7 November 2013
EMA/PRAC/708968/2013 Corr. *
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC minutes of the meeting on 7-10 October 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)

* Jevtana - correction on page 18

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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 7-10 October 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 7-10 October 2013

The agenda was adopted with some modifications upon request from the members of the Committee and the EMA secretariat.

1.3. Adoption of minutes of the previous PRAC meeting on 2-5 September 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 2-5 September 2013 EMA/PRAC/586155/2013 were published on the EMA website on 11 October 2013.

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

2.1. Newly triggered procedures

None

2.2. Ongoing Procedures

None

2.3. Procedures for finalisation

2.3.1. 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 and re-examination of PRAC recommendations under Article 31 (see below 3.4.1.) for HES-containing solutions are to be concluded (see minutes of the PRAC 2-5 September 2013 meeting for background). A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs on the new evidence gathered after the conclusion of the Article 31 procedure in June 2013, further expert advice received following an ad-hoc expert meeting held on 13 September 2013, and new proposals for additional risk minimisation measures. Three oral explanations took place at the meeting. The PRAC recommended that HES-containing solutions should no longer be used in patients with sepsis or burn injuries or in critically ill patients because of an increased risk of kidney injury and mortality but concluded that the benefit-risk balance for these solutions remains favourable in the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient - subject to new contraindications, warnings, and other changes to the product information and additional risk minimisation measures. The PRAC requested that, to provide more evidence on the efficacy and safety of hydroxyethyl starch in the perioperative setting and in trauma patients, studies should be conducted.

Summary of recommendation(s)/conclusions

The PRAC adopted, by majority vote, a variation of the marketing authorisations for HES-containing medicines and adopted a recommendation to be considered by CMDh – see Q&A EMA/606303/2013. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

Nineteen members/alternates, out of 33 eligible to vote present in the room, voted in favour of the variation together with Iceland, while fourteen members/alternates[1] and Norway had divergent views (see Appendix to PRAC assessment report on medicinal products containing hydroxyethyl starch[2]).

Post-meeting note: the press release 'Hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients – CMDh endorses PRAC recommendations' representing the position reached by the CMDh EMA/640658/2013 was published on the EMA website on 25 October 2013.

[1] Maria Popova-Kiradjieva (BG); Huber Martin (DE); Almath Spooner (IE); Carmela Macchiarulo (IT); Jacqueline Genoux-Hames (LU); Amy Tanti (MT); Sabine Straus (NL); Kamila Czajkowska (PL); Kirsti Villika (FI); Doris Stenver (DK); Julie Williams(UK); Marie Louise (Marieke) De Bruin, Brigitte Keller-Stanislawski; Stephen J. W. Evans (independent scientific experts nominated by the EC).
[2] See www.ema.europa.eu Home>Find medicine>Human medicines>Referrals - Publication pending at 31 October 2013

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

3.1. Newly triggered Procedures

3.1.1. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium; valpromide – (NAP)

- Review of the benefit-risk balance following notification by UK 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: Julie Williams (UK)

Background

Results of studies providing further information on the known risk of longer term potential neurodevelopmental effects in children following in-utero exposure to sodium valproate (or valproic acid) were published recently. The signal of neurodevelopmental effects following in-utero exposure to these medicines had been previously discussed by the PRAC; see PRAC Minutes April 2013. Following the publication of these new results, the UK Medicines Agency (MHRA) sent a letter of notification dated 7 October 2013 of a referral under Article 31 of Directive 2001/83/EC for a review of the benefit-risk of valproate-containing medicines during pregnancy in all authorised indications.

Discussion

The PRAC noted the notification letter from the UK 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 Julie Williams (UK) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/611881/2013 published on the EMA website link) and a timetable for the procedure (EMA/PRAC/606970/2013).

3.2. Ongoing Procedures

3.2.1. 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 for acipimox-containing medicines (see minutes of the PRAC 2-5 September 2013 meeting for background) is ongoing. An updated assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and the outcome of the expert meeting which was held within the procedure on 6 September 2013. The PRAC agreed that the product information for acipimox containing medicines should be updated. The MAH was asked to comment on a proposal for a revised product information as part of a second list of outstanding issues (EMA/PRAC/138312/2013rev2).

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

- Review of the benefit-risk balance following a 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: Brigitte Keller-Stanislawski (DE)
PRAC Co-Rapporteur: Ulla Wändel Liminga (SE)

Background

A referral procedure under Article 20(8) of Regulation (EC) No 726/2004 is ongoing for the octocog alpha-containing medicines Helixate Nexgen and Kogenate Bayer (see PRAC minutes 4-7 March 2013).

The Rapporteurs circulated their assessment reports in accordance to the agreed timetable for the procedure.

Summary of recommendation(s)/conclusions

The PRAC discussed the available evidence on a potential higher risk of inhibitor development, in comparison with other factor VIII products, for the above mentioned medicines and concluded that available data do not point to a difference with respect to degree of inhibitor development between various factor VIII products. A proposal for updating the product information as part of a list of questions to be addressed by the MAHs was agreed. The MAHs will be invited to address the outstanding issues in an oral explanation at the December 2013 PRAC meeting.

Post meeting note: an updated timetable for the review was finalised via written procedure on 21 October 2013.

3.2.3. 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) is ongoing for strontium ranelate-containing medicines (see PRAC minutes 2-5 September 2013). An expert meeting took place on 10 September 2013.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion of the ad-hoc expert meeting and agreed a revised list of questions for the MAH. The MAH will be invited to address the outstanding issues in an oral explanation at the

January 2014 PRAC meeting, in accordance with the agreed timetable for the review (EMA/PRAC/283428/2013 – Rev1).

3.3. Procedures for finalisation

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

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for combined hormonal contraceptives (see minutes of the PRAC 8-11 July 2013 meeting for background) is to be concluded. A final 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 and the evidence on the risks of venous and arterial thromboembolism for the different substances. Four oral explanations took place at the meeting.

The PRAC concluded that the benefit-risk balance of all combined hormonal contraceptives (CHCs) continued to be favourable in the indication of contraception provided that updates to warnings and other changes to the product information were made. These included updates to the risk estimates for venous thromboembolism (VTE), to reflect the most up to date evidence, to be included in the product information for the different CHC products (see 'PRAC confirms that benefits of all combined hormonal contraceptives (CHCs) continue to outweigh risks' EMA/607314/2013).

Furthermore the PRAC agreed that complete information is provided on the risk factors for VTE and arterial thromboembolism (ATE), and that greater clarity, particularly in the product information for patients, is provided on the signs and symptoms of VTE and ATE. The PRAC endorsed that the risk of VTE with CHCs differs between products depending on the type of progestogen they contain.

In order to reduce the risk of thromboembolic events, the PRAC recommended that HCPs are informed that the decision to prescribe a CHC should take into consideration the individual woman's current risk factors, particularly those for VTE (obesity, prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma, positive family history, other medical conditions associated with VTE and increasing age) and how the risk of VTE for a specific product compares with other CHCs.

Finally, PRAC considered that further data on the risk of VTE were required for combined hormonal contraceptives containing chlormadinone and imposed a requirement to conduct a post authorisation safety study (PASS) to evaluate the relative risk of venous thromboembolic events due to these products compared with those containing levonogestrel.

Summary of recommendation(s) / conclusions

The PRAC adopted, by majority, a recommendation for the variation of the marketing authorisations for the combined hormonal contraceptives included in the review, including some risk minimisation measures, and adopted a recommendation to be considered by the CHMP at their November 2013 meeting. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

Twenty-three members/alternates, out of 32 eligible to vote present in the room, voted in favour of the variation together with Iceland and Norway, while nine members/alternates – who overall agreed on the conclusions of the scientific assessment - had divergent views[3] (see PRAC assessment report[4]) on the regulatory actions to take forward, regarding the wording of the therapeutic indications of the product information.

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

Following 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 submitted to the EMA by some of the MAHs the PRAC was to take a final decision on the re-examination procedure (see PRAC minutes of the 2-5 September 2013 meeting and 'Recommendation to suspend marketing authorisations for hydroxyethyl-starch solutions to be re-examined' EMA/349341/2013 for background). The appointed Rapporteurs for the re-examination procedure circulated their assessment on the MAHs' submitted grounds for re-examination.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusions reached by the Rapporteurs and voted on whether the June 2013 recommendations should be maintained.

Since the re-examination procedure was based only on the scientific data available when the Committee adopted the initial recommendation, the PRAC considered by majority that those recommendations reached in June 2013 should remain unchanged (twenty-two members voted in favour of this position out of 33 eligible to vote present in the room whilst 11 members/alternates[5] together with Iceland and Norway had divergent views – see PRAC assessment report[6]).

[3] Huber Martin (DE); Jean Michel Dogné (BE), Isabelle Robine (FR); Jacqueline Genoux-Hames (LU); Amy Tanti (MT); Sabine Straus (NL); Marie Louise (Marieke) De Bruin, Brigitte Keller-Stanislawski; Hervé Le Louet (independent scientific experts nominated by the EC).
[4] See www.ema.europa.eu Home>Find medicine>Human medicines>Referrals - Publication pending at 31 October 2013
[5] Eva Jirsova (CZ); Isabelle Robine (FR); Maia Uusküla (EE), Jolanta Gulbinovic (LT); Andis Lacis (LV), Sabine Straus (NL), Margarida Guimarães (PT), Qun-Ying Yue (SE), Tatiana Magalova (SK); Jane Ahlqvist Rastad, Hervé Le Louet (independent scientific expert nominated by the European Commission)
[6] See www.ema.europa.eu Home>Find medicine>Human medicines>Referrals - Publication pending at the time of publication of these minutes. The AR will be published after CHMP opinion and European Commission decision.

However, in parallel to this procedure the PRAC has assessed and adopted a recommendation on the HES containing medicinal products under Article 107i of Directive 2001/83/EC, considering new data and a broader scope, see above 2.3.1.

Post-meeting note: since the assessment in the frame of Article 107i of Directive 2001/83/EC included more data and was broader in scope, the CMDh considered this procedure as a basis for their decision on the HES containing medicinal products. The press release 'Hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients – CMDh endorses PRAC recommendations' representing the position reached by the CMDh EMA/640658/2013 and published on the EMA website on 25 October 2013.

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

3.5.1. GLP-1 based therapy products (glucagon-like-peptide-1 (GLP-1) agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors) (CAP)

- Follow-up to actions recommended in the completed review on pancreatic risks under Article 5(3) of Regulation (EC) No 726/2004

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
PRAC Co-Rapporteur: Menno van der Elst (NL)

Background

The CHMP recently provided a scientific opinion for GLP-1 based therapies as an outcome of a review under Article 5(3) of Regulation (EC) No 726/2004 EMA/474117/2013. Based on this outcome the CHMP provided a briefing note to the PRAC for consideration.

Summary of recommendation(s)/conclusions

The PRAC agreed on a proposal for the implementation of actions recommended in the Article 5(3) procedure. PRAC will participate in the evaluation of the type II variations with regard to the RMP updates and the review of study protocols - once submitted - according to set timelines for all products involved.

4. Signals assessment and prioritisation[7]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Aflibercept - EYLEA (CAP)

- Signal of blindness

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

[7] 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

Aflibercept is a recombinant fusion protein that binds to vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF), used as intravitreal administration for the treatment of neovascular (wet) age-related macular degeneration (AMD) and of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) in adults.

The exposure for Eylea, a centrally authorised medicine containing aflibercept for intravitreal use, is estimated to have been more than 110 000 patient-years worldwide cumulatively up to March 2013.

During routine signal detection activities, a signal of blindness and other related conditions including reduced visual acuity was identified by the EMA, based on 57 cases reported as blindness 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 most of the reviewed cases were reported in association with known adverse drug reactions of intravitreal administration of aflibercept. These conditions (endophthalmitis, iritis, uveitis, eye inflammation, vitritis and retinal tear) could themselves result in visual loss. Nevertheless, some of the cases reported did not include any concomitant know risk. For the same cases, the time to onset was mostly the same day and most of them recovered.
Given the potential seriousness of the reaction and the fact that it is currently not included in the product information the PRAC agreed that the signal needed further investigation.

Summary of recommendation(s)

- The MAH for Eylea (aflibercept) should submit to the EMA, a review of the signal of blindness within the next PSUR (DLP 30/11/2013).

4.1.2. **Amiodarone** (NAP)

- Signal of carcinogenicity

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

Background

Amiodarone is an antiarrhythmic used in the treatment of severe heart rhythm disorders.

Based on sales data of the brand leader product, it is estimated that yearly worldwide more than one million patients are exposed to medicines containing amiodarone. These nationally authorised products have been first authorised in the 80s'.

A signal of carcinogenicity was identified by the NL, triggered by the recent publication of the results of a nationwide population-based study[8]. The NL confirmed that the signal needed initial analysis and prioritisation by the PRAC.

[8] Su VY, Hu YW, Chou KT, Ou SM, Lee YC, Lin EY, Chen TJ, Tzeng CH, Liu CJ.Amiodarone and the risk of cancer: a nationwide population-based study. Cancer. 2013 May 1;119(9):1699-705. doi: 10.1002/cncr.27881. Epub 2013 Apr 8.

Discussion

The PRAC discussed the strength and limitations of the findings. PRAC pointed out that the authors did not adjust for the smoking status of the patients included and some other potential sources of bias. Despite some possible methodological weaknesses in the study, considering the wide use of amiodarone, the seriousness of the risk and the fact that some preclinical data on thyroid tumours in rats are listed in the labelling of some amiodarone-containing medicines in other regions, the PRAC agreed that the signal should be further investigated.

The PRAC appointed Menno Van der Elst (NL) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for the reference nationally authorised amiodarone containing medicine should submit to the EMA, within 60 days, a cumulative review of the signal of carcinogenicity.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Cabazitaxel - JEVTANA (CAP)

- Signal of medication error, potentially leading to inappropriate dose

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Jevtana (cabazitaxel) is a centrally authorised antineoplastic agent available as concentrate and solvent for solution, used in combination with prednisone or prednisolone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

The exposure for Jevtana, a centrally authorised medicine containing cabazitaxel, is estimated to have been more than 22,000 patients worldwide, cumulatively up to September 2012.

A signal of medication errors potentially leading to inappropriate dose administration was identified by the Netherlands following a communication from the Netherlands Organisation for Medication Incidents (CMR) reporting cases of 8 patients who received a higher dose than intended. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted that the preparation of the solution for infusion for Jevtana (cabazitaxel) involves a two steps dilution including the dilution of the entire content of the concentrate and solvent vials in a first dilution step (reconstitution). Both the concentrate and the solvent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the entire contents of the accompanying solvent, there is an initial diluted solution containing 10 mg/ml cabazitaxel.

The dose to be administered is then taken from this reconstituted premix to be further diluted for administration. If the correct volume of solvent (including the overfill) is not used in the reconstitution phase, the premix becomes more concentrated than it is supposed to be, leading to administration of higher doses of cabazitaxel than recommended.

The PRAC agreed that since an update of the product information for Jevtana had been agreed in September 2012 to clarify the fill volume of the concentrate and solvent vials, the instruction for preparation were accurate in the current product information, clearly indicating that the entire content of the vials must be used in the first dilution step.

The MAH had submitted a risk assessment of the issues as well as a cumulative review of data from their pharmacovigilance databases for evaluation by the Rapporteur. The PRAC endorsed the request for further improvement of the preparation instructions in the product information with pictures illustrating the steps for reconstitution, and agreed that a reformulation of the product, in order to have only one vial concentrate for solution for infusion with no need of a prior dilution with a solvent, would be useful. A DHPC was endorsed to inform prescribers and healthcare professionals – in particular hospital pharmacists - about the risk of possible medication errors and to remind them of the right method for preparation of Jevtana. Finally, the PRAC agreed that further information on the cases reported was needed.

Summary of recommendation(s)

- The MAH for Jevtana should submit to the EMA by 30 days a variation for an update of the product information and of the RMP as well as a DHPC to be sent in line with the Communication plan endorsed by the PRAC. Moreover additional information on the case reports should be provided.

For the full PRAC recommendation see EMA/PRAC/625262/2013, published on the EMA website.

4.1.4. Cefuroxime for intracameral use (NAP)

- Signal of eye inflammation and macular oedema

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

Background

Cefuroxime is an antibiotic of the cephalosporin class. Cefuroxime for intracameral use is indicated for the antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery..

A signal of eye inflammation and macular oedema was identified in France, where a regional Pharmacovigilance Centre had reported an increase in cases of eye inflammation and macular oedema associated with decreased visual acuity after use of cefuroxime for antibiotic prophylaxis following cataract surgery. Sweden as reference member state for the relevant medicine (authorised through the mutual recognition procedure), confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported and noted that a further search in EudraVigilance had retrieved 18 serious cases of eye inflammation and /or macular oedema associated with cefuroxime for intracameral use which was the only suspected drug in all cases reported. The PRAC noted that anterior chamber eye inflammation and macular oedema are complications associated with cataract surgery; macular oedema is also more common after cataract surgery in patients with diabetes and/or other uveoretinal diseases. However, information on concomitant diseases or conditions was missing in the cases reported and therefore the PRAC agreed that the signal needed further investigation.

The PRAC appointed Ulla Wändel Liminga (SE) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Aprokam (cefuroxime) should submit to the RMS (SE), a cumulative review of the signal, within the next PSUR (DLP 15 Nov 2013).
- Further PRAC recommendation will be provided upon request of the MSs, as appropriate.

4.1.5. **Doxycycline** (NAP)

- Signal of photo-onycholysis

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

Background

Doxycycline is an antibiotic used in the treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

Doxycycline-containing medicines are widely used since the time of their first authorisation in the '60s.

During routine signal detection activities, a signal of photo-onycholysis was identified by the NL, based on 12 cases reported in the Netherlands. The UK as lead member state for the signal detection activities of doxycycline-containing products confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of photo-onycholysis and noted that doxycycline was the only suspected medicine reported in most of the cases described. In most of the cases the medicine had been prescribed for treatment of Lyme disease or for malaria prophylaxis and the time-to onset of the suspected reaction was variable. The PRAC recognised that photodermatitis or photosensitivity are known reactions associated with doxycycline and noted that there were some published literature case reports of photo-onycholysis following doxycycline exposure. A possible biological mechanism for phototoxic nail reaction with doxycycline may involve it being triggered by ultraviolet radiation. There is less melanin and, therefore, less ultraviolet protection in the fingernail beds than in other sites. In consideration of the available evidence agreed that an update of the product information was warranted for doxycycline-containing medicines which do not already include photo-onycholysis as an adverse reaction in the product information.

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

Summary of recommendation(s)

- The MAH for doxycycline-containing medicines should submit to the NCAs of the MSs, within 60 days, a variation to update the product information to include "photo-onycholysis"[9] as an undesirable effect.

For the full PRAC recommendations see EMA/PRAC/625262/2013, published on the EMA website

[9] Section 4.8 of the Summary of Product Characteristics

4.1.6. Exenatide – **BYETTA** (CAP), **BYDUREON** (CAP); **liraglutide** - **VICTOZA** (CAP)

- Signal of cholecystitis and cholelithiasis

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE), Menno van der Elst (NL)

Background

Exenatide and liraglutide are substances belonging to the class of glucagon-like peptide-1 (GLP-1) receptor agonists, used in the treatment of type II diabetes.

The exposure for centrally authorised medicine containing exenatide and liraglutide is estimated to have been more than 2.4 million patient-years and 1.2 million patients years worldwide respectively, in the period from first authorisation (in 2006 and 2009) to 2013.

During routine signal detection activities, a signal of cholecystitis and cholelithiasis was identified by the EMA, following the publication of an article[10] describing how exenatide reduced cholecystokinin-induced gallbladder emptying compared with placebo in fasting healthy subjects, triggering a further review of cases reported to EudraVigilance. The Rapporteurs confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of cholecystitis and cholelithiasis. The PRAC pointed out that the majority of all cases also reported pancreatitis. A number of cases with cholelithiasis included patients who experienced weight loss or rapid weight loss. There was also a cluster of cases in a study with liraglutide carried out in diabetic and non-diabetic individuals with obesity. Rapid weight loss is included as an 'Important Identified Risk' in the RMP of Byetta (exenatide) with consequences including loss of lean body mass and increased risk for gallstone formation. Based on this information the PRAC agreed that the signal should be further investigated and proposed that data on the GLP-1 agonists' effect on gallstone formation should be reviewed, examining data from literature, post-marketing and clinical trials and including a discussion on the contribution of rapid weight loss to gallstone formation.

Summary of recommendation(s)

- The MAHs for Byetta/Bydureon (exenatide) and Victoza (liraglutide), should submit to the EMA a cumulative review of the signal.
- The cumulative review should be submitted within the next PSUR (DLP 30/9/2013) for Byetta/Bydureon and within the PSUR under assessment for Victoza (liraglutide) (DLP 30/06/2013).

4.1.7. **Gabapentin** (NAP)

- Signal of severe hypoglycaemia

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

[10] Keller J, Trautmann ME, Haber H, Tham LS, Hunt T, Mace K, Linnebjerg H . Effect of exenatide on cholecystokinin-induced gallbladder emptying in fasting healthy subjects. Regul Pept. 2012 Nov 10; 179(1-3):77-83

Background

Gabapentin is a substance structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) used in the treatment of epilepsy and peripheral neuropathic pain.

The exposure for the reference nationally authorised medicine containing gabapentin is estimated to have been more than 19 million patient-years worldwide in the period from first authorisation in to 2013.

During routine signal detection activities, a signal of severe hypoglycaemia was identified by the NL based on 6 cases retrieved from the Netherlands Pharmacovigilance Centre (Lareb) database. DE, as reference member state (RMS) for the relevant medicine (authorised through the mutual recognition procedure), confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the reported cases of severe hypoglycaemia and noted that an additional search in EudraVigilance yielded further cases with a positive de-challenge, suggestive of a temporal association with the suspected reaction. A case-report[11] describing gabapentin-induced hypoglycaemia in a non-diabetic patient undergoing long-term peritoneal dialysis was described in the literature. Increased insulin release by enhancing voltage dependent Ca2+ channels or from an agonist action on the gamma-aminobutyric acid (GABA) receptor had been suggested as a potential biological mechanism. Furthermore the reaction is listed for a chemically related substance (pregabalin). Therefore the PRAC agreed that the signal should be further investigated.

The PRAC appointed Martin Huber (DE) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Neurontin (gabapentin) should submit to the RMS (DE) a cumulative review of the signal, within the PSUR under assessment (DLP 01/02/2013).
- Further PRAC recommendation will be provided upon request of the Member States, as appropriate.

4.1.8. Human papillomavirus vaccine [type 6, 11, 16, 18] (recombinant, absorbed) – **GARDASIL** (CAP), **SILGARD** (CAP)

- Signal of postural orthostatic tachycardia syndrome (POTS)

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

Background

Gardasil is a centrally authorised vaccine for use from the age of 9 years for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) types and for genital warts (condyloma acuminata) causally related to specific HPV types.

Current estimations report that more than 42 million people worldwide have been vaccinated with HPV vaccines since their market introduction until the beginning of 2013.

[11] Penumalee S, Kissner P, Migdal S. Gabapentin induced hypoglycemia in a long-term peritoneal dialysis patient. American Journal of Kidney Diseases 2003;42(6 (E24)):3-5

During routine signal detection activities, a signal of postural orthostatic tachycardia syndrome (POTS), was raised by DK based on 7 cases reported to the Danish Health and Medicines Authority (DHMA). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of POTS reported. The PRAC noted that there was no consensus in the scientific community on diagnostic criteria for paediatric POTS nor any biological rationale that could explain the reaction. The condition is variably described as chronic orthostatic intolerance, lasting for more than 3 months, and excessive postural tachycardia in the absence of orthostatic hypotension. The PRAC concluded that the available evidence did not support a causal association between Gardasil and POTS at this stage. However, a routine analysis of all cases reported in clinical trials and in the post marketing experience, including any cases in the literature, should be completed.

Summary of recommendation(s)

- The MAH for Gardasil/Silgard should submit to the EMA a cumulative review of the signal within the next PSUR (DLP 31/5/2013).

4.1.9. Human papillomavirus vaccine [type 16, 18] (recombinant, adjuvanted, adsorbed] – CERVARIX (CAP)

- Signal of primary premature ovarian failure

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

Background

Cervarix is a centrally authorised vaccine indicated in females from nine years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPV).

Current estimations report that more than 42 million people worldwide have been vaccinated with HPV vaccines since their market introduction until the beginning of 2013.

BE identified a recently published article[12] on human papillomavirus vaccine and primary ovarian failure and confirmed that this information needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed premature (primary) ovarian failure, a condition in which the ovaries do not function normally in women who are below 40 years of age. The annual incidence of the condition in the general population has been reported to be 10/100,000 persons-years between the ages of 15 and 29 years, and differences in incidence have been reported in relation to ethnicity. The PRAC agreed that a routine analysis of all cases of reported in clinical trials and in the post marketing experience, including any cases in the literature, should be completed. However, it concluded that the available evidence did not support a causal association between Cervarix and premature ovarian failure at this stage.

[12] Colafrancesco S, et al. Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants. Am J Repro Immunol 2013; 70: 309-316

Summary of recommendation(s)

- The MAH for Cervarix should submit to the EMA, a cumulative review of the signal within the next PSUR (DLP: 17/11/2013).

4.1.10. **Quetiapine** (NAP)

- Signal of suicidality in major depressive disorder (MDD) patients

Regulatory details:
PRAC Rapporteur: *to be appointed*

Background

Quetiapine is an atypical antipsychotic agent used in the treatment of schizophrenia and bipolar disorder (both manic and depressive episodes). A pharmaceutical form of extended release quetiapine is also indicated as add-on treatment of major depressive episodes in major depressive disorder (MDD).

The exposure for nationally authorised medicines containing quetiapine is estimated to have been more than 36 million patients worldwide, in the period from first authorisation in 1997 to 2013.

A signal of suicidality in MDD patients was identified by the NL, after the MAH of the reference medicine containing quetiapine had submitted preliminary data from a post-authorisation safety study (PASS) performed in the General Practice Research Database (GPRD). The Netherlands as reference member state for the relevant quetiapine-containing medicine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the preliminary data of the study report submitted. The results suggested that the population of MDD patients treated with quetiapine may have had an elevated risk of 'death from all causes' and 'suicide or suicidal attempt/ideation' as compared to other MDD patients receiving different treatments. The investigators indicated that overall mortality was a heterogeneous endpoint, and the analyses were not adjusted for all potential confounders as this was not feasible due to low numbers and unknown reasons of death in most cases.

The PRAC agreed that methodological limitations of the GPRD study meant that the interpretation of the observed increased risks of all-cause mortality and suicide or suicidal attempt/ideation in patients with MDD treated with quetiapine compared with comparator treatments was difficult. The PRAC noted that a general warning on the risk of suicidality in patients suffering from depression is already included in the product information for Seroquel (quetiapine) and its RMP includes several PASS studies that were currently on-going and include suicidality among the end-points studied.
In particular the results of a prescription-event monitoring study are due at the end of 2013 and are expected to contain more detailed patient characteristics to enable better detection of differences between patient populations as compared to the GPRD study. The PRAC agreed that in order to draw some preliminary conclusions on the signal, further clarification should be obtained on the results presented and supported by the final results of the studies to be completed.

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

Summary of recommendation(s)

- The MAH for Seroquel XR (quetiapine) should submit to the Rapporteur, within 60 days, a final assessment of the study discussed above and by the end of 2013 a combined interpretation of the GPRD study and the results of the first package of the modified prescription-event monitoring study together with additional analysis requested by the PRAC.
- A 60-day timetable was recommended for the assessment of this review, leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. **Mefloquine** (NAP)

- Signal of long term and permanent vestibular side effects

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Background

Mefloquine is an antimalarial medicine used for malaria treatment and prophylaxis.

A signal of possibly permanent vestibular side effects was investigated by DE following the publication of a Drug Safety Communication from the US Food and Drug Administration (FDA) advising the public about strengthened and updated warnings regarding neurological and psychiatric side effects associated with mefloquine. Germany as signal management lead member state for mefloquine-containing medicines confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the reported cases which described how vestibular symptoms developed early in the course of treatment, sometimes after one or two doses of mefloquine. Patients who reported vestibular adverse reactions were otherwise healthy with no known major medical problems prior to taking mefloquine for malaria prophylaxis. Dizziness, loss of balance, tinnitus, or vertigo persisted for months to years after mefloquine was discontinued, and permanent vestibular damage was diagnosed in some cases. The PRAC agreed that the product information of mefloquine-containing medicines in the EU would need to be updated in order to inform about the possibility of persistent or permanent vestibular disorders.

The PRAC appointed Martin Huber (DE) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Lariam (mefloquine) should submit to the Rapporteur, within 60 days, a cumulative review of the signal of vestibular disorders including a proposal for an update to the product information.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Signals follow-up and prioritisation

4.2.2. **Adalimumab – HUMIRA** (CAP); **etanercept – ENBREL** (CAP); **infliximab – REMICADE** (CAP)

- Signal of glioblastoma and other brain neoplasms

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE) (Humira, Remicade), Julia Dunne (UK) (Enbrel)

Background

For background information, see PRAC Minutes April 2013.

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

Discussion

The PRAC discussed the assessments of the evidence reviewed for infliximab and adalimumab respectively, which consisted of cumulative reviews of cases of malignant brain neoplasms and glioblastoma reported in the respective companies' safety databases, as well as of clinical data and relevant literature information. The PRAC agreed that the rarity of glioblastoma in the general population made it very challenging to evaluate it within registries or clinical studies; thus the assessment had to focus on spontaneous reporting which has intrinsic limitations. However the estimated post-marketing incidence rate in molecular spontaneous reports did not seem to exceed the incidence in the general population. Moreover, due to their size, it was considered unlikely that the molecules of both adalimumab and infliximab will cross the blood brain barrier, and there was thus no obvious biological explanation as to how they would cause malignancies in the brain. Therefore the PRAC concluded that there was insufficient evidence to justify any strengthened wording of the existing statements on malignancy in the product information. The signal will be kept under routine monitoring, but at the moment the evidence did not support any potential causal relationship.

Similarly for etanercept limited evidence was found in the clinical trial databases and no cases were reported in the medical literature. Spontaneous reporting rates of primary malignant brain neoplasms and glioblastoma were lower or similar to the estimated incidence in general population. The PRAC agreed that the evidence presented so far did not warrant any changes to the product information. Nevertheless, certain clarifications were needed on the methodology adopted by the MAH for performing the cumulative review, and therefore the PRAC agreed that further information was necessary before a final conclusion can be reached within this procedure.

Summary of recommendation(s)

- The MAHs for Adalimumab (Humira) should monitor the above mentioned signal in the next PSUR (DLP 31/12/2013), and it should be specifically addressed in upcoming registry reports.
- The MAHs for Remicade (Infliximab) should monitor the above mentioned signal in the next PSUR (DLP 23/08/2013), and it should be specifically addressed in coming registry reports.
- The MAH for Enbrel (etanercept) should submit to the EMA, within 60 days responses to a list of questions which will be assessed with a 60-day timetable. The MAH should review the above mentioned signal in the next PSUR (DLP 2/02/2014).

For the full PRAC recommendations see EMA/PRAC/625262/2013 published on the EMA website.

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

- Signal of QT prolongation

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

Background

For background information, see PRAC minutes of 13-16 May 2013.
The MAH replied to the request for information on the signal and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the outcome of the review and agreed that preclinical as well as clinical pharmacological studies did not indicate a pro-arrhythmic potential for agomelatine. From the spontaneously reported cases, other factors could provide an alternative explanation for the onset of the reaction, including other medicines known to be associated with QT prolongation and underlying medical conditions. Some cases were reported in association with intentional overdose.
Overall, although the case reports of QT prolongation - as presented by the MAH in their response - did not seem to provide strong evidence of agomelatine-induced QT prolongation, an effect on the QT interval cannot be excluded based on these data.
QT prolongation has also been generated as a signal in the WHO database. The WHO experts concluded that agomelatine can cause QT prolongation in patients with predisposing factors or in connection with overdose.
In conclusion, the PRAC considered that the evidence that agomelatine can prolong the QT interval was limited and did not justify any changes to the product information at this stage. However, since, based on the data presented, an association cannot be entirely excluded the signal should be kept under monitoring.

Summary of recommendation(s)

- The MAHs for the Valdoxan (agomelatine) should monitor the above mentioned signal in the next PSUR (DLP 19/02/2014).

For the full PRAC recommendations see EMA/PRAC/625262/2013 published on the EMA website.

4.2.4. Azithromycin (NAP)

- Signal of potentially fatal heart events

Regulatory details:
PRAC Rapporteur: Terhi Lehtinen (FI)

Background

For background information, see PRAC minutes of 13-16 May 2013.
The MAH replied to the additional request for information on the signal and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the conclusion of the assessment on the new information submitted, including interpretation of the published study on azithromycin and cardiac mortality by Svanström et al. - performed in the Danish Civil Registration System - in the light of previously published literature. The PRAC also discussed possible future strategies to identify and characterise possible risk groups for increased risk of cardiac mortality with azithromycin use as proposed by the MAH.
The MAH intends to perform an observational study, using large electronic healthcare records, with the aim of examining the acute effect of azithromycin on cardiac effects (Kaiser Permanente of Northern California and prospectively also Kaiser Permanente of Southern California databases).

The PRAC agreed on some improvements needed for the analysis to be performed; a draft study protocol and timelines for study completion will be provided to the PRAC.

Regarding long-term safety of azithromycin and ischaemic cardiovascular events, the PRAC noted that data from two large, randomised and controlled clinical trials (Azithromycin and Coronary Events Study ACES and Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders WIZARD) were included in the review that suggested no long-term cardiovascular risk in patients with stable coronary artery disease. It was noted that to further address this issue, the MAH plans to engage an independent expert to review the data and provide a more detailed assessment.

The PRAC agreed that the updated product information as recently implemented (during the PSUR work-sharing procedure) is sufficient at the moment to address any cardiovascular or arrhythmogenic risk associated with azithromycin, but strengthening of the wording will be considered, as appropriate, when additional analyses concerning groups at potentially increased risk become available.

Further details and clarifications should be requested on timelines for completion of the planned studies.

Summary of recommendation(s)

- The MAHs for the reference, azithromycin-containing medicine should submit by 31 January 2014 to the Rapporteur the proposed expert review of the data in the randomised, controlled clinical trials to address the issue of the long-term safety of azithromycin and ischemic cardiovascular events. The PRAC should be kept informed about the timetable for the planned observational study to be performed in the Kaiser Permanente of Northern California (KPNC) and Kaiser Permanente Southern California (KPSC).
- Further PRAC recommendations will be provided upon request of the MSs, as applicable.

For the full PRAC recommendation se EMA/PRAC/625262/2013 published on the EMA website.

4.2.5. Boceprevir – VICTRELIS (CAP); **indinavir – CRIXIVAN** (CAP)
Quetiapine (NAP)

- Signal of drug interaction between protease inhibitors and quetiapine

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

For background information see PRAC minutes 8-11 July 2013.
Following the recommendation agreed by the PRAC in July, the MAH of Crixivan (indinavir) and Victrelis

(boceprevir) provided a justification for not updating the product information with a specific contra-indication against concomitant use with quetiapine. These responses were reviewed by the Rapporteur.

Discussion

The PRAC discussed the justification presented and acknowledged that no case of drug interaction with quetiapine had been reported to date with indinavir and boceprevir. However, the PRAC agreed that there was no rationale to distinguish these active substances from other protease inhibitors as regards this effect. The PRAC restated that the interaction and contraindication for concomitant use is already acknowledged in the SmPC of quetiapine-containing products and should be clearly reflected in the product information of all protease inhibitor-containing medicinal products.

Summary of recommendation(s)

- The MAH for Crixivan (indinavir) and Victrelis (boceprevir) should be requested to submit to the EMA within 30 days a variation to update the product information in line with the July 2013 PRAC recommendations.

For the full PRAC recommendation see EMA/PRAC/625262/2013 published on the EMA website.

4.2.6. Clarithromycin (NAP)

- Signal of cardiovascular events

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Background

For background information, see PRAC Minutes May 2013.
The MAH replied to the request for information on the signal of and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the responses received. From review of the available literature, studies have shown conflicting results. The CLARICOR[13] trial and its follow up[14] and the recent publication of the observational study in the British Medical Journal by Schembri al., 2013[15] demonstrated an increased risk of cardiovascular mortality associated with clarithromycin use. A number of meta-analyses, some of which included the CLARICOR data, have been published. These studies failed to show any association between macrolide antibiotic use and cardiovascular morbidity and mortality or all-cause mortality.

[13] Jespersen CM, Als-Nielsen B, Damgaard M, Hansen JF, Hansen S, Helø OH, Hildebrandt P, Hilden J, Jensen GB, Kastrup J, Kolmos HJ, Kjøller E, Lind I, Nielsen H, Petersen L, Gluud C; CLARICOR Trial Group. Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. BMJ. 2005;332(7532):22-7.
[14] Gluud C, Als-Nielsen B, Damgaard M, Fischer Hansen J, Hansen S, Helø OH, Hildebrandt P, Hilden J, Jensen GB, Kastrup J, Kolmos HJ, Kjøller E, Lind I, Nielsen H, Petersen L, Jespersen CM; CLARICOR Trial Group. Clarithromycin for 2 weeks for stable coronary heart disease: 6-year follow-up of the CLARICOR randomized trial and updated meta-analysis of antibiotics for coronary heart disease. Cardiology. 2008;111(4):280-7.
[15] Schembri S, Williamson PA, Short PM, Singanayagam A, Akram A, Taylor J, Singanayagam A, Hill AT, Chalmers JD. Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. BMJ. 2013;346:f1235.

Overall, taking into consideration the limitations of the currently available evidence and in particular the potential for confounding by disease severity, the PRAC agreed that it was not possible to conclude at this time that clarithromycin is associated with long-term ischaemic effects. It was noted that acute arrhythmogenic effects are already labelled. However, the PRAC agreed that there should be further exploration of the available clinical trial data particularly with a view to considering any potential for long term ischemic effects.

Summary of recommendation(s)

- The MAHs for the reference, nationally authorised [16] clarithromycin-containing medicine should be requested to submit to the RMS (IE) a more complete analysis of the available clinical trial data relevant to evaluation of cardiovascular safety and of the published literature, within the next PSUR (DLP to be brought forward for submission by 1 April 2014).

For the full PRAC recommendation see EMA/PRAC/625262/2013 published on the EMA website.

4.2.7. Efavirenz - **STOCRIN** (CAP), **SUSTIVA** (CAP) **Emtricitabine**, **efavirenz**, **tenofovir** – **ATRIPLA** (CAP)

- Signal of interaction with Ginkgo biloba

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Background

For background information, see PRAC Minutes May 2013.

Following the recommendation agreed by the PRAC in May 2013, the MAHs of efavirenz-containing medicinal products (Sustiva, Stocrin and Atripla) provided a justification for not updating their product information with a contra-indication against concomitant use with Ginkgo biloba. This justification was reviewed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the data presented, arising from the safety databases of the MAHs and from the literature. In conclusion, the MAHs recognised the biological plausibility for an interaction between efavirenz and Ginkgo biloba extracts via CYP3A4 and/or P-gp but argued that given the large number of patients who may have been exposed concomitantly to both products, there would be more cases or evidence of a deleterious interaction than the two published cases identified to date[17,18].

After reviewing the MAHs' response, the PRAC still considered that information on a potential deleterious pharmacokinetic interaction between efavirenz and Ginkgo biloba extracts – the effect being biologically plausible - should be reflected in the product information of efavirenz-containing medicinal products. However, the PRAC acknowledged that the current level of evidence and the

[16] 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
[17] Wiegman DJ, Brinkman K, Franssen EJ. Interaction of Ginkgo biloba with efavirenz. AIDS. 2009 Jun 1;23(9):1184-5.
[18] Naccarato M, Yoong D, Gough K. A Potential Drug-Herbal Interaction between Ginkgo biloba and Efavirenz. J Int Assoc Physicians AIDS Care (Chic). 2012 Mar-Apr;11(2):98-100

expected magnitude of the risk did not warrant an absolute contra-indication at this stage. The PRAC also considered that it would be of interest to inform the Committee on Herbal Medicinal Products (HMPC) of these findings.

Summary of recommendation(s)

- The MAHs for efavirenz-containing medicinal products (Stocrin/Sustiva, Atripla) should submit to the EMA, within 30 days, a variation to update the product information relating to the interaction of efavirenz with Ginkgo biloba in accordance with a revised wording agreed by the PRAC.
- The MAHs should continue to monitor this interaction in the next PSURs.

For the full PRAC recommendation see EMA/PRAC/625262/2013 published on the EMA website.

4.2.8. Fondaparinux – **ARIXTRA** (CAP)

- Signal of heparin-induced thrombocytopenia (HIT)

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

Background

For background information, see PRAC Minutes July 2013.
The MAH replied to the request for information on the signal and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the new information available. Regarding biological plausibility, available data showed that fondaparinux does not bind to platelet factor 4, which is believed to be a fundamental mediator of the HIT syndrome. In support, small in-vitro studies have failed to demonstrate that fondaparinux cross-reacts with sera from HIT patients. The PRAC agreed that it was difficult to draw conclusions on causality from the assessment of the spontaneous reports in this clinical disorder based on the data provided and given the lack of reliable diagnostic criteria and the presence of confounding factors.

It was recognised that all aspects of the mechanisms behind HIT are not fully understood and also that there is some scientific controversy as to whether fondaparinux can potentially be associated with HIT in very rare cases. However the PRAC concurred that the current product information makes clinicians adequately aware of the syndrome, allowing them to act appropriately and promptly if a suspicion of HIT is sufficiently justified.

Summary of recommendation(s)

- The current product information covers the issue in an appropriate manner. No further regulatory action is considered necessary at this point in time.

For the full PRAC recommendation se EMA/PRAC/625262/2013 published on the EMA website.

4.2.9. Orlistat – ALLI (CAP), **XENICAL** (CAP)
Atazanavir - REYATAZ (CAP); **darunavir - PREZISTA** (CAP); **efavirenz – STOCRIN** (CAP), **SUSTIVA** (CAP); **emtricitabine, efavirenz, tenofovir** – **ATRIPLA** (CAP); **emtricitabine, tenofovir - TRUVADA** (CAP); **lopinavir, ritonavir – KALETRA** (CAP)

- Signal of pharmacokinetic drug interaction (at absorption) with highly active antiretroviral therapy (HAART) leading to loss of HAART efficacy

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

For background information, see PRAC Minutes May 2013.

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

Discussion

The PRAC discussed the assessment of the data provided and noted that drug interactions of orlistat are recognised risks associated with orlistat treatment and are reflected in EU-SmPC and RMP (interactions with ciclosporin, amiodarone, anticoagulants, and fat soluble vitamins A, D, E, K and betacarotene as identified risks and interactions with the oral-contraceptive pill, antiepileptic medication and levothyroxine as potential risks). Post-marketing data suggested that these interactions may not be limited to lipophilic substances (interactions have been observed also with lithium and levothyroxine), with orlistat-induced diarrhoea providing yet another plausible mechanism for decreased absorption of coadministered drugs.

Few case reports were identified as being possibly linked to an interaction between orlistat and antiretroviral drugs, including the 2 literature reports which prompted the signal. Although the number of reports was considered low in the context of total exposure to orlistat, they raised concerns that coadministration may adversely impact on the efficacy of the antiretroviral medicines (including risk of viral resistance emergence). The PRAC concurred with the MAH proposal and agreed that in view of the critical importance of adequate therapeutic management of HIV infection and taking into account the OTC status of orlistat, the risk of reduced efficacy of antiretroviral treatment and the subsequent risk of emergence of viral resistance, the concomitant use of orlistat with HAART should be contraindicated.

Summary of recommendation(s)

For the full PRAC recommendation se EMA/PRAC/625262/2013 published on the EMA website.

*Post meeting note: following the PRAC recommendation for a contraindication, the CHMP agreed to further investigate the possible mechanism for this interaction in collaboration with the PRAC and the MAH before providing an opinion. Further PRAC recommendation on this issue can be expected in January 2014..

Pandemic H1N1 and seasonal trivalent influenza vaccines (CAP, NAP)

- Review of latest evidence for Guillain-Barré sydrome (GBS)

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

Background

In 2011, the PhVWP discussed surveillance for neurological and autoimmune disorders and Guillain-Barre Syndrome associated with influenza vaccines in the context of signal management activities. A follow-up review had been performed by the UK who confirmed that results should be brought to the attention of the PRAC.

Discussion

The PRAC discussed the assessment of two additional recently published studies assessing the association between H1N1 pandemic / seasonal trivalent influenza vaccines and GBS.

The PRAC agreed that both studies added support to previous research which has suggested that a very small increased risk of GBS cannot be ruled out following influenza vaccination, but the data did not suggest product specific differences. The PRAC also acknowledged that there are some limitations in these findings since influenza vaccination and circulation of influenza virus happen at the same time. Therefore, it is not possible to fully distinguish a causal association of GBS with influenza vaccination given that exposure to influenza virus is known to be associated with an increased risk of GBS.

The PRAC concluded that the benefits of influenza vaccination (pandemic H1N1 or seasonal trivalent) in terms of reduction in influenza-associated morbidity and mortality outweighs any small vaccine-associated risk of GBS.

Summary of recommendation(s)

- No further regulatory action with regard to the product information of pandemic H1N1 or seasonal trivalent vaccines is warranted on the basis of these recent publications. For the full PRAC recommendation se EMA/PRAC/625262/2013 published on the EMA website.

4.2.10. Tapentadol (NAP)

- Signal of suicidal ideation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Background

For background information, see PRAC Minutes May 2013.

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

Discussion

The PRAC discussed the assessment of the further information provided. In the clinical development program (including all phase I to phase IIIb trials with a final study report prior to 20 May 2013) the reported adverse events associated with suicidality were equally distributed over all treatment groups including active comparators and placebo. The qualitative analysis of the spontaneously reported cases contained information that provided plausible alternative explanations or confounding factors such as pre-existing psychiatric disorders, medications which have a known potential to induce psychiatric events, social circumstances, or inadequate analgesia. An association of chronic pain and increased risk for suicidality is a well-known phenomenon, which likely introduces a bias by the indication/target population for tapentadol and could be an explanation for the initially seen disproportion in reporting.

The PRAC agreed that overall, the analysis did not provide any robust evidence that tapentadol could induce suicidality in its target population. However, clarification of the analysis provided is still required to draw final conclusions on the signal.

Summary of recommendation(s)

- The MAHs for the reference nationally authorised tapentadol-containing medicine should be requested to submit to the Rapporteur a further analysis of the signal addressing some clarifications requested by the PRAC within 60 days.

For the full PRAC recommendation se EMA/PRAC/625262/2013 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. Insulin glargine

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

5.1.2. Masitinib

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

5.1.3. Misoprostol

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

5.1.4. Mixture of polynuclear iron(iii)-oxyhydroxide, sucrose and starches

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

5.1.5. Serelaxin

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

5.1.6. Simoctocog alfa

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

5.1.7. Vortioxetine

- 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

See section 14.

RMP in the context of a variation

5.2.1. Dexamethasone – OZURDEX (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Ozurdex is a centrally authorised medicine containing dexamethasone, a corticosteroid, used for the treatment of macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO), and for the inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

The CHMP is evaluating an extension of the therapeutic indication for Ozurdex (dexamethasone), to include the treatment of adult patients with diabetic macular oedema (DME). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 3 for Ozurdex (dexamethasone), submitted in the context of the extension of indication under evaluation by the CHMP, was considered acceptable provided some modifications are implemented as agreed by the PRAC. These include a revision of the 'important potential risks' section and a revision to reflect changes to the adverse drug reactions sections in the product information, as suggested.

5.2.2. Ferumoxytol – RIENSO (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Background

Ferumoxytol is a colloidal iron-carbohydrate complex, used for the treatment of iron deficiency anaemia in adults with chronic kidney disease.

The CHMP is evaluating an extension of the therapeutic indication for Rienso, a centrally authorised product containing ferumoxytol, to include all cause iron deficiency anaemia when oral therapy is ineffective or inappropriate or where there is a need for rapid iron repletion. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 3 for Rienso (ferumoxytol) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable provided that the MAH provides some amendment and clarifications as recommended by the PRAC.
- In particular, the PRAC recommended that educational materials for healthcare professionals and for patients are provided to address the risk of hypersensitivity reactions. Furthermore the

PRAC agreed that a PASS to further characterise the safety concerns about the hypersensitivity reactions should be a condition of the MA; the MAHs should also be requested to submit annual cumulative reviews of hypersensitivity case reports.

5.2.3. Ranibizumab – **LUCENTIS** (CAP)

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

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

Background

Ranimizumab is a monoconal antibody used in the treatment of neovascular (wet) age-related macular degeneration as well as in the treatment of visual impairment due other macular conditions.

The CHMP is evaluating a type II variation procedure for Lucentis, a centrally authorised product containing ranimizumab, to introduce a new pre-filled syringe presentation for Lucentis and include some administrative related changes. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 12.1 for Lucentis (ranimizumab) in the context of the variation 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 under section 8 or 14 as applicable.

RMP in the context of a stand-alone RMP procedure

5.2.4. Epoetin theta – **BIOPOIN** (CAP), **EPORATIO** (CAP)

- Evaluation of an RMP in the context of stand-alone RMP procedures

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Biopoin and Eporatio are centrally authorised medicines containing epoetin theta indicated in treatment of symptomatic anaemia associated with chronic renal failure in adult patients and treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

An updated risk management plan was submitted to include some necessary revisions taking into account the current review of the recommended dose of epoetins and target haemoglobin for patients with chronic kidney disease (see PRAC minutes May 2013) - including both those undergoing and those not undergoing dialysis - with regard with the risk of cardio-vascular events, as well as to include data related to tumour progression with results of 5 years follow-up (3 clinical studies 'XM01-21-22-23'). The PRAC is responsible for providing advice to the CHMP on this updated RMP.

Summary of advice

- The RMP version 11 for Biopoin/Eporatio (epoetin theta) in the context of the variation under evaluation by the CHMP was considered acceptable provided that replies to some points raised by the PRAC are provided by the MAH.
- The MAH should thoroughly discuss a difference in survival observed in study XM01-23 between the two treatments groups in the study, especially with analysis by treatment group for each haematological malignancy. As more severe status of the underlying disease may explain the results on median overall survival, the MAH should thoroughly discuss the patient's haematological malignancy characteristics at baseline. Furthermore clarification should be provided on the cause of death for all fatal cases.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1.1. Aprepitant – **EMEND** (CAP), **fosaprepitant – IVEMEND** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Aprepitant is a selective high-affinity antagonist of human substance P neurokinin 1 (NK_1) receptors indicated for the prevention of postoperative nausea and vomiting (PONV) in adults. Fosaprepitant, a prodrug of aprepitant, is converted to aprepitant when administered intravenously.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Emend and Ivemend, centrally authorised medicines containing aprepitant and fosaprepitant respectively, 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 Emend (aprepitant) and Ivemend (fosaprepitant) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to reflect the possible drug-drug interaction between aprepitant and ifosfamide following cases of neurotoxicity, a potential adverse reaction of ifosfamide, reported after co-administration of aprepitant and ifosfamide. Therefore the current terms of the marketing authorisation(s) should be varied[19].

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

6.1.2. Belimumab – **BENLYSTA** (CAP)

- Evaluation of a PSUR procedure

[19] Update of SmPC section 4.5. 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: Ulla Wändel Liminga (SE)

Background

Belimumab is a human IgG1λ monoclonal antibody indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Benlysta, a centrally authorised medicine containing belimumab, 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 Benlysta (belimumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add delayed-type non–acute hypersensitivity as a warning and as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide a detailed review of any potential case(s) of progressive multifocal leukoencephalopathy (PML).

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. Bimatoprost – LUMIGAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

Bimatoprost is an ocular hypotensive agent indicated for the reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension in adults (as monotherapy or as adjunctive therapy to beta-blockers).

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

[20] 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.

- Nevertheless, the product information should be updated to refine the warning on respiratory disorders and add as undesirable effects asthma, asthma exacerbation, chronic obstructive pulmonary disease (COPD) exacerbation and dyspnoea with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should closely monitor several undesirable effects, in particular cases of retinal vein occlusion, eye pain and blurred vision.

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

6.1.4. Eculizumab – SOLIRIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Background

Eculizumab is a recombinant humanised monoclonal $IgG_{2/4k}$ indicated for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uremic syndrome (aHUS) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Soliris, a centrally authorised medicine containing eculizumab, 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 Soliris (eculizumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add aspergillus infections as an undesirable effect with a common frequency. In addition, the key message of the educational materials under the conditions of the marketing authorisation should be revised to communicate on the risk of aspergillus infections. Therefore the current terms of the marketing authorisation(s) should be varied[22].

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. Etravirine – INTELENCE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

[21] 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.
[22] Update of SmPC section 4.8 and Annex II. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Background

Etravirine is a non-nucleoside reverse transcriptase inhibitors indicated in combination with a boosted protease inhibitor for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients and in antiretroviral treatment-experienced paediatric patients from 6 years of age.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Intelence, a centrally authorised medicine containing etravirine, 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 Intelence (etravirine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to reflect the possible drug-drug interaction between etravirine and boceprevir, as a clinically significant reduction in etravirine pharmacokinetic parameters has been identified when both drugs are concomitantly administered. Therefore the current terms of the marketing authorisation(s) should be varied[23].

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.

6.1.6. Exenatide – **BYDUREON** (CAP), **BYETTA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated for treatment of type 2 diabetes mellitus under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bydureon and Byetta, centrally authorised medicines containing exenatide, 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 Bydureon and Byetta (exenatide) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) for Byetta should be maintained.
- Nevertheless, the product information for Bydureon should be updated to reflect that renal and urinary disorders have been observed with Bydureon, not only with exenatide twice daily

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

(Byetta), with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].

- In the next PSUR, the MAH should provide a detailed review of injection site abscess/ cellulitis and a review of increased liver enzymes, and should consider updating the product information accordingly.

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. Fingolimod – GILENYA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Gilenