10 October 2013
EMA/PRAC/586155/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 2-5 September 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)

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The RMP describes what is known and not known about the safety of a medicine and states how the side effects will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects.
RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)
(Item 6 of the PRAC Minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.
PSURs summarise data on the benefits and risks of a medicine and include the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)
(Item 7 of the PRAC Minutes)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk minimisation activities that have been introduced. The results of a PASS help regulatory agencies to further evaluate the safety and benefit-risk profile of a medicine already in use.

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

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

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

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1. Introduction

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

The Chairperson opened the meeting, welcoming all participants to the 2-5 September 2013 meeting of the PRAC.

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

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

1.2. Adoption of agenda of the meeting on 2-5 September 2013

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

1.3. Adoption of minutes of the previous PRAC meeting on 8-11 July 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 8-11 July 2013 EMA/PRAC/509108/2013 were published on 20 September 2013.

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

2.1. Newly triggered procedures

None

2.2. Ongoing Procedures

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

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

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

Background

A referral procedure under Article 107i of Directive 2001/83/EC is ongoing for hydroxyethyl starch, solutions for infusion (see PRAC minutes 8-11 July 2013).

An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s)/conclusions

The Rapporteurs presented the outcome of a preliminary assessment of the data submitted for this procedure. The principal investigator Professor Djillali Annane[1] – who had submitted data relevant to the procedure as a stakeholder – presented the results of the CRYSTAL study ('colloids compared to crystalloids in fluid resuscitation of critically ill patients: a multinational randomised controlled trial') at the meeting. Observers from the US Food and Drug Administration (FDA) and Health Canada were connected via teleconference during the presentation in accordance with current agreements between drug regulatory authorities. Following his presentation, the PRAC agreed some points to be addressed to the investigator to clarify the interpretation of some of the findings.

2.3. Procedures for finalisation

2.3.1. Solutions for parenteral nutrition, combination - NUMETA G13%E and NUMETA G16%E EMULSION FOR INFUSION and associated names (NAP)

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

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)
PRAC Co-Rapporteur: Ulla Wändel Liminga (SE)

Background

A referral procedure under Article 107i of Directive 2001/83/EC for NUMETA G13%E and NUMETA G16%E (see PRAC minutes 10-13 June 2013 meeting for background) is to be concluded. An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs on the risks of hypermagnesaemia related to NUMETA G13%E in preterm newborns. Having considered the reported cases of hypermagnesaemia, available guidelines and relevant literature and considering the magnesium content of Numeta G13%E, the PRAC concluded that the administration of Numeta G13%E could be associated with a risk of hypermagnesaemia. In addition, the PRAC noted that this risk is further increased in premature newborns due to immaturity of the renal system. The PRAC noted the difficulty in identifying clinical signs and symptoms of hypermagnesaemia in this population and agreed that a suspension of the product was recommended until a reformulated presentation is made available.

For NUMETA G16%E - used in full-term newborns and children up to 2 years of age - the PRAC considered that the benefit-risk balance remained positive, provided that the product information is updated to inform healthcare professionals of the potential risk of hypermagnesaemia, which is increased in infants with impaired renal function and those whose mothers were receiving supplemental magnesium before delivery. In addition, the PRAC recommended a study be carried out

[1] See Public declaration of interest Annane 2013-08-20

to further evaluate serum magnesium levels in term newborn infants and children up to two years of age treated with Numeta G16%E in routine clinical practice. The PRAC agreed that a Direct Healthcare Professionals Communication (DHPC) was needed to inform healthcare professionals of the recommended changes to the product information for NUMETA G16%E and of the action taken for NUMETA G13%E.

Summary of recommendation(s)/conclusions

The PRAC adopted by consensus a recommendation for the suspension of the marketing authorisations for NUMETA G13%E and a variation of the Marketing Authorisation for NUMETA G16%E, and adopted a recommendation EMA/531101/2013 to be considered by CMDh for a position. A DHPC and communication plan were also endorsed.

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

3.1. Newly triggered Procedures

3.1.1. **Aceclofenac** (NAP)

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

Regulatory details:

PRAC Rapporteur: N/A
PRAC Co-Rapporteur: N/A

Background

The Spanish Medicines Agency (AEMPS) sent a letter of notification dated 30 August 2013 of a referral under Article 31 of Directive 2001/83/EC for the review of aceclofenac-containing medicines due to the possibility of similar cardiovascular risk to diclofenac.

The notification was circulated following the conclusion reached by the PRAC for diclofenac to consider whether, due to similarities between diclofenac and aceclofenac, the conclusion of the referral should also be applied to aceclofenac.

Summary of recommendation(s)/conclusions

The PRAC noted the notification letter from the Spanish Medicines Agency and noted the data provided in the notification that aceclofenac is both structurally related to diclofenac and undergoes similar metabolism. In-vitro, in-vivo and epidemiological studies (Safety Of non-Steroidal anti-inflammatory drugs (SOS) project) - including a case control study[2] - seemed to confirm the possibility of similar cardiovascular risk with aceclofenac to diclofenac.

At the meeting the PRAC was notified of the intention of the MAH for the innovator of the aceclofenac-containing medicines to submit a variation to update the product information regarding cardiovascular risk, in line with the PRAC recommendations for diclofenac (see PRAC minutes 10-13 June 2013).

[2] Bueno H, Bardají A, Patrignani P, Martín-Merino E, García-Rodríguez LA; Spanish Case-Control Study to Assess NSAID-Associated ACS Risk Investigators. Use of non-steroidal antiinflammatory drugs and type-specific risk of acute coronary syndrome. Bueno H, Bardají A, Patrignani P, Martín-Merino E, García-Rodríguez LA; Spanish Case-Control Study to Assess NSAID-Associated ACS Risk Investigators. Am J Cardiol. 2010 Apr 15;105(8):1102-6. doi: 10.1016/j.amjcard.2009.12.008. Epub 2010 Feb 20.

Therefore Spain concluded that a referral procedure was redundant as the safety concerns were addressed by the variation procedure.

Post-meeting note: a withdrawal of the referral notification letter was received from the Spanish Medicines Agency on 12 September 2013.

3.1.2. **Bromocriptine** (NAP)

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

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

Background

The French Medicines Agency (ANSM) sent a letter of notification dated 17 July 2013 of a referral under Article 31 of Directive 2001/83/EC for the review of bromocriptine-containing medicines indicated for the prevention or suppression of physiological lactation in the immediate and late post-partum period, due to reported cases of very rare but serious cardiovascular, neurological and psychiatric adverse reactions despite the risk minimisation measures implemented since the mid '90s.

Discussion

The PRAC noted the notification letter from the French 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 Sabine Straus (NL) as Rapporteur and Evelyne Falip (FR) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (published on the EMA website EMA/PRAC/493207/2013) and a timetable for the procedure (EMA/PRAC/493206/2013).

3.2. Ongoing Procedures

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

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

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

Background

A referral procedure under Article 20(8) of Regulation (EC) No 726/2004 is ongoing for Protelos and Osseor (strontium ranelate) (see PRAC minutes 8-11 July 2013) and an ad-hoc expert meeting is planned. The Rapporteur produced an assessment report of the data submitted according to the established timelines.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusions reached by the Rapporteurs on the assessment of the data submitted by the MAH. The PRAC discussed a list of outstanding issues including aspects of the benefit-risk balance in osteoporosis patients to be addressed by the MAH in an oral explanation at the PRAC 6-9 January 2014 meeting and a revised timetable for the procedure (EMA/PRAC/283428/2013).

The PRAC also agreed a revised list of experts for the ad-hoc expert meeting to be held on 10 September 2013.

3.2.2. Substances related to nicotinic acid: acipimox (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for acipimox-containing medicines (see PRAC minutes 8-11 July 2013).

Summary of recommendation(s)/conclusions

The PRAC adopted an updated list of experts for the ad-hoc expert meeting to be held on 6 September 2013.

3.3. Procedures for finalisation

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

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for short-acting beta agonists (see minutes of the PRAC 8-11 July 2013 meeting for background) is to be concluded.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs. An oral explanation took place at the meeting. The PRAC discussed the evidence on the risks of adverse reactions – and in particular cardiovascular adverse reactions - associated with the treatment with SABAs in the context of the clinical management of tocolysis. The PRAC agreed that oral and suppository formulations of SABAs (salbutamol, terbutaline, fenoterol, ritodrine, hexoprenaline and isoxsuprine) should not be used in any obstetric indication, since the benefits do not outweigh the risks.

With regard to parenteral formulations of SABAs, the PRAC noted the authorised obstetric indications vary across the EU. Having considered the available data the PRAC concluded that the benefit-risk

balance was favourable for the majority of these indications as the benefits continued to outweigh the risks.

However, for the indications relating to prophylaxis of threatened abortion and the prevention of uterine contractions following surgical procedures, it was considered that in these indications the benefits did not outweigh the risks and therefore the indications should be removed from all parenteral SABA products. For the remaining obstetric indications, in order to help improve safe use, an update of the product information was recommended; the parenteral products should only remain authorised for short-term obstetric use (up to 48 hours) in patients between 22 and 37 weeks of gestation. Patients should be closely monitored for signs of cardiovascular adverse reactions throughout treatment.

The PRAC concluded that there was a need to inform healthcare professionals of the new restrictions on use and monitoring requirements for the parenteral formulations, and the unfavourable benefit-risk balance of the oral and suppository formulations, in obstetric indications.

Summary of recommendation(s) / conclusions

The PRAC adopted by consensus a recommendation for variation of the terms of the marketing authorisations, or revocation - as applicable - for all medicinal products reviewed and adopted a recommendation EMA/533740/2013 to be considered by CMDh for a position. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

3.4. Re-examination procedures

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

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

Regulatory details:

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

Background

A request for a re-examination of the PRAC recommendation on hydroxyethyl starch solutions for infusion provided under Article 31 of Directive 2001/83/EC and grounds for this request had been submitted to the EMA (see minutes of the PRAC 8-11 July 2013 meeting and 'Recommendation to suspend marketing authorisations for hydroxyethyl-starch solutions to be re-examined' EMA/349341/2013 for background).

Summary of recommendation(s) / conclusions

The PRAC noted the published timetable for the re-examination procedure EMA/PRAC/751078/2012 Rev.2. The PRAC discussed and agreed an agenda and a list of questions for the experts for an ad-hoc expert group to be convened on 13 September 2013 in the framework of the re-examination procedure.

Post meeting-note: a final list of experts to participate in the meeting was agreed via written procedure on 12 September 2013.

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

None

3.6. Others

3.6.1. **Dihydrocodeine** (NAP)

- Follow-up of finalised referral for codeine-containing medicines under Article 31 of Directive 2001/83/EC based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: N/A

Background

Spain requested the PRAC to discuss whether the conclusions of the recently concluded referral procedure for codeine (see PRAC minutes 10-13 June 2013) could also be applicable for dihydrocodeine-containing medicines.

Summary of recommendation(s)/conclusions

Spain presented a brief review on dihydrocodeine which concluded that the metabolism of dihydrodeine showed some similarities with the metabolism of codeine. However any evidence of a similar risk profile between these medicines appeared to be limited. Overall, there were very limited data on the correlation between dihydrocodeine and the analgesic effects of its active metabolites.

The PRAC recommended a data-gathering exercise to identify those dihydrocodeine medicinal products approved for the treatment of pain in children in the EU Member States, and their current usage.

It was recommended to consult the Pharmacogenomics Working Party about the risks of opiate toxicity in CYP 2D6 high metabolisers and on the genetic polymorphisms involved in the metabolism of dihydrocodeine. The PRAC also agreed to collect information from EudraVigilance on morphine toxicity in children taking dihydrocodeine.

Further PRAC advice to the EU Member States will be provided once this information is collected. Follow-up discussion will be planned for the next meetings.

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Chloroquine** (NAP); **hydroxychloroquine** (NAP)

- Signal of hypoglycaemia

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

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

Background

Chloroquine and hydroxychloroquine are 4-aminoquinolines used for the treatment of malaria and also for the treatment of rheumatic and dermatological conditions.

The exposure for Plaquenil, a nationally authorised medicine and the originator product for hydroxychloroquine, is estimated to have been more than 400 million days of treatment worldwide, in the period from 2009 to 2012.

During a national PSUR assessment procedure for Plaquenil (hydroxychloroquine) in Ireland, a signal of hypoglycaemia had been reviewed by the Irish Medicines Agency (IMB). Denmark, as responsible Member State for signal monitoring of the substance, confirmed that the signal needed further analysis and prioritisation by the PRAC, as well as for the chemically related substance chloroquine.

Discussion

The PRAC was informed that following evaluation of the PSUR procedure for Plaquenil the product information will be updated to include information on the risk of hypoglycaemia.

The PRAC discussed case reports of hypoglycaemia with hydroxychloroquine and chloroquine from EudraVigilance and the literature, and concluded that based on the described mechanism of action in the literature, in particular in a study by Sharma et al.[4] and Ajani et al.[5], the risk of hypoglycaemia is not restricted to hydroxychloroquine and should be considered a class effect.

Therefore the PRAC agreed that the product information for all approved pharmaceutical agents containing chloroquine or hydroxychloroquine should be updated regarding this signal of hypoglycaemia.

The PRAC appointed Doris Stenver (DK) as Rapporteur for this signal.

Summary of recommendation(s)

- The MAH for chloroquine and hydroxychloroquine–containing medicines should submit to the NCAs of the MS[6], within 60 days, a variation in order to update the product information regarding hypoglycaemia.

For the full PRAC recommendations see EMA/PRAC/550442/2013, published on the EMA website.

4.1.2. Denosumab – PROLIA (CAP), **XGEVA** (CAP)

- Signal of vasculitis

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

[4] Sharma N, Varma S. Unusual life-threatening adverse drug effects with chloroquine in a young girl. J Postgrad Med. 2003;49(2):187
[5] Ajani EO, Salau BA, Fagbohun TR, Ogun AO Combined effect of chloroquine and insulin administration on some biochemical parameters in rats placed on high fat and calcium diet. Afr J Med Med Sci. 2004 Dec;33(4):365-9.
[6] In line with Article 16(3) of Regulation No (EC) 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.

Background

Denosumab is a monoclonal antibody authorised for treatment of osteoporosis and prevention of skeletal-related events in patients with bone metastases from solid tumours.

The exposure for Prolia and Xgeva, centrally authorised medicines containing denosumab, is estimated to have been more than 680,000 patient-years worldwide, in the period from first authorisation in 2010 to 2012.

During routine signal detection activities, a signal of vasculitis was identified by the EMA, based on 33 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 vasculitis and noted that they mainly consisted of cutaneous manifestations. Some cases were confirmed by skin biopsy and a temporal association was apparent in several cases. Therefore the PRAC agreed that the signal needed further investigation.

Summary of recommendation(s)

- The MAH for Prolia/Xgeva (denosumab) should submit to the EMA a cumulative review of the signal of vasculitis within the next PSUR (DLP: 26 September 2013).

4.1.3. Dexmedetomidine – DEXDOR (CAP)

- Signal of infantile apnoeic attack

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Dexmedetomidine is an alpha-2 receptor agonist used for sedation of adult intensive-care unit patients requiring a sedation level not deeper than arousal in response to verbal stimulation.

The exposure for Dexdor, a centrally authorised medicine containing dexmedetomidine, is estimated to have been more than 11,000 patient-years worldwide, in the period from first authorisation in 1999 to 2013.

During routine signal detection activities, a signal of infantile apnoeic attack was identified by the EMA, based on 3 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 reported cases of infantile apnoeic attack and noted that dexmedetomidine is not currently approved for use in children in the EU. However, the product information reports that data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to maintenance doses of 0.2 micrograms/kg/h or less, and that a single case of hypothermic bradycardia in a neonate has been reported in the literature. The PRAC agreed that there was a need to evaluate whether the product information should be updated on the basis of the new information. In particular, the PRAC considered that the potential impact of the route of administration on the plasma levels of dexmedetomidine and differing pharmacokinetic profile in neonates should be clarified. Therefore PRAC agreed to request further information on apnoea and respiratory depression and on

adverse events in general described in the paediatric population, including preterm babies (less than 37 weeks gestation), as well as factors that might account for an increased risk.

Summary of recommendation(s)

- The MAH for Dexdor (dexmedetomidine) should submit to the EMA, within 60 days, a cumulative review of the signal of infantile apnoeic attack.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.4. Fingolimod – GILENYA (CAP)

- Signal of spontaneous abortion and blighted ovum

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

Background

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

The exposure for Gilenya, a centrally authorised medicine containing fingolimod, is estimated to have been more than 70 000 patient-years worldwide from the time of first authorisation in 2011 to 2013, including patients exposed during clinical trials.

During routine signal detection activities, a signal of blighted ovum (early pregnancy failure) was identified by PT, based on 2 cases reported to the national competent authority. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of spontaneous abortion and blighted ovum and noted that reproductive toxicity is listed as an 'important identified risk' in the Risk Management Plan and active contraception is recommended during treatment with fingolimod. A further search for all cases of adverse reactions during pregnancy, puerperium and perinatal conditions with fingolimod detected some additional cases of spontaneous abortion but no common pattern of pregnancy-related adverse reactions could be identified as data on baseline risk of spontaneous abortion in the multiple sclerosis population are not robust and because of the lack of detailed data in the latest PSUR assessed. The PRAC concluded that the risk of reproductive toxicity is currently managed adequately by appropriate information in the product information and RMP. Nevertheless, it should be important to further investigate pregnancy outcomes after exposure to fingolimod.

Summary of recommendation(s)

- The MAH for Gilenya (fingolimod) should assess the signal within the next PSUR (DLP: 31 August 2013).

4.1.5. Interferon beta 1a – AVONEX (CAP), REBIF (CAP) Interferon beta 1b - BETAFERON (CAP), EXTAVIA (CAP)

- Signal of thrombotic microangiopathy (TMA)

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Interferons are a group of endogenous glycoproteins with immunomodulatory, antiviral and antiproliferative properties. Interferons have various indications. Interferon beta is used for the treatment of multiple sclerosis.

The exposure for centrally authorised medicine containing beta interferons, is estimated to have been more than 5 million patient-years worldwide, in the period from first authorisation in 1998 to 2013.

During routine signal detection activities, a signal of TMA was identified by the UK, based on 5 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 reported and noted that the patients had developed renal failure requiring dialysis following exposure to interferon for between 3 and 10 years.

When an expanded search for the signal was performed, including haemolytic-uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and idiopathic thrombocytopenic purpura (ITP), further cases were retrieved. From the reviewed cases to date, it seemed that the condition could progress to organ failure before TMA is diagnosed. A causal relationship with the medicine was also suspected. There were some common features of the cases which suggested that monitoring all patients for early key symptoms could improve early detection of possible TMA so that the drug can be withdrawn and treatment for the TMA initiated. These early symptoms include new onset hypertension, impaired renal function and thrombocytopenia. Therefore the PRAC agreed that the signal should be further investigated and that a cumulative review for all interferon beta products was needed to determine whether the product information should be updated regarding TMA and related risk minimisation measures.

The PRAC appointed Julie Williams (UK) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Betaferon and Extavia (interferon beta 1b) and Rebif (interferon beta 1a), should submit to the EMA, within 60 days, a cumulative review of the signal of TMA, including a proposal for amending the product information.
- The MAH for Avonex (interferon beta 1a) should be requested to perform the same review, as applicable, within a parallel currently ongoing procedure (see 10.3.2.).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.6. **Triamcinolone acetonide** (NAP)

- Signal of postmenopausal haemorrhage

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Triamcinolone acetonide is a synthetic glucocorticoid corticosteroid. Injectable formulations of triamcinolone acetonide are used in the treatment of different conditions where anti-inflammatory action is required.

The exposure for nationally authorised medicines containing triamcinolone acetonide (all formulations) is estimated to have been more than 320 million patients worldwide, in the period from 2009 to 2012.

During routine signal detection activities, a signal of postmenopausal haemorrhage was identified by the Netherlands, based on 9 cases retrieved by the Netherlands Pharmacovigilance Centre Lareb. UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported with triamcinolone acetonide injections and noted that a widened search had also been performed on the WHO database and the Eudravigilance database by NL. Some factors (such as a plausible biological mechanism via a direct effect on the endometrium and lack of previous history of vaginal blood loss prior to the corticosteroid injection in the cases reported) suggested a possible causal association. Therefore the PRAC agreed that the signal warranted further investigation.

The PRAC appointed Julie Williams (UK) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for reference triamcinolone acetonide-nationally authorised medicines (for injection) should submit to the PRAC Rapporteur, within 60 days, a cumulative review of the signal.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.7. Ustekinumab – STELARA (CAP)

- Signal of exfoliative dermatitis

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Ustekinumab is a monoclonal antibody used for treatment of moderate to severe plaque psoriasis and psoriatic arthritis.

The exposure for Stelara, a centrally authorised medicine containing ustekinumab, is estimated to have been more than 155,000 patient-years worldwide, in the period from first authorisation in 2008 to 2012.

During routine signal detection activities, a signal of exfoliative dermatitis was identified by the UK, based on 27 cases (12 cases of exfoliative dermatitis and 15 cases of erythrodermic psoriasis). UK as Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported, which included symptoms of exfoliative dermatitis include erythema, scaling, and pruritis. This clinical presentation is similar to erythrodermic

psoriasis. Exfoliative dermatitis and erythrodermic psoriasis are medical emergencies which can be life threatening, and hospitalisation is often required. Because of the similarity in symptoms, cases of exfoliative and erythrodermic skin reactions in psoriasis patients receiving ustekinumab are reported using both the exfoliative dermatitis and erythrodermic psoriasis terms.

The PRAC considered that an allergic response to ustekinumab could provide a plausible biological mechanism underlying the reaction. However, a potential for confounding by indication (psoriasis) was also recognised in the reported cases. In conclusion the PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

- The MAH for Stelara (ustekinumab) should submit to the EMA, within 60 days, a cumulative review of the signal.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.8. Vemurafenib – ZELBORAF (CAP)

- Signal of renal failure

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

Background

Vemurafenib is a protein kinase inhibitor used as an antineoplastic agent for the treatment of adult patients with BRAF-V600-mutation-positive unresectable or metastatic melanoma.

The exposure for Zelboraf, a centrally authorised medicine containing vemurafenib, is estimated to have been more than 9,500 patients worldwide, in the period from first authorisation in 2011 to 2012.

During routine signal detection activities, a signal of renal failure, including acute renal failure, was identified by the EMA, based on 37 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 reported cases. In some cases information indicating a positive dechallenge and rechallenge was present. The PRAC agreed that there was a need to understand more about this signal, including the basis for any plausible biological mechanism, the role of concomitant medications in the occurrence of dehydration or exacerbation of the renal failure and adherence to recommendations for dose modification provided in the product information.

Summary of recommendation(s)

- The MAH for Zelboraf (vemurafenib) should submit to the EMA a cumulative review of the signal of renal failure within the next PSUR (DLP: 16 August 2013).

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Brentuximab vedotin - ADCETRIS (CAP)

- Signal of pulmonary toxicity

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background & Summary of recommendation(s)

The PRAC agreed via written procedure, on 19 August 2013, a recommendation on the signal of pulmonary toxicity with Adcetris (brentuximab vedotin). The MAH for Adcetris was requested to submit a variation to the EMA to include pulmonary toxicity as warning in the product information as well as an update to the RMP to address this risk.

For the full PRAC recommendations see EMA/PRAC/550442/2013, published on the EMA website.

4.3.2. Nicardipine (NAP)

- Signal of acute pulmonary oedema in off-label use as a tocolytic in pregnancy

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

For background information, see PRAC minutes of 13-16 May 2013.

The MAHs replied to the request for information on the signal of acute pulmonary oedema in off-label use of nicardipine as a tocolytic in pregnancy and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the responses provided by the various MAHs as well as the replies to a NUI request sent to the EU Member States. The PRAC noted that calcium channel blockers were used as tocolytics in the management of threatened preterm delivery and for severe hypertension in pre-eclampsia and noted a WHO Reproductive Health Library commentary[7] relating to this. However, the PRAC noted that the use of nicardipine in pregnancy was currently contraindicated in most EU countries.

The PRAC agreed that the reaction was supported by a plausible biological effect relating to the negative inotropic effect of nicardipine and its effects on vascular permeability, when combined with the haemodynamic changes of pregnancy. The risk of oedema seemed greater in multiple pregnancies and when beta-2 agonists were also used as tocolytic agents. The majority of the reported cases were observed with intravenous formulations of nicardipine. However, the PRAC agreed that there was no specific evidence to support a differential risk between the different routes of administration of nicardipine.

[7] Özmen Ş. Tocolytics for preterm labour: RHL commentary (last revised: 27 January 2006). The WHO Reproductive Health Library; Geneva: World Health Organization

The PRAC confirmed that overall the evidence was suggestive of a causal relationship between the use of nicardipine in tocolysis and pulmonary oedema and therefore agreed that the current product information should be updated to reflect this new information.

Summary of recommendation(s)

- The MAHs for the reference and nationally authorised[8] medicines containing nicardipine should be requested to submit a variation to the NCAs within 60 days to update the product information in order to highlight the risk of acute pulmonary oedema when nicardipine is used in pregnancy as a tocolytic, especially in cases of multiple pregnancies and/or concomitant use of beta-2 agonists[9].
- The MAHs of generic products should then be requested to submit to the EMA or to the national competent authorities of the MSs, as applicable, a variation to align their product information to that of the originator.

For the full PRAC recommendations see EMA/PRAC/550442/2013, published on the EMA website.

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. Balugrastim

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

5.1.2. Bedaquiline

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

5.1.3. Cholic acid

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

5.1.4. Fluticasone, vilanterol

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

5.1.5. Lidocaine, prilocaine

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

[8] 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

[9] Section 4.6 and 4.8 of the Summary of Product Characteristics and package leaflet

5.1.6. Macitentan

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

5.1.7. Masitinib

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

5.1.8. Memantine

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

5.1.9. Tacrolimus

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

5.1.10. Umeclidinium bromide

- 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. Degarelix – FIRMAGON (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Degarelix is a gonadotrophin releasing hormone (GnRH) antagonist used for treatment of adult male patients with advanced hormone-dependent prostate cancer.

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

Summary of advice

- The updated RMP version 12 for Firmagon (degarelix) was considered acceptable.
- The next update of the RMP should take into account some points highlighted by the PRAC including the relevance of addressing glucose intolerance and type 2 diabetes as potential risks.
- The second annual report of the non-interventional study in prostate cancer patients 'CS39 study' was noted; the report did not raise concern since the profile of adverse drug reactions reported were in the range of those expected in the population studied.

5.2.2. Fampridine – FAMPYRA (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background

Fampridine is a potassium channel blocker used for the improvement of walking in adult patients with multiple sclerosis with walking disability.

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

Summary of advice

- The updated RMP version 7 for Fampyra (fampridine) was considered acceptable provided an updated risk management plan including some necessary amendments to the safety specifications and amendments to the PASS protocol of the study LIBERATE (An Observational Study to Collect Information on Safety and to Document the Drug Utilization of Fampyra When Used In Routine Medical Practice) agreed by the PRAC are submitted in September 2013 in parallel to the submission of the fourth PSUR (DLP: 21 July 2013).

RMP in the context of a variation

5.2.3. Bortezomib – VELCADE (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Bortezomib is a proteasome inhibitor, used as antineoplastic agent for the treatment of selected adult patients with multiple myeloma.

The CHMP is evaluating an extension of the therapeutic indication for Velcade, a centrally authorised product containing bortezomib, for the treatment - in combination with doxorubicin or dexamethasone - of patients with relapsed and/or progressive multiple myeloma. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication. In parallel to this extension other variations have been evaluated; the RMP version submitted for this procedure also supports those procedures.

Summary of advice

- The RMP version 25 for Velcade (bortezomib) submitted in the context of the extension of indication variation under evaluation by the CHMP could be considered acceptable provided that it is updated taking into account some additions and clarifications requested by the PRAC with regards to the educational material, which should remind prescribers that the induction therapy includes thalidomide for which a pregnancy prevention plan is in place.
- Cases of progressive multifocal leukoencephalopathy (PML) should be closely monitored and the MAH should discuss the role of the presence of anti- John Cunningham virus (JCV) antibodies as a risk factor for PML and suggest prevention measures.

5.2.4. Dabigatran – PRADAXA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

Dabigatran is an antithrombotic agent used in the prevention of venous thromboembolic events.

The CHMP is evaluating a variation procedure for Pradaxa, a centrally authorised product containing dabigatran, to include treatment of deep vein thrombosis and/or pulmonary embolism. 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 versions 26 and 27 for Pradaxa (dabigatran) in the context of the variation under evaluation by the CHMP were considered acceptable.
- The next update of the RMP should address some points raised by the PRAC regarding clarification to be provided on co-morbidities present in the population studied, prevalence of which should be compared to those in the background population, and clarification on various efficacy outcomes.

5.2.5. Pramipexole – OPRYMEA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

Pramipexole is a dopamine agonist used for treatment of the signs and symptoms of idiopathic Parkinson's disease in selected patients.

The CHMP is evaluating an extension of the therapeutic indication for Oprymea, a centrally authorised product containing pramipexole, to include prolonged-release tablets as a new pharmaceutical form. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation for a line extension.

Summary of advice

- The updated RMP version 1.1 for Oprymea (pramipexole) in the context of variation for a line extension under evaluation by the CHMP was considered acceptable.

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

See human fibrogen, human thrombin (EVICEL), pneumococcal polysaccharide conjugate vaccine (SYNFLORIX) under section 8 or 17 as applicable.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[10]

6.1.1. Aclidinium bromide – **BRETARIS GENUAIR** (CAP), **EKLIRA GENUAIR** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Aclidinium bromide is an anticholinergic indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bretaris Genuair and Eklira Genuair, centrally authorised medicines containing aclidinium bromide, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bretaris Genuair and Eklira Genuair (aclidinium bromide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to improve and clarify instructions on how to administer the medicinal product correctly. Therefore the current terms of the marketing authorisation(s) should be varied[11].
- In addition, the MAH should submit to EMA within 60 days an analysis of any further cases reported since the data lock point (DLP: 20 January 2013) of the assessed PSUR which may relate to patients having difficulty with using the Genuair device. Depending on the number and nature of such cases, the MAH should consider the need to further update and simplify the instructions for use in the product information and to implement educational materials as an additional risk minimisation measure in an updated RMP.
- In the next PSUR, the MAH should provide further information, in particular a cumulative review of cases of rash, pruritus, and hypersensitivity. In addition, the MAH should include in the RMP these undesirable effects as important potential risks.

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

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

- Evaluation of a PSUR procedure

[10] Where a regulatory action is recommended (variation, suspension or revocation of the terms of Marketing Authorisation(s)), the assessment report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion. Where PRAC recommends the maintenance of the terms of the marketing authorisation(s), the procedure finishes at the PRAC level.
[11] Update of SmPC section 4.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

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

Background

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist indicated for the treatment of major depressive episodes in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Thymanax and Valdoxan, centrally authorised medicines containing agomelatine, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Thymanax and Valdoxan (agomelatine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new contraindication for patients whose serum transaminase levels are raised to over three times the upper limit of normal and to add to the posology a statement that agomelatine should not be used in patients aged 75 years old and over due to the lack of documented effects in this age group. In addition, the product information should be amended to reinforce the undesirable effects section and warnings relating to cases of liver injury, to reflect the occurrence of cases of hepatic failure leading to liver transplantation or fatal outcome in patients with hepatic risk factors. Finally, restless leg syndrome and tinnitus, both with an uncommon frequency, should be reflected in the product information. Therefore the current terms of the marketing authorisation(s) should be varied[12].
- The dissemination of a Direct Healthcare Professional Communication (DHPC) was recommended as a risk minimisation measure. The purpose of the DHPC is to inform prescribers that agomelatine is now contraindicated where transaminases exceed 3 times the upper limit of normal and remind about efforts to be taken to minimise the risk of serious hepatic adverse drug reactions. The content of the DHPC and draft communication plan were endorsed by the PRAC by written procedure.
- In the next PSUR, the MAH should closely monitor several adverse drug reactions and provide additional information, in particular an analysis of whether liver function tests have been performed in line with the product information.

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

6.1.3. Alitretinoin – PANRETIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

[12] Update of SmPC sections 4.2, 4.3, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion. The DHPC was also transmitted to CHMP for agreement.

Background

Alitretinoin gel is an antineoplastic agent indicated for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (KS) under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Panretin (alitretinoin gel) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In future submissions, the MAH should confirm its processes for reviewing literature and provide a summary audit of the literature searches and reviews undertaken.

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

6.1.4. Anidulafungin – ECALTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background

Anidulafungin is an antimycotic for systemic use indicated for the treatment of invasive candidiasis in adult non-neutropenic patients.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ecalta (anidulafungin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 60 days a comprehensive cumulative analysis of all cases suggesting cardiotoxicity following administration of anidulafungin, including literature data and post-marketing reports, with particular emphasis on non-confounded cases and adverse events not currently listed in the product information.

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

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 indicated for 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 issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Edarbi and Ipreziv (azilsartan medoxomil) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add angioedema as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAH should closely monitor cases indicative of severe or acute renal impairment, taking into account any effects of long-term exposure to azilsartan medoxomil.

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

6.1.6. Caspofungin – CANCIDAS (CAP)

- Evaluation of a PSUR procedure

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

Background

Caspofungin is an antimycotic for systemic use indicated for the treatment of invasive candidiasis and for the treatment of invasive candidiasis under certain conditions. Caspofungin is also used as an empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropenic adult or paediatric patients.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Cancidas (caspofungin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 60 days a comprehensive cumulative analysis of all cases suggesting cardiotoxicity following administration of caspofungin, including literature data and post-marketing reports, with particular emphasis on non-confounded cases and adverse events not currently listed in the product information.

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

6.1.7. Degarelix – FIRMAGON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Degarelix is a gonadotrophin releasing hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Firmagon (degarelix) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning highlighting that cardiovascular disease such as stroke and myocardial infarction has been reported in the medical literature in patients receiving androgen deprivation therapy and recommending prescribers to take into account all cardiovascular risk factors when prescribing Degarelix. Therefore the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should closely monitor several undesirable effects, in particular cases of cardiovascular disease for which the MAH should provide an analysis, including cases of stroke and myocardial infarction and an estimation of the frequency, allowing for a potential update of the product information.

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

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

6.1.8. Dronedarone – **MULTAQ** (CAP)

- Evaluation of a PSUR procedure

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

Background

Dronedarone is an antiarrhythmic indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF) under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Multaq (dronedarone) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the existing warning related to renal failure by recommending regular monitoring of renal function and further investigations as needed. In the case of increased blood urea nitrogen, dronedarone treatment should be stopped. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- The MAH should also ensure a consistent approach in the reflection of drug-drug interactions and assess if those should be reclassified as identified risks in the next update of the RMP.

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

6.1.9. Filgrastim – **FILGRASTIM HEXAL** (CAP), **ZARZIO** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Filgrastim is a granulocyte colony-stimulating factor analogue indicated for the reduction of the duration of neutropenia under certain conditions, as well as for mobilising peripheral-blood progenitor cells (PBPC). In addition, filgrastim is indicated in patients with severe congenital, cyclic or idiopathic neutropenia under certain conditions, and in the treatment of persistent neutropenia in patients with advanced HIV infection.

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Filgrastim Hexal and Zarzio, centrally authorised medicines containing filgrastim, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Filgrastim Hexal and Zarzio (filgrastim) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- Further review of the signal of venous thromboembolism (VTE) in patients and healthy volunteers exposed to G-CSF therapy is needed. Therefore, the MAH should submit to EMA within 90 days a cumulative review of all available evidence from all sources, stratified by type of cancer or healthy donor status, and analyse whether this is product-specific or not. The MAH should also discuss the need to include VTE as an important potential risk in the RMP.
- Given that a causal association between the risk of extramedullary haematopoiesis (EMH) and filgrastim treatment cannot be excluded, the MAH should also include EMH as an important potential risk in the RMP. The MAH should propose pharmacovigilance activities as appropriate.

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

6.1.10. Ivacaftor – KALYDECO (CAP)

- Evaluation of a PSUR procedure

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

Background

Ivacaftor is a selective potentiator of the CFTR protein indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Kalydeco (ivacaftor) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the information provided under 'undesirable effects' for the adverse drug reactions rash, headache and dizziness following the reporting of some serious cases. Therefore the current terms of the marketing authorisation(s) should be varied[16].

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

- In the next PSUR, the MAH should provide further information, including data on the outcome of ongoing pregnancies at the time of treatment with ivacaftor, and an analysis of the cases of hepatic disorders considering the medical history. The MAH should also provide an analysis of the cases of increased transaminases (twice the upper limit of normal), considering the time to onset, medical history and Hy's Law. Finally the MAH should further discuss the results of study 105 related to the concern about pulmonary exacerbation of cystic fibrosis after long term treatment.

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

6.1.11. Lenalidomide – REVLIMID (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Lenalidomide is an anti-neoplastic, anti-angiogenic, pro-erythropoietic and immunomodulatory drug indicated for the treatment of multiple myeloma under certain conditions and for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Revlimid (lenalidomide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add rhabdomyolysis as an undesirable effect with a rare frequency and to reflect that there is an increased risk of rhabdomyolysis when statins are combined with lenalidomide. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should provide further information, in particular a cumulative review of cases of immune thrombocytopenia and updated reviews on optic nerve disorders and on posterior reversible encephalopathy syndrome (PRES).

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

6.1.12. Nilotinib – TASIGNA (CAP)

- Evaluation of a PSUR procedure

[17] Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

Nilotinib is a protein kinase inhibitor indicated for the treatment of newly diagnosed Philadelphia-chromosome-positive CML in the chronic phase; chronic phase and accelerated phase Philadelphia-chromosome-positive CML with resistance or intolerance to prior therapy including imatinib.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Tasigna (nilotinib) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA no later than January 2014 a variation to introduce the risk of fluid retention as a warning in the product information. In addition, the MAH should conduct a review of cardiovascular events, including peripheral arterial occlusive disease (PAOD), integrating additional data from several recently completed studies. The product information should be updated accordingly. Moreover, the MAH should review whether the preclinical data on endothelial function and clinical data on increased risk of PAOD in nilotinib-treated patients compared to patients treated with other kinase inhibitors for the same indication warrants further updates of the product indication.
- In the next PSUR, the MAH should review the publication by *Kim et al.*[18] where hepatitis reactivation was reported in nilotinib-treated patients as well as the publication by *Shoukier et al.*[19] indicating an increased risk of pancreatitis potentially linked to an interaction between nilotinib and hydrochlorothiazide. The MAH should also present a cumulative review of both fluid retention and cardiovascular events.

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

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

Background

The combination nomegestrol/estradiol is used as a combined oral contraceptive.

[18] Kim S-H, Kim, HJ, Kwak J-Y. Hepatitis B virus reactivation in chronic myeloid leukemia treated with various tyrosine kinase inhibitors: Multicenter, retrospective study. 2012. Blood; 120 (21)
[19] Shoukier M, Kantarjian HM, Jabbour E et al. Clinical or subclinical pancreatitis associated with nilotinib as frontline for chronic myelogenous leukemia. Blood. 2011; 118 (21); 4443

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ioa and Zoely, centrally authorised medicines containing nomegestrol and estradiol, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ioa and Zoely (nomegestrol/estradiol) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should start the venous thromboembolism (VTE) characterisation PASS study in an expedited fashion. In the next PSUR, the MAH should provide further information, in particular, a discussion on the feasibility of setting up a retrospective cohort study using large national databases, in order to approximate the VTE risk awaiting for the PASS study results.

In view of the ongoing referral procedure under Article 31 of Directive No 2001/83/EC for combined hormonal contraceptives (EMEA/H/A-31/1356) and the concern of VTE, and due to the fact that the PASS exploring the risk of VTE and arterial thromboembolism (ATE) has not yet started (see PRAC Minutes July 2013, protocol under discussion), the PSUR submission frequency should be amended and return on a 6-monthly basis. In accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, the EURD list should be updated to reflect that the frequency of submission of PSURs should be changed from 3-yearly to 6-monthly. In order to avoid any gap in PSUR submission, an ad-hoc PSUR, covering the period from 27 January 2013 to 26 July 2013, is required no later than 27 October 2013.

6.1.14. Pegfilgrastim – NEULASTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Pegfilgrastim is a granulocyte colony stimulating factor (G-CSF) indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

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

Summary of recommendation(s) and conclusions

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

- Nevertheless, the product information should be updated to add a statement on the traceability of pegfilgrastim in line with other G-CSF products. Therefore the current terms of the marketing authorisation(s) should be varied[20].
- In addition, the MAH should submit to EMA within 90 days a cumulative review of cases of venous thromboembolism (VTE) and available evidence from all sources stratified by type of cancer or healthy donor status and analyse whether this is product-specific or not. The MAH should also discuss the need to include VTE as an important potential risk in the RMP.
- In the next PSUR, the MAH should provide further information, in particular, a review of the cases of palmar-plantar erythrodysesthesia and of blast cells and an estimate of the extent of off-label use.

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

6.1.15. Perampanel – FYCOMPA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Perampanel is an antiepileptic indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Fycompa (perampanel) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to strengthen the current warning on aggression. Therefore the current terms of the marketing authorisation should be varied[21].

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

6.1.16. Perflutren – OPTISON (CAP)

- Evaluation of a PSUR procedure

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

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

Background

Perflutren is a transpulmonary echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers, enhance left ventricular endocardial border delineation with resulting improvement in wall motion visualisation.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Optison (perflutren) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should consider updating the product information to reflect the results of the Optison pulmonary hemodynamic study, once further evidence is gathered.

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

6.1.17. Pioglitazone – ACTOS (CAP), **GLUSTIN** (CAP)
Pioglitazone, **glimepiride – TANDEMACT** (CAP)
Pioglitazone, **metformin – COMPETACT** (CAP), **GLUBRAVA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Background

Pioglitazone and its combinations are indicated for the treatment of type 2 diabetes mellitus under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Actos, Competact, Glubrava, Glustin and Tandemact, centrally authorised medicines containing pioglitazone, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Actos, Competact, Glubrava, Glustin and Tandemact (pioglitazone and combinations) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to further expand the information in undesirable effects section on the risk of heart failure with pioglitazone particularly in patients receiving concomitant insulin and in patients aged 65 years or above compared with those less than 65 years. Information should also be added to the product information on post-marketing cases of peripheral oedema and cardiac failure in patients treated concomitantly with pioglitazone and nonsteroidal anti-inflammatory drugs. The product information should also be updated to highlight that epidemiological studies have suggested a similarly increased risk of

fracture in both men and women. Therefore the current terms of the marketing authorisation should be varied[22].

- In the next PSUR, the MAH should provide further information, in particular, a review of cases of atrial fibrillation and cases of non-bladder urological tumours. Cases of blood dyscrasias should also be closely monitored.
- Finally, the MAH should address within the next RMP update, the safety concern of bone fractures taking into account the observational data indicating an increased risk in both men and women. In view of the timing of previous Drug Utilisation Studies (close to the implementation of additional risk minimisation measures) and their consequentially inconclusive findings, the MAH should make further proposals to evaluate the effectiveness of risk minimisation measures to address the identified risk of bladder cancer.

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

6.1.18. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) – PREVENAR 13 (CAP)

- Evaluation of a PSUR procedure

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

Background

Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) is indicated for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prevenar 13, a centrally authorised medicine containing pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed), and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Prevenar 13 (pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to reflect an increased risk of convulsions (with or without fever) and hypotonic hyporesponsive episodes as a warning and undesirable effects when Prevenar 13 is given with Infanrix Hexa (diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type b conjugate vaccine (adsorbed)). Therefore the current terms of the marketing authorisation(s) should be varied[23].

[22] The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.
[23] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

- In the next PSUR, the MAH should provide further information, in particular a cumulative review of cases of empyema, with microbiological data when available, and clarify the classification of wheezing diagnoses and lack of effectiveness as potential risks rather than missing information.

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

Since the identified safety information and corresponding product information changes are relevant to Infanrix Hexa, the PRAC recommended that the MAH for Infanrix Hexa is requested to assess the impact and submit a variation to EMA within 60 days to update its product information accordingly.

6.1.19. **Pregabalin – LYRICA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background

Pregabalin is an antiepileptic indicated for the treatment of peripheral and central neuropathic pain and generalised anxiety disorder (GAD) as well as an adjunctive therapy in adults with partial seizures with or without secondary generalisation under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Lyrica (pregabalin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 60 days a cumulative review on abuse, misuse and dependence, providing data in absolute numbers and in relation to usage, considering all relevant data sources, including literature. In addition, the MAH should make a distinction between abuse/misuse and drug dependence by providing the data separately. In the light of this review, the MAH should consider updating the product information, including the package leaflet, relating to abuse, misuse and dependence.
- In addition, the MAH should submit to EMA within 60 days a detailed review of cases of weight increase, evaluating the reasons and discussing the potential need to amend the frequency of weight increase in the product information.

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

6.1.20. **Pyronaridine**, **artesunate – PYRAMAX** (Art 58)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Pyronaridine/artesunate is indicated in the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in adults and children weighing 20 kg or more, in areas of low transmission with evidence of artemisinin resistance.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Pyramax, taking into account the scientific opinion on medicines containing pyronaridine/artesunate, and issued a recommendation on the CHMP's scientific opinion(s)[24].

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Pyramax (pyronaridine/artesunate) in the approved indication(s) remains favourable.
- The current terms of the scientific opinion should be maintained.
- Nevertheless, the Scientific Opinion Holder (SOH) should submit to EMA within 60 days a variation to reflect in the product information under 'other specific populations' the higher risk of hepatic disorders in Caucasians. The RMP should also be updated accordingly to reflect this as an important identified risk.
- In the next PSUR, and pending the submission of the interim results of study SP-C-13-11, the SOH should provide further information on cases of hepatotoxicity, particularly the number of excluded subjects due to increased transaminases (5 times the upper limit of normal) or Hy's law criteria, specifying the period between redosing. The SOH should also discussed cases of worsening of hepatic ADRs in patients who have reported transaminases values or Hy's law criteria and the delay for transaminases normalisation.

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.

6.1.21. Ranolazine – RANEXA (CAP)

- Evaluation of a PSUR procedure

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

Background

Ranolazine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies (such as beta-blockers and/or calcium antagonists).

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ranexa (ranolazine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add muscular weakness as an undesirable effect with a frequency of uncommon. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should provide further information, in particular, an updated cumulative analysis of cases of hyponatraemia and inappropriate antidiuretic hormone secretion (SIADH).

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

6.1.22. Rasagiline – AZILECT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Maria Alexandra Pêgo (PT)

Background

Rasagiline is a selective irreversible MAO-B inhibitor indicated for the treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end-of-dose fluctuations.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Azilect (rasagiline) in the approved indication remains favourable.
- Nevertheless, the product information should be updated to include information on the risk of impulse control disorders as a warning and an undesirable effect, to add a warning relating to hypotensive effects as well as exacerbated dopaminergic side effects, and worsening of pre-existing dyskinesia when rasagiline is used in combination with levodopa. Therefore the current terms of the marketing authorisation should be varied[26].
- In the next PSUR, the MAH should provide further information, in particular, an analysis of cases of decreased blood pressure when rasagiline is taken concomitantly with levodopa.

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

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

6.1.23. Ruxolitinib – JAKAVI (CAP)

- Evaluation of a PSUR procedure

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

Background

Ruxolitinib is a protein kinase inhibitor indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis) or myelofibrosis following polycythaemia vera or essential thrombocythaemia.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Jakavi (ruxolitinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include as a warning and undesirable effect the reported cases of tuberculosis, and to provide recommendations to evaluate patients for active and inactive tuberculosis before starting treatment. Therefore the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should include a cumulative review of sepsis / septic shock and pneumonia. Furthermore, the MAH should provide a description of suspected microorganisms across the range of reported infections and discuss any observed pattern. Changes to the product information should be considered as warranted.

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

6.1.24. Silodosin – SILODYX (CAP), UROREC (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Silodosin is an alpha-adrenoreceptor antagonist indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Silodyx and Urorec, centrally authorised medicines containing silodosin, and issued a recommendation on their marketing authorisation(s).

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

Summary of recommendations and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Silodyx and Urorec (silodosin) in the approved indication remains favourable.
- Nevertheless, the product information should be updated to reflect the reported occurrence of facial swelling, swollen tongue and pharyngeal oedema as undesirable effects with a very rare frequency. In addition, hypotension and loss of consciousness should be listed as undesirable effects with an uncommon and a rare frequency respectively. Therefore the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide further information, in particular an analysis of cases of dysuria, urinary incontinence and urinary retention, as well as a review of cases of arrhythmia, somnolence, increased lacrimation, blurred vision and ejaculation disorder and should consider whether an update to product information is warranted.

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

6.1.25. Sugammadex – BRIDION (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Background

Sugammadex is a selective relaxant-binding agent used for the reversal of neuromuscular blockade induced by rocuronium or vecuronium under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bridion (sugammadex) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 60 days a cumulative review of hypersensitivity-related reactions and discuss whether existing risk management measures are sufficient or further actions are warranted.

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

[28] The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

6.2. Follow-up to PSUR procedures[29]

6.2.1. Adefovir dipivoxil – HEPSERA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

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

Summary of recommendation(s) and conclusions

- The MAH for Hepsera (adefovir dipivoxil) should submit to EMA within 60 days a variation to reflect in the product information the available data suggesting a possible progressive alteration of renal function in patients receiving long–term adefovir dipivoxil therapy. Serum phosphate should be monitored as part of the monitoring of renal function. As part of this variation, the MAH should include a discussion on the relevance of monitoring alkaline phosphatase in clinical practice.
- In the next PSUR, the MAH should closely monitor cases of severe cutaneous reactions.

6.2.2. Interferon beta-1a – AVONEX (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

Background

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

Summary of recommendation(s) and conclusions

- The MAH for Avonex (interferon beta-1a) should submit to EMA within 60 days a variation to include in the product information a warning regarding the risk of collapsing focal segmental glomerulosclerosis during interferon-beta treatment and reflect this as an undesirable effect. As part of this variation, the MAH should include an additional cumulative review of all cases of nephrotic syndrome associated with interferon beta-1a and consider further amendment to the product information if warranted.
- The MAH is requested to submit to EMA within 60 days a comprehensive review of the published literature on all thrombocytopenia-related disorders.

See also under 10.3.2.

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

6.2.3. **Lopinavir**, **ritonavir – ALUVIA** (Art 58), **KALETRA** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Following the evaluation of the most recently submitted PSUR-related discussion for the above mentioned medicine, the PRAC requested the MAH/Scientific Opinion Holder (SOH) to submit further data (see PRAC Minutes April 2013). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of recommendation(s)/conclusions

- In order to support the fact, that the analysis of the fatal reports did not identify any new signal, the MAH/SOH for Kaletra, Aluvia (lopinavir/ritonavir) should submit to EMA within 60 days further information on all cases reporting a fatal outcome (including the cause of death), including cases from the literature, clinical studies and solicited reports serious suspected adverse drug reaction.

6.2.4. **Ribavirin – REBETOL** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

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

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

Summary of recommendation(s)/conclusions

- In the next PSUR, the MAH for Rebetol (ribavirin) should closely monitor any suspected cases of mitochondrial toxicity.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[30]

7.1.1. **Glycopyrronium bromide – ENUREV BREEZHALER** (CAP), **SEEBRI BREEZHALER** (CAP), **TOVANOR BREEZHALER** (CAP)

- Evaluation of an imposed PASS protocol

[30] In accordance with Article 107n of Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Background

Enurev Breezhaler, Tovanor Breezhaler and Seebri Breezhaler are centrally authorised medicines containing glycopyrronium bromide, indicated for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). As a condition of the marketing authorisations the MAH was recommended to perform a PASS study on cardiovascular and cerebrovascular outcomes compared to patients using long-acting muscarinic antagonists (LAMAs) or long acting beta-2 agonists (LABAs). A protocol for such study was discussed at the PRAC April 2013 meeting. The Rapporteur assessed a revised protocol provided in response to the previous PRAC recommendations.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.10 considered that some clarifications on the analysis to be performed needed to be provided. Therefore in accordance with Article 107n of Directive 2001/83/EC, a letter of objection was agreed and the MAH should submit a revised PASS protocol within 15 days to the EMA. A 15 day-assessment timetable will be applied.

7.1.2. Lenalidomide – **REVLIMID** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Revlimid is a centrally authorised medicine containing lenalidomide. It is indicated for treatment of multiple myeloma or myelodysplastic syndromes in selected patients.

A non-interventional PASS was requested as a condition of the MAH. A protocol for a non-interventional PASS to gather safety data on patients with myelodysplastic syndromes treated with lenalidomide and to monitor off-label use submitted by the MAH was assessed by the Rapporteur[31].

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.0 agreed that the design of the study did not fulfil the study objectives. Furthermore, the PRAC discussed the collection of data and agreed that a disease registry collecting data about real world use of Revlimid and other therapies in patients with myelodysplastic syndromes would be of greater value than a product specific registry. The reasons include allowing continued data collection in patients who switch between treatments, assessment of comparative safety and evaluation of long-term safety in a more complete way. Therefore, some amendments were proposed and in accordance with Article 107n of Directive 2001/83/EC, a letter of objection was agreed. The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 day-assessment timetable will be applied.

[31] The protocol was brought for discussion for the September 2013 meeting following comments received in the consultation phase that needed to be addressed at plenary level

7.1.3. Rivaroxaban – XARELTO (CAP)

- Evaluation of an imposed PASS protocol

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

Background

Xarelto, a centrally authorised medicine containing rivaroxaban, is indicated with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

A protocol for a PASS to be performed with rivaroxaban – 'XAMACS: Non-interventional study of bleeding events with Xarelto used in combination with antiplatelet therapy or dual antiplatelet therapy for secondary prevention of major cardiovascular events in patients after acute coronary syndrome (ACS) with elevated biomarkers' – was presented for review by the PRAC.

Endorsement/Refusal of the protocol

The PRAC agreed that some aspects of the proposed protocol needed to be further clarified. These include measures to minimise confounding by indication. Furthermore some aspects should be simplified with the aim of reinforcing the observational nature of the study. Therefore, in accordance with Article 107n of Directive 2001/83/EC, having considered the draft protocol version 1.0, a letter of objection was agreed. The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 day-assessment timetable will be applied.

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

See ANNEX I as applicable

7.3. Results of PASS imposed in the marketing authorisation(s)[33]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)34

None

7.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS[35]

7.5.1. Fentanyl – INSTANYL (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

[32] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004
[33] In accordance with Article 107p-q of Directive 2001/83/EC
[34] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013
[35] In line with the revised variations regulation for any submission before 4 August 2013

Background

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

As part of the RMP for Instanyl, the MAH was required to conduct a drug utilisation study (Record Linkage Instanyl Use [LINUS] study) to investigate the prescribing and use of Instanyl in the target population and more specifically to clarify and estimate any degree of off-label use. As anticipated at the PRAC July 2013 meeting, the MAH submitted the final study report which was assessed by the Rapporteur. The PRAC is to provide advice to CHMP following assessment of these results.

Summary of advice

The results of the LINUS study appeared to be in line with data from the PIUS study and highlighted a prevalence of Instanyl (fentanyl) use in the absence of a record of cancer diagnosis or maintenance opioid therapy, in the European countries where the study was conducted. However, the PRAC noted that indicators used to analyse this usage appeared to be variable depending on the characteristics of the sources data and their intrinsic characteristics.

However, they are consistent with those of previous studies in favour of a high prevalence of off label use in no diagnose cancer patients or no opiod maintenance treatments. The MAH is requested to consider the impact of risk minimisation measures recently implemented and the need for further ones to minimise any risk of abuse, misuse and diversion. This risk will be further investigated in the PSUR currently under assessment by the Rapporteur (DLP: 30 April 2013).

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

8.1.1. Amifampridine – FIRDAPSE (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

As part of the ongoing annual reassessment procedure, the PRAC provided advice to the CHMP on this procedure with regard to safety and risk management aspects (see PRAC Minutes May 2013). The MAH's responses relating to the PRAC advice were assessed by the Rapporteur for further PRAC advice.

Summary of advice

Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, and the assessment of the MAH's responses to the CHMP's request for supplementary information specific to the PRAC advice, the PRAC considered that the annual re-assessment procedure for Firdapse could only be finalised if satisfactory clarification is given on some pending issues. This includes questions relating to the provision of an update on the progression of the QT study. Further PRAC advice will be provided as applicable.

8.1.2. Human fibrogen, human thrombin – EVICEL (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

Background

The combination human fibrogen/human thrombin is a local haemostatic used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis and also indicated as suture support for haemostasis in vascular surgery and for suture line sealing in dura mater closure.

Evicel, a centrally authorised medicine containing human fibrogen/human thrombin, was 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 procedure with regard to safety and risk management aspects.

Summary of advice

Based on the review of the risk management system for Evicel, and the CHMP Rapporteur's assessment report, the PRAC considered that this first five-year renewal procedure could be concluded provided satisfactory responses relating to a deficiency in the presentation of RMP version 10 are provided, in line with the EC decision of 13 February 2013 for the Article 20 of Regulation (EC) No 726/2004.

8.1.3. Pneumococcal polysaccharide conjugate vaccine – SYNFLORIX (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

Background

Pneumococcal polysaccharide conjugate vaccine is used for active immunisation against invasive disease and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 5 years of age under certain conditions.

Synflorix, a centrally authorised pneumococcal polysaccharide conjugate vaccine, was authorised in 2009.

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

Summary of advice

Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, the PRAC considered that the renewal for Synflorix could only be finalised if satisfactory clarification is given on some pending issues.

Based on the review of the risk management system for Synflorix, ,and the CHMP Rapporteur's assessment report, the PRAC considered that an additional renewal after five years should be required based on the pharmacovigilance grounds, mainly relating to serotype replacement. The PRAC endorsed the conclusions of the Rapporteur on the assessment of the RMP version 6.0 and considered that the

renewal procedure could be finalised if satisfactory clarification is given on some pending issues relating to the RMP.

9. Product related pharmacovigilance inspections

None

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. **Cetuximab – ERBITUX** (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Erbitux is a centrally authorised medicine containing cetuximab, a chimeric monoclonal immunoglobulin G1 (IgG1) antibody directed against the epidermal growth factor receptor (EGFR).

A variation was submitted by the MAH in reply to a request of the PRAC to address the signal of cytokine release syndrome. Further information was requested in the framework of this variation procedure following a first PRAC discussion in June 2013 (see PRAC Minutes June 2013).

The PRAC was requested to provide advice on the assessment of the supplementary information received.

Summary of advice

Based on the review of the information submitted the PRAC agreed that the clinical usefulness of a test predictive for hypersensitivity reactions, based on the presence of anti-alpha 3Gal IgE Ab, and how to handle patients who are diagnosed with preformed antibodies, should be further discussed by the MAHs. Further PRAC advice will be provided following submission of this new information.

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

None

10.3. Other requests

10.3.1. **Gadolinium-containing products** (NAP, CAP)

- PRAC consultation on a post-authorisation measure, upon CHMP request

Regulatory details:
PRAC Rapporteur (lead): Julie Williams (UK)

Background

Gadolinium-containing contrast agents (GdCAs) are intravenous agents used for contrast enhancement with magnetic resonance imaging (MRI) and with magnetic resonance angiography (MRA).

The CHMP concluded in March 2010 (see Questions and answers on the review of gadolinium-containing contrast agents EMEA/727399/2009 rev.) that GdCAs are associated with nephrogenic systemic fibrosis (NSF) and that the risk is increased in renally impaired patients, liver transplant patients, the paediatric population, during pregnancy and lactation and in the elderly. The CHMP also recognised that the GdCAs can be classified into three NSF risk categories: high, medium and low.

Following the conclusion of the Article 31 referral procedures, as requested, the MAHs submitted annual cumulative reviews of NSF cases in July 2011, 2012 and 2013; and submitted protocols for a requested study of the long-term accumulation of gadolinium in human bone. However, the final study reports are not expected until 2015.

Therefore, given the severity of NSF and its potential impact on public health and the late availability of the results of the bone studies that could potentially affect the benefit-risk balance of individual gadolinium-containing contrast agents, the CHMP requested the advice of the PRAC on whether the MAHs should be required to continue to submit annual cumulative reviews of NSF.

Summary of advice

Based on the review of the available information the PRAC agreed that the MAHs should continue to submit an annual cumulative review of NSF, updated to reflect the additional cases.

10.3.2. Interferon beta-1a – AVONEX (CAP)

- PRAC consultation on a post-authorisation measure, upon CHMP request

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

Background

Interferon beta-1a is an immunostimulant used in the treatment of multiple sclerosis.

As agreed at the May 2013 PRAC meeting, the MAH for Avonex (interferon beta-1a) was requested to submit to the EMA a variation to include in the product information a warning regarding the risk of collapsing focal segmental glomerulosclerosis during interferon-beta treatment and reflect this as an undesirable effect. At the same time, a request was put forward to all MAHs of centrally authorised interferon beta-containing medicines to submit a cumulative review on cases of glomerulosclerosis (particularly collapsing FSGS) (see below for the other interferon beta containing medicines and related conclusions). Furthermore, a cumulative review of cases of thrombotic microangiopathy, haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura was requested for Avonex.

A response from the MAH on these requests was assessed by the Rapporteur. The PRAC would provide further advice to CHMP on the assessment of this reply as a follow-up of the previous request.

Summary of advice

Based on the review of the available information the PRAC reiterated that the MAH should be required to submit a variation to update the product information to warn physicians of the risk of collapsing focal segmental glomerulosclerosis during Avonex treatment. Furthermore a cumulative review of all cases of nephrotic syndrome associated with Avonex should also be submitted.

The MAH should also be requested to submit a refined comprehensive review of the published literature on all thrombocytopenia-related disorders. Further PRAC advice will be provided as applicable.

10.3.3. Interferon beta-1a – **REBIF** (CAP)

- PRAC consultation on a post-authorisation measure, upon CHMP request

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

Background

Following the request made to the MAH of Rebif (interferon beta-1a) for a cumulative review (see above 10.3.2. for background) the reply from the MAH was assessed by the Rapporteur. The PRAC would provide advice to the CHMP on the assessment of this review.

Summary of advice

Based on the review of the available information the PRAC agreed that the MAH should be requested to submit a variation to update the product information to warn physicians of collapsing focal segmental glomerulosclerosis during Rebif (interferon beta-1a) treatment. Furthermore a cumulative review of all cases of nephrotic syndrome associated with Rebif (interferon beta-1a) should be submitted.

10.3.4. Interferon beta-1b – **BETAFERON** (CAP), **EXTAVIA** (CAP)

- PRAC consultation on a post-authorisation measure, upon CHMP request

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Following the request made to the MAH of Extavia (interferon beta-1b) for a cumulative review (see above 10.3.2. for background) a reply from the MAH was assessed by the Rapporteur. The PRAC would provide advice to CHMP on the assessment of this review.

Summary of advice

Based on the review of the available information the PRAC agreed that the MAH should be required to submit a variation to update the product information to warn physicians of collapsing focal segmental glomerulosclerosis during Extavia (interferon beta-1b) treatment. Furthermore a cumulative review of all cases of nephrotic syndrome associated with Extavia (interferon beta-1b)) should also be submitted. Moreover some clarification on the modalities of the review performed should be provided.

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

11.3.1. **Nebivolol** (NAP)

- PRAC consultation on a PSUR worksharing procedure, on Member State's request

Regulatory details:
Lead member: Menno van der Elst (NL)

Background

Nebivolol is a beta-receptor blocker used in treatment of hypertension and in the treatment of left ventricular failure. Nebivolol containing medicines are nationally authorised in the EU. A PSUR-Worksharing (NL/H/PSUR/0029/002) procedure was started for nebivolol in 2012.

Currently the product information of Gilenya, a centrally authorised product containing fingolimod indicates that treatment should not be initiated in patients receiving beta-blockers because of the potential additive effect on slowing heart rate. Following comments received during the procedure, the PSUR reference member state (P-RMS), NL requested PRAC advice on whether information for the interaction with fingolimod should be explicitly included in the product information for nebivolol-containing medicines since nebivolol is a beta-blocker and can induce bradycardia.

Summary of advice

The PRAC agreed that the Gilenya product information provides appropriate and sufficient information on the interaction between fingolimod and nebivolol. The interaction is also addressed in the RMP of Gilenya. These are considered the most important tools to manage any risk associated with this interaction in clinical practice given the current use of both medicines and likelihood of co-administration. Therefore, PRAC considered the inclusion of a specific reference to the interaction in the product information of nebivolol-containing medicines not to be necessary.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. Simplifications and efficiency gains of PRAC-related activities

- Draft proposal of simplification proposals

During the organisational matters teleconference of the PRAC on 19 September 2013, PRAC delegates discussed a proposal prepared by the EMA compiling a number of suggestions from PRAC members and assessment teams aimed at optimising process flows and reducing administrative burdens of PRAC related activities. The PRAC made further suggestions at the teleconference in various domains that will be taken into account in a revised version. Follow-up discussion will take place at future meetings of the PRAC.

12.2. Pharmacovigilance audits and inspections

None

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

12.3.1. Union Reference Date List

12.3.1.1. Consultation on the draft List, version September 2013

The PRAC endorsed the EURD list version September 2013. The PRAC was reminded of the legal requirements provided in Article 107c(7) of Directive 2001/83/EC that *'any change to the dates of submission and frequency of periodic safety update reports specified in the marketing authorisation (…) shall take effect 6 months after the date of such publication'*. Therefore, the EURD list would only be including Data Lock Points (DLP) of PSURs for which the submission deadlines fall after the date when the change published in the list becomes legally binding. As a consequence, if PRAC recommends a reduction of a PSUR frequency to 6-monthly, an *"ad hoc"* PSUR should be requested from the concerned MAHs, while the DLP of the subsequent PSURs will be reflected in the EURD list. A note on this ad hoc PSUR will also be included in the EURD list. By analogy, any changes to the PSUR frequency from 6-monthly to yearly or over will only take effect directly if the DLP published in the list at the time of the PRAC recommendation is still in the future.

The PRAC was also updated on the handling of PRAC Rapporteur's assessment report(s) (AR) in PSUR single assessment procedures (PSUSA): a unique version of the AR will be sent to all MAHs that submitted a PSUR as part of a single assessment procedure. The EMA will redact the documents deleting confidential commercial information (CCI) and patient personal data (PPD) in accordance with the criteria described in the HMA/EMA document on handling requests for access to PSURs applied (EMEA/743133/2009). A disclaimer will also be added to the EURD list, informing MAHs that their PSUR data will be shared through the AR with the other MAHs involved in the single assessment (i.e. those which submitted a PSUR).

12.4. Signal Management

12.4.1. Signal Management

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

The PRAC heard a progress report of one year of activity of the SMART working group including an overview of signals analysed, templates developed, efficiency gains and future improvements. The PRAC congratulated the chair and the group for the achievement and advocated the publication of the activity reports. EMA also presented a revised draft document covering 'Questions & answers on signal management' addressing a number of questions which stakeholders, in particular marketing authorisation holders (MAHs), may have on the management of safety signals. Following implementation of comments received the document will be published on the EMA website. Plans for publication of stand-alone documents with the detailed recommendations of the PRAC arising from assessment of signals were also presented. PRAC made some suggestions for improvement of content and format.

On a different note, the PRAC also discussed that – as it was apparent for some cases – some MAHs enter in their own safety database and possibly transmit to EudraVigilance cases without reporting any adverse reactions (e.g. exposure during pregnancy or medications errors). The consequences of such a process might interact with the signal detection process and the chance to detect any new signal. The PRAC agreed that this issue should be the subject of a clear guidance and enhanced communication to MAHs. The SMART will discuss this matter in further details.

Post-meeting note: the Questions & answers on signal management EMA/261758/2013, was published on the EMA website on 4 October 2013.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Additional Monitoring and black inverted triangle symbol

- Next steps on the communication campaign

EMA presented the next steps to be taken in promoting awareness on additional monitoring and the related campaign. The communication campaign for the black triangle is scheduled to go ahead on 1 October 2013. The communication material will be circulated prior to the publication date so that national competent authorities can download and use it for their own national communications.

12.5.2. List of Product under Additional Monitoring

- Consultation on the draft List, version September 2013

The PRAC was informed of the creation of a new mailbox that should be used for any questions/comments related to the additional monitoring list: Additionalmonitoring@ema.europa.eu. The PRAC was informed of the new products falling within the mandatory scope of the list that have been added to the version for publication by the end of September 2013.

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of risk Minimisations

12.7.1. Risk Management Systems

12.7.2. Champions in the review of the assessment process of RMPs

- Progress report on the activity

EMA presented a progress report on the review of the assessment process of risk management plans for new marketing authorisation applications. Further discussion will take place at the joint PRAC and CHMP session during the PRAC meeting under the Lithuanian presidency of the EU in Vilnius, October 2013.

12.8. Post-authorisation Safety Studies

None

12.9. Community Procedures

None

12.10. Risk communication and Transparency

12.10.1. Public Participation in Pharmacovigilance

- Draft rules of procedure on public hearings

EMA announced that rules of procedures for public hearings are being drafted. A call for volunteers for a review of the draft was launched and PRAC members were invited to respond to the call before the October 2013 PRAC meeting.

12.11. Continuous pharmacovigilance

12.11.1. Continuous Pharmacovigilance, Ongoing Benefit-Risk Evaluation, Regulatory Status and Planning of Public Communication

12.11.1.1. Benefit risk evaluation of marketing authorisation applications for new substances

- Benefit risk tables as part of the evaluation of marketing authorisation applications for new substances, pilot phase

As part of a project to improve transparency, communication and consistency of benefit risk assessment, the EMA presented at the organisational matters teleconference of the PRAC on 19 September 2013 the outcome of a pilot phase developing a toolkit for benefit risk evaluation consisting of effects tables displaying a summary of known effects and information relevant to the benefit-risk balance. The PRAC commented on the usefulness of these tables in the assessment of risk management plans. EMA will take forward these comments and provide feed-back to the PRAC during future discussions on next steps of the project. CHMP is starting a new pilot phase of the effects table including on-going procedures and EMA will invite the involved PRAC rapporteurs to provide feedback on the usefulness of the tables by means of a questionnaire.

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Committees

None

12.12.2. Working Parties

12.12.2.1. Healthcare Professionals' Working Party (HCPWP)

- Nominations of alternate

The PRAC endorsed the nomination of Jane Ahlqvist Rastad (member nominated by the EC) as additional alternate with aim of providing enhanced communication with the working party.

12.12.2.2. Vaccine Working Party (VWP)

- Nominations for VWP/PRAC drafting group on methodology of effectiveness studies for seasonal influenza vaccines

Following a call for nominations to participate in a VWP/PRAC drafting group to provide input into the new influenza guideline, the following PRAC delegates were confirmed at the organisational matters teleconference of the PRAC on 19 September 2013: Ingebjørg Buajordet (NO), Jean-Michel Dogné (BE), Stephen Evans (member nominated by the EC) and Brigitte Keller-Stanislawski (member nominated by the EC).

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

12.13.1. Interaction with other Drug Regulatory Authorities

- Announcement of the new EMA International Pharmacovigilance cluster teleconference

At the organisational matters teleconference of the PRAC on 19 September 2013, the EMA presented the scope and agreed dates for the new EMA International Pharmacovigilance cluster teleconference with FDA and Drug Regulatory Authorities (DRAs). The teleconferences will be held monthly and will be organised between the EMA and the FDA for mutual exchange of information. Liaison officials at EMA from Health Canada and Pharmaceuticals and Medical Devices Agency, Japan (PDMA-J) will participate as observers. PRAC Chair and Vice Chair will be in the core groups of participants and PRAC members will be invited as optional or required attendants in accordance with the topics to be discussed.

12.13.2. European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

- Proposal for an EMA funded study on antidepressant exposure in utero and subsequent childhood autism spectrum disorders

EMA proposed an invitation to tender for an ENCePP study looking at the use of antidepressants during pregnancy and any association with autistic spectrum disorders in the children who are subsequently born. This would be in line with previous similar drug safety studies (see EMA/2012/08/CN). The PRAC supported the proposal and made some methodological comments. Once the protocol is agreed and the procurement process finalised, the invitation to tender will be launched. PRAC members (UK, Denmark) volunteered to provide input to the EMA assessment of the protocols and study results, if a tender is successful.

Post meeting note: an invitation to tender was launched by EMA on 20 September 2013.

13. Any other business

13.1.1. Implementation of the revised variations guidelines

Following a presentation at the July 2013 PRAC meeting, EMA provided further detail and clarifications on the implementation of the revised variation guideline (EC Guidelines on the details of the various categories of variations[36]) at the organisational matters teleconference of the PRAC on 19 September 2013.

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

ANNEX I – List of other advice and recommendations adopted at the meeting

14. ANNEX I Risk Management Plans

14.1. Medicines in the pre-authorisation phase

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

14.1.1. 4-aminosalicylic acid

14.1.2. Aripiprazole

14.1.3. Ataluren

14.1.4. Canagliflozin

14.1.5. Dapagliflozin, metformin

14.1.6. Dexamethasone

14.1.7. Elvitegravir

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

14.1.9. Levetiracetam

14.1.10. Levodopa, carbidopa, entacapone

14.1.11. Obinutuzumab

14.1.12. Oseltamivir

14.1.13. Radium-223

14.1.14. Recombinant human n-acetylgalactosamine-6-sulfatase

14.1.15. Simeprevir

14.1.16. Sofosbuvir

14.1.17. Trastuzumab emtansine

14.1.18. Turoctocog alfa

14.1.19. Umeclidinium bromide, vilanterol

14.2. Medicines already authorised

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

RMP in the context of a PSUR procedure

See also related PSUR under 6 or 15 as applicable.

14.2.1. Aclidinium bromide – **BRETARIS GENUAIR** (CAP), **EKLIRA GENUAIR** (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.2. Anidulafungin – ECALTA (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.3. Asenapine – SYCREST (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.4. Axitinib – INLYTA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.5. Brentuximab vedotin – ADCETRIS (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.6. Ceftaroline fosamil – ZINFORO (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.7. Clofarabine – EVOLTRA (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

14.2.8. Collagenase clostridium histolyticum – XIAPEX (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.9. Dronedarone – MULTAQ (CAP)

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

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

14.2.10. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.11. Etanercept – ENBREL (CAP)

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

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

14.2.12. Ivacaftor – KALYDECO (CAP)

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

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

14.2.13. Linagliptin, metformin – JENTADUETO (CAP)

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

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

14.2.14. Nilotinib – TASIGNA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.15. Prasugrel – EFIENT (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.16. Pregabalin – LYRICA (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.17. Pyronaridine, artesunate – PYRAMAX (Art 58)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

See also 6.1.20.

14.2.18. Ranolazine – **RANEXA** (CAP)

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

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

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

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

Regulatory details:
PRAC Rapporteur: Maria Alexandra Pêgo (PT)

14.2.20. Ruxolitinib – **JAKAVI** (CAP)

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

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

See also 6.1.23.

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

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

RMP in the context of a variation

14.2.22. Anakinra – **KINERET** (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.23. Catridecacog – **NOVOTHIRTEEN** (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

14.2.24. 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)

14.2.25. Denosumab – **XGEVA** (CAP)

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

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

14.2.26. Doxorubicin – CAELYX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

14.2.27. Human normal immunoglobulin – HIZENTRA (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.28. Insulin aspart – NOVORAPID (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.29. Ipilimumab – YERVOY (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.30. Peginterferon alfa-2B – PEGINTRON (CAP), **VIRAFERONPEG** (CAP)

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

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

14.2.31. Ribavirin – REBETOL (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

14.2.32. Ulipristal – ESMYA (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.33. Vinflunine – JAVLOR (CAP)

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

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

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

See Human fibrogen, human thrombin (EVICEL) 8.1.2. , Pneumococcal polysaccharide conjugate vaccine (SYNFLORIX) 8.1.3.

RMP in the context of a stand-alone RMP procedure

14.2.34. Atosiban – TRACTOCILE (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

14.2.35. Colestilan – BINDREN (CAP)

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

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

14.2.36. Imatinib – GLIVEC (CAP)

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

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

14.2.37. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) – PREVENAR 13 (CAP)

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

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

14.2.38. Rituximab – MABTHERA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.39. Sirolimus – RAPAMUNE (CAP)

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

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

14.2.40. Tegafur, gimeracil, oteracil – TEYSUNO (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.41. Vardenafil – LEVITRA (CAP), VIVANZA (CAP)

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

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

15. ANNEX I Assessment of Periodic Safety Update Reports (PSURs)

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

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

15.1. Evaluation of PSUR procedures[37]

15.1.1. A/H5N1 prepandemic influenza vaccine (whole virion, vero-cell derived, inactivated) – VEPACEL (CAP)

- Evaluation of a PSUR procedure

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

15.1.2. Aflibercept – ZALTRAP (CAP)

- Evaluation of a PSUR procedure

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

15.1.3. Aliskiren, amlodipine – RASILAMLO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

15.1.4. Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

[37] Where a regulatory action is recommended (variation, suspension or revocation of the terms of Marketing Authorisation(s)), the assessment report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion. Where PRAC recommends the maintenance of the terms of the marketing authorisation(s), the procedure finishes at the PRAC level.

15.1.5. Asenapine – SYCREST (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

See also 14.2.3.

15.1.6. Axitinib – INLYTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

See also 14.2.4.

15.1.7. Brentuximab vedotin – ADCETRIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

See also 14.2.5.

15.1.8. ^{13}C-urea – HELICOBACTER TEST INFAI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

15.1.9. Catridecacog – NOVOTHIRTEEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

15.1.10. Ceftaroline fosamil – ZINFORO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

See also 14.2.6.

15.1.11. Clofarabine – EVOLTRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

See also 14.2.7.

15.1.12. Colistimethate sodium – COLOBREATHE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

15.1.13. Collagenase clostridium histolyticum – XIAPEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

See also 14.2.8.

15.1.14. Crizotinib – XALKORI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

15.1.15. Dexamethasone – OZURDEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

15.1.16. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

See also 14.2.10.

15.1.17. Entacapone – COMTAN (CAP), COMTESS (CAP), ENTACAPONE ORION (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

15.1.18. Epoetin zeta – RETACRIT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

15.1.19. Etanercept – ENBREL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

See also 14.2.11.

15.1.20. Fampridine – FAMPYRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

See also 5.2.2.

15.1.21. Gadoversetamide – OPTIMARK (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

15.1.22. Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed) – FENDRIX (CAP)

- Evaluation of a PSUR procedure

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

15.1.23. Insulin analogue human recombinant – ACTRAPHANE (CAP), ACTRAPID (CAP), INSULATARD (CAP), MIXTARD (CAP), PROTAPHANE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

15.1.24. Linagliptin, metformin – JENTADUETO (CAP)

- Evaluation of a PSUR procedure

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

See also 14.2.13.

15.1.25. Nitisinone – ORFADIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

15.1.26. Octocog alfa – ADVATE (CAP)

- Evaluation of a PSUR procedure

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

15.1.27. Paclitaxel – ABRAXANE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

15.1.28. Prasugrel – EFIENT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

See also 14.2.15.

15.1.29. Rivastigmine – EXELON (CAP), PROMETAX (CAP), RIVASTIGMINE 1A PHARMA (CAP), RIVASTIGMINE HEXAL (CAP), RIVASTIGMINE SANDOZ (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

15.1.30. Rotigotine – LEGANTO (CAP), NEUPRO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Maria Alexandra Pêgo (PT)

See also 14.2.19.

15.1.31. Rufinamide – INOVELON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

15.1.32. Samarium (^{153}Sm) lexidronam pentasodium – QUADRAMET (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

15.1.33. Ulipristal – ESMYA (CAP)

- Evaluation of a PSUR procedure

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

15.1.34. Vardenafil – LEVITRA (CAP), VIVANZA (CAP)

- Evaluation of a PSUR procedure

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

15.1.35. Velaglucerase alfa – VPRIV (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

15.1.36. Vemurafenib – ZELBORAF (CAP)

- Evaluation of a PSUR procedure

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

15.1.37. Yttrium (90Y) chloride – YTTRIGA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

15.2. Follow-up to PSUR procedures[38]

15.2.1. Dabigatran – PRADAXA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

15.2.2. Irbesartan – APROVEL (CAP), IRBESARTAN ZENTIVA (CAP), KARVEA (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

15.2.3. Levetiracetam – KEPPRA (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

15.2.4. Maraviroc – CELSENTRI (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

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

15.2.5. Micafungin – MYCAMINE (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

15.2.6. Thalidomide – THALIDOMIDE CELGENE (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

15.2.7. Trastuzumab – HERCEPTIN (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

16. ANNEX I Post-authorisation Safety Studies (PASS)

Since all comments received on the assessment of these measures were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below.

16.1. Protocols of PASS imposed in the marketing authorisation(s)[39]

See section 7.

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[40]

16.2.1. Aflibercept – ZALTRAP (CAP)

- Evaluation of a PASS protocol

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

16.2.2. Aripiprazole – ABILIFY (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

16.2.3. Bivalirudin – ANGIOX (CAP)

- Evaluation of a PASS protocol

[39] In accordance with Article 107n of Directive 2001/83/EC
[40] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

16.2.4. Bromelain enriched proteolytic enzyme preparation from ananas comosus – NEXOBRID (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

16.2.5. Deferasirox – EXJADE (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

16.2.6. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

16.2.7. Enzalutamide – XTANDI (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

16.2.8. Etanercept – ENBREL (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

16.2.9. Glycopyrronium bromide – ENUREV BREEZHALER (CAP), SEEBRI BREEZHALER (CAP), TOVANOR BREEZHALER (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

16.2.10. Human normal immunoglobulin – HYQVIA (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

16.2.11. Orlistat – ALLI (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

16.2.12. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of a PASS protocol

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

16.3. Results of PASS imposed in the marketing authorisation(s)[41]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[42]

None

16.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS[43]

16.5.1. Caffeine – PEYONA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

16.5.2. Etanercept – ENBREL (CAP)

- Evaluation of PASS study results

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

16.5.3. Mannitol – BRONCHITOL (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

16.5.4. Paliperidone – INVEGA (CAP)

- Evaluation of interim PASS results

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

16.5.5. Romiplostim – NPLATE (CAP)

- Evaluation of interim PASS results

[41] In accordance with Article 107p-q of Directive 2001/83/EC
[42] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013
[43] In line with the revised variations regulation for any submission before 4 August 2013

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

16.5.6. Ulipristal – ESMYA (CAP)

- Evaluation of interim PASS results

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

17. ANNEX I Renewals of the Marketing Authorisation, Conditional Renewals and Annual Reassessments

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal of the marketing authorisation procedure could be concluded, and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

17.1.1. Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

17.1.2. Degarelix – FIRMAGON (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

17.1.3. Filgrastim – FILGRASTIM HEXAL (CAP), ZARZIO (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

17.1.4. Ibandronic acid – BONVIVA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

17.1.5. Mifamurtide – MEPACT (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

17.1.6. Moroctocog alfa – REFACTO AF (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

17.1.7. Sapropterin – KUVAN (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

17.1.8. Prasugrel – EFIENT (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Based on the review of the available information on the status of fulfilment of specific obligations and the safety data submitted, the PRAC considered that the annual re-assessment procedures for the medicines listed below could be concluded. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

17.1.9. Laronidase – ALDURAZYME (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

17.1.10. Nelarabine – ATRIANCE (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

17.1.11. Ziconotide – PRIALT (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

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

ANNEX II – List of participants: *including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 2-5 September 2013 meeeting.*

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	Combined hormonal contraceptives, Radium-223
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Marin Banovac	Croatia	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Jana Mladá	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
George Aislaitner	Greece	Full involvement	
Julia Pallos	Hungary	Full involvement	
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Daniela Pomponiu	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Julia Dunne	United Kingdom	Full involvement	
June Munro Raine	United Kingdom	Full involvement	
Julie Williams	United kingdom	Full involvement	

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

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

Additional European experts participating at the meeting for specific Agenda items	**Country**	
Veerle Verlinden	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Ravi Goud	FDA	
Wei Hua	FDA	
Laurence Landow	FDA	

Additional European experts participating at the meeting for specific Agenda items	Country
Djillali Annane	France
Christine Diesinger	Germany
Jutta Krappweis	Germany
Anna-Maria Coleman	Ireland
Fabio Facchinetti	Italy
Kristin Kvande	Norway
Charlotte Backman	Sweden
Rolf Gedeborg	Sweden
Elina Ronnemaa	Sweden
Patrick Batty	United Kingdom
Shahin Kauser	United Kingdom
Sarah Mee	United Kingdom
Alison Shaw	United Kingdom
Andrew Thomson	United Kingdom
Andrea Wallington	United Kingdom

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

European Medicines Agency
Peter Arlett – Sector Head, Pharmacovigilance and Risk Management
Maria Boulos – Scientific Administrator, Regulatory Affairs
Roberto De Lisa - Scientific Administrator, PRAC Secretariat
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
Geraldine Portier - Scientific Administrator, PRAC Secretariat
Tanya Sepehr – Assistant, PRAC Secretariat
Tania Teixeira - Scientific Administrator, Community Procedures

ANNEX III – List of abbreviations

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

www.ema.europa.eu

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