIDA, a prospective, observational cohort of 18,295 HIV-1 patients in 105 centres across 31 European countries, Israel and Argentina, and these results were assessed by the Rapporteur. The PRAC was to provide advice to CHMP on the results submitted by the MAH.

Summary of advice/conclusion

- The PRAC noted that stavudine use has decreased significantly over the study period in each region, each HIV-RNA category and CD4 cell count category. However, there remained a proportion of patients in Eastern Europe taking stavudine in June 2011 (3.8% of patients on combination antiretroviral therapy).
- The MAH is requested to submit to the EMA detailed sales data (over time and geographic area) in the next PSUR (to be submitted in June 2014), which may provide an estimation on whether the restricted indication is followed, or if the prescribing pattern is mainly determined by non-medical factors.

8. Renewals of the Marketing Authorisation, Conditional Renewals and Annual Reassessments[15]

8.1.1. Anagrelide – XAGRID (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

[15] Since all comments received on the assessment of some procedures listed under this section of the minutes were addressed before the plenary, the PRAC endorsed the conclusion of the Rapporteurs for these procedures without further discussion at the plenary

Background

Xagrid is a centrally authorised medicine containing anagrelide, an inhibitor of cyclic AMP phosphodiesterase III used for the reduction of elevated platelet counts in selected, at-risk patients with essential thrombocythaemia. The MAH for Xagrid 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 information on the status of the fulfilment of Specific Obligations and safety data submitted, the PRAC considered that the annual re-assessment procedure for Xagrid (anagrelide) could only be finalised at CHMP level if some clarification was provided on the proportion of subjects experiencing pre-defined events in the study SPD422-401 'A non-interventional, post authorisation safety study, to continuously monitor safety and pregnancy outcomes in a cohort of at-risk Essential Thrombocythaemia (ET) subjects exposed to Xagrid compared to other conventional cytoreductive treatments'.

8.1.2. Etravirine – INTELENCE (CAP)

- PRAC consultation on a renewal procedure of the conditional marketing authorisation

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Since all comments received were addressed during the consultation phase, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur that no relevant safety concerns had arisen from the assessment of this renewal procedure of the conditional marketing authorisation. The PRAC recommended the renewal of the conditional Marketing Authorisation.

8.1.3. Everolimus –VOTUBIA (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Since all comments received were addressed during the consultation phase, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur that no relevant safety concerns had arisen from the assessment of this renewal procedure of the marketing authorisation.

8.1.4. Fampridine – FAMPYRA (CAP)

- PRAC consultation on a renewal procedure of the conditional marketing authorisation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Fampyra is a centrally authorised medicine containing fampridine, a potassium channel blocker used in the treatment of multiple sclerosis.

Fampyra was authorised under a conditional marketing authorisation in 2011. A request for 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.

Summary of advice

- Based on the review of the available information on the status of the fulfilment of Specific Obligations and safety data submitted, the PRAC considered that the annual re-assessment procedure for Fampyra (fampridine) could only be finalised at CHMP level if satisfactory clarification is given on some pending issues. These include further information on some aspects of the results of a study of fampridine extended-release tablets in patients with multiple sclerosis; on retention rates of the long-term extension studies; on measurements that can accelerate the generation of the data of the phase III trial as part of the conditional marketing authorisation.

8.1.5. Filgrastim – **BIOGRASTIM** (CAP), **RATIOGRASTIM** (CAP), **TEVAGRASTIM** (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Since all comments were addressed during the consultation phase the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur that no relevant safety concerns had arisen from the assessment of this renewal procedure. The RMP and product information should be updated in line with the current PRAC recommendations and the MAH should submit to the EMA an updated RMP to properly reflect the latest safety information (see 4.3.1.) along with the next PSUR.

8.1.6. Iloprost – **VENTAVIS** (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation (including annual reassessment)

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Ventavis is a centrally authorised medicine containing iloprost, a synthetic prostacyclin (PGI_2) analogue. Ventatis (iloprost) was authorised under exceptional circumstances in 2003. The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC was to provide 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 information the PRAC considered that the renewal procedure (including the annual reassessment) could not yet be finalised, pending the assessment of the Specific Obligation. Further PRAC advice will be provided as applicable.

8.1.7. Lacosamide – VIMPAT (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Vimpat is a centrally authorised medicine containing lacosamide, an antiepileptic used as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in selected patients with epilepsy. Vimpat (lacosamide) was first authorised in 2008.

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 Vimpat (lacosamide), and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this renewal procedure which can be finalised at CHMP level. The RMP should be updated in accordance with the assessment of the Rapporteur (5.2.32.).

8.1.8. Methylnaltrexone Bromide – RELISTOR (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Since all comments received were addressed during the consultation phase, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur that no relevant safety concerns had arisen from the assessment of this renewal procedure of the conditional marketing authorisation.

Apart from minor issues the RMP was considered adequate. An updated version including the requested changes should be submitted with the next PSUR (see 5.2.33.).

8.1.9. Olanzapine – OLANZAPINE MYLAN (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Terhi Lehtinen (FI)

Since all comments received were addressed during the consultation phase, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur that no relevant safety concerns had arisen from the assessment of this renewal procedure of the marketing authorisation.

8.1.10. Rivaroxaban – XARELTO (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Xarelto is a centrally authorised medicine containing rivaroxaban, an antithrombotic agent for the prevention of stroke and systemic embolism in selected patients with non-valvular atrial fibrillation, first authorised in 2008.

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 Xarelto (rivaroxaban), and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this renewal procedure which can be finalised at CHMP level.
- The PRAC considered that a second renewal of the marketing authorisation was required due to the risk of bleeding.

8.1.11. Tadalafil – ADCIRCA (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Background

Adcirca is a centrally authorised medicine containing tadalafil, an inhibitor of phosphodiesterase type 5 (PDE5) used in the treatment of pulmonary arterial hypertension in selected patients (functional class II and III), to improve exercise capacity. Adcirca (tadalafil) was first authorised in 2008.

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 Adcirca (tadalafil), and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this renewal procedure which can be finalised at CHMP level.

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

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. Telaprevir – INCIVO (CAP)

- PRAC consultation on a safety-related type II variation upon CHMP request

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Telaprevir is an antiviral used in the treatment of genotype 1 chronic hepatitis C in selected patients, in combination with peginterferon alfa and ribavirin.

Severe cutaneous adverse reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome (SJS), were recognised as side effects of Incivo (telaprevir) at the time of the marketing authorisation. They were considered in the benefit-risk assessment and appropriate information was included in the product information.

The CHMP is evaluating a type II variation for Incivo (telaprevir) to update the product information to reflect new information following 2 reported cases of toxic epidermal necrolysis (TEN). Following discussion at the PRAC in February 2013, the MAH proposed to issue a DHPC to draw the attention of the treating physicians to the occurrence of these ADRs. Following the advice provided on the same procedure in February 2013, the advice of the PRAC was requested on this variation and on its communication plan and DHPC.

Summary of advice

The PRAC discussed the content of the DHPC and provided some comments. The PRAC will discuss any further necessary risk minimisation in the context of next discussion on the PSUR assessment (DLP 19/9/2013).

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

None

10.3. Other requests

10.3.1. Mipomersen

- PRAC consultation on a re-examination procedure of an initial Marketing Authorisation

Background

On 13 December 2012, the CHMP adopted a negative opinion, recommending the refusal of the marketing authorisation for the Kynamro (mipomersen) (EMEA/H/C/002429), intended for the treatment of patients with certain forms of familial hypercholesterolaemia. The applicant requested a re-examination of the opinion.

Upon CHMP request the PRAC provided advice, relating to risk management aspects, in the context of the re-examination procedure.

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 March 2013 (see EMA Q&A EMA/177547/2013).

See also: dapaglifloxin 7.1.1. ; mifamurtide7.1.3.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Renewals of the Marketing Authorisation

None

11.3. Other requests

See Finasteride 7.2.1.

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. Good Pharmacovigilance Practices (GVP) Module VII Periodic Safety Update Reports

- Revision 1 of GVP Module VII for consultation

This topic was discussed at the organisational matters teleconference of the PRAC on the 22 March 2013. EMA presented Revision 1 of GVP Module VII for consultation. This revision takes into account the finalisation of the ICH-E2C(R2) guideline on "Periodic Benefit-Risk Evaluation Report (PBRER)" and also incorporates some technical aspects on the implementation of the PSUR procedure in the EU. The revised Module will be published on the EMA website for public consultation in the giving months.

12.3.2. Union Reference Date List

- Consultation on the draft List, version March 2013

This topic was discussed at the organisational matters teleconference of the PRAC on the 22nd of March 2013. The CMDh adopted the URD list version March 2013. The substances for which the PSUR single assessment will not start, have now been removed from the list. A revised cover letter will accompany the publication of the revised list to maximise communication with stakeholders.

Post-meeting note: an introductory cover note to the list of European Union reference dates and frequency of submission of periodic safety update reports (EMA/606369/2012 Rev.4) was published on the EMA website together with the revised list on 27 March 2013.

12.4. Signal Management

12.4.1. Signal Management

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

EMA presented a pilot phase for an early exchange of information on signals under evaluation between the Agency the Food and Drug Administration and EMA on centrally authorised medicines. According to the proposal, signals received by each party will be subject to validation and investigation according to the normal procedures in place in each agency.
The PRAC made some suggestions to maximise the exchange of information and supported this proposal in principle. However, the PRAC recommended that additional clarity is needed on the details of the procedure before it can start. Further discussion will take place at the April 2013 meeting.

The PRAC also recommended having an update on the work programme of the SMART group.

12.4.2. PRAC Recommendations for updates of the product information arising from assessment of signals

- Update on current plans for implementation of the recommendations and coordination with CMDh for nationally authorised products

EMA clarified the information flow to facilitate communication between EMA committees and CMDh on the adopted PRAC recommendations. The PRAC recommended improving communication and coordination of activities with the CMDh and advocated enhanced and systematic communication with the object of fostering implementation of the PRAC recommendations for non-centrally authorised medicines in a coordinated and harmonised fashion across the EU. The PRAC underlined the need for increased clarity on the proposed product information wording to be implemented and EMA proposed to explore enhanced communication with the publication of stand-alone documents describing the

product information changes requested for nationally and centrally authorised medicines, that were agreed upon.

The PRAC requested discussion of a proposal to gain further understanding of the planned actions.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Management and Reporting of Adverse Drug Reactions (ADR) to Medicinal Products

- New Legislation: Impact on ADR Reporting

Status: *for information*

L Waldenlind presented an analysis of the impact of the new legislation on spontaneous reporting with specific analysis comparing reports from consumers and healthcare professionals. The PRAC emphasised the value of the analysis performed and proposed to repeat such analysis. Modalities for performing future analyses, any additional aspects to be considered and their timing will be further discussed.

12.5.2. List of Products under Additional Monitoring

- Update on creation and maintenance of the List

This topic was discussed at the organisational matters teleconference of the PRAC on the 22nd of March 2013. EMA informed the PRAC that a list is being compiled with information from all MS and a draft list for agreement and subsequent publication on the EMA website will be discussed at the April 2013 meeting.

12.6. EudraVigilance Database

12.6.1. Other

- 2012 EudraVigilance (human) Annual report

Status: *for information*

EMA presented the main findings and results contained in the draft EudraVigilance annual report. The PRAC made some comments to enhance the presentation of the data in advance of publication. The report will be transmitted to the EMA Management Board for discussion at their March 2013 meeting and then transmitted to the European Parliament, the European Council and the European Commission and will be subsequently published on the EMA website.

12.7. Risk Management Plans and Effectiveness of risk Minimisations

12.7.1. Summaries of RMPs

- Publication process

This topic was discussed at the organisational matters teleconference of the PRAC on the 22nd of March 2013. EMA outlined the process for the publication of the RMPs summaries which is expected to start in 3Q 2013. The format of the summaries will be standardised to facilitate ease of access to information, improved readability and consistency across different medicines. The PRAC supported the initiative.

12.7.2. Timetables for RMP assessment

- Proposal for a revised timetable for RMP assessment in pre-authorisation phase

Status: *for discussion*

A proposal for a revision of the current timetable in use for RMP assessment in pre-authorisation phase was proposed to the PRAC following discussion at the CHMP level, with the aim to facilitate the exchange of information between the two committees. The proposal was further discussed at the organisational matters teleconference of the PRAC on the 22nd of March 2013 following comments received from PRAC members. The PRAC agreed to have further discussions on alternative proposals at the April 2013 meeting. The current timetables will remain in operation.

12.7.3. Templates for CHMP assessment of new MAAs

- Revised template

Status: *for discussion*

A proposal for a revision of the CHMP assessment report template was presented to improve coordination and clarity of roles between PRAC and CHMP in the assessment phase. The change to the CHMP template clarifies and confirms the lead role of the PRAC Rapporteur in the assessment of the RMP. The CHMP AR will highlight relevant issues identified during the assessment of the dossier which, in the view of the CHMP Rapporteurs, should be taken forward in the pharmacovigilance planning by the PRAC.

Regarding the RMP and the pharmacovigilance planning, the role of the CHMP assessment report is to characterize the safety profile of the product, and to provide the basis of the RMP Safety Specifications discussions in the PRAC Rapporteur's assessment report. The PRAC supported the revision. The template will be published on the EMA website.

Post-meeting note: the updated templates were published on the EMA website on 5 March 2013 under:

Home > Regulatory > Human medicines > Pre-authorisation > Templates for assessors

12.7.4. Champions for the review of the process for assessment of the RMPs in the pre-authorisation phase

- Progress report of the activity

Status: *for information*

EMA presented a progress report on the activity of a group of 'champions' chosen from both the PRAC and CHMP who are currently looking at the process for assessment of the RMPs in the pre-authorisation phase.

The PRAC welcomed the initiative and endorsed the preliminary recommendations proposed to improve the efficiency of the review. On the other hand, the PRAC reinforced the importance of the group continuing to work within the agreed mandate in order to maximise the potential of the current framework. In particular, the PRAC expects a further report analysing the impact following the application of the principles for Rapporteruship appointment for centrally authorised products - in terms of new marketing authorisation applications as of July 2012 - described in 'Countdown to July 2012: the establishment and functioning of the PRAC' EMA/315258/2012.

12.8. Post-authorisation Safety Studies

None

12.9. Community Procedures

None

12.10. Risk communication and Transparency

12.10.1. EMA Communication strategies

- EMA communication strategy on the review of combined hormonal contraceptives

Status: *for discussion*

This topic was discussed at the organisational matters teleconference of the PRAC on the 22nd of March 2013. EMA presented the current plans to enhance and maximise the communication of the Agency with all stakeholders at the conclusion of the ongoing referral on combined hormonal contraceptives. The PRAC made suggestions on the overall strategy, its content, intended target audience and mechanisms to monitor the impact of our communication and adapt the strategy as necessary.

It was proposed that a dedicated communications group related to the combined hormonal contraceptives (CCs) and medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms (see 2.2.1.) should be setup. The group would provide strategic input, peer review communications materials and contribute ideas for reaching out to relevant stakeholders. A call for expressions of interest to join this group will be sent to the Pharmacovigilance Risk Assessment Committee (PRAC). A proposal for a mandate of this group will be prepared for the April PRAC meeting.

Once concluded, the communication should aim to support patients and healthcare professional in their treatment choices and effective communications can help in achieving this. In particular the PRAC recommended that the patient representatives and healthcare professionals are fully involved in the development of the strategy. These should include gynaecologists, general practitioners, community pharmacists and patients and consumers who can represent the views of healthy women taking these medicines.

The PRAC requested to have more discussion on communication aspects related to the current review during the next steps of the evaluation phase. EMA will follow-up on this.

12.11. Continuous pharmacovigilance

None

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Blood Products Working Party

- Draft Letter to the Editor of Haemophilia; comment on: P.M. Mannucci. Evaluation of the European Guidelines for the Clinical Development of Factor VIII products: little progress towards improved patient management.

The PRAC noted the draft letter provided as a comment on the article by P.M. Mannucci, who recently criticised that the evolution of European regulatory requirements towards an increasing numbers of patients in relation to its impact on clinical studies and availability of new products, to provide a reply to such concerns.

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. Highly Active Antiretroviral Therapy (HAART)

- Data Collection on Adverse events of Anti-HIV Drugs (D:A:D); regulatory representation in the HAART Oversight Committee

The PRAC confirmed the nomination of Deborah Ashby and Filip Josephson as EMA representatives in the HAART Oversight Committee. The PRAC agreed a response to the HAART Oversight Committee informing them that 'PRAC continues to find the D:A:D study a very valuable resource. It is in this light, and given these considerations, that the PRAC looks forward to a continued fruitful collaboration with the D:A:D study group and the HAART-OC in the years to come.'.

12.14.2. International conference on harmonisation (ICH)

- Revision of ICH E2C (R2)

The revision to ICH E2C has introduced new concepts and principles linked to an evolution of the traditional PSUR from an interval safety report to cumulative benefit-risk report and with a change in focus from individual case reports to more aggregate data evaluation. As the concepts and principles are novel in this context, an Implementation Working Group (IWG) on ICH E2C(R2) is established. A call for volunteers was made to the PRAC. PRAC members were invited to express their interests by 22 March 2013.

13. 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

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 4-7 March 2013 meeting

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
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogne	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	cyproterone, ethinylestradiol, fluoroquinolones, regorafenib, aflibercept, iloprost, rivaroxaban
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Jana Mlada	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:	moroctocog alfa, nonacog alfa, voriconalzole, collagenase clostridium histolyticum
Julia Pallos	Hungary		
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	
Ingebjorg Buajordet	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimaraes	Portugal	Full involvement	
Alexandra Pego	Portugal	Full involvement	
Daniela Pomponiu	Romania	Full involvement	
Tatiana Magalova	Slovakia	Full involvement	
Milena Radoha-	Slovenia	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*
Bergoc			
Miguel-Angel Macia	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Ulla Wandel 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 Evans		Cannot act as Rapporteur or Peer-reviewer for:	pandemic influenza vaccine, lapatinib
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Cannot act as Rapporteur or Peer-reviewer for:	strontium ranelate
Lennart Waldenlind		Full involvement	

Additional European experts participating at the meeting for specific Agenda items	Country	
Cedric Gigot	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Bruno De Schuiteneer	Belgium	
Jamila Hamdani	Belgium	
Arnaud Batz	France	
Anna-Marie Coleman	Ireland	
John J Borg	Malta	
Charlotte Backman	Sweden	
Rolf Gedeborg	Sweden	

Additional European experts participating at the meeting for specific Agenda items	Country
Filip Josephson	Sweden
Hans Sjögren	Sweden
Deborah Ashby	United Kingdom
Alison Cave	United Kingdom

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

European Medicines Agency
Peter Arlett - Head of Sector for Pharmacovigilance and Risk Management
Roberto De Lisa - Scientific Administrator, PRAC Secretariat
Zaide Frias - Section Head, Regulatory Affairs
Georgy Genov – Section Head, Signal Detection and Data Analysis
Ana Hidalgo-Simon – Section Head, Risk Management
Sheila Kennedy – Section Head, Scientific Committee Support
Kasia Kmiecik – Assistant, PRAC Secretariat
Anabela Marcal – Section Head, Community Procedures
Geraldine Portier - Scientific Administrator, PRAC Secretariat
Tanya Sepehr – Assistant, PRAC Secretariat
Noel Wathion – Head of Unit, Patient Health Protection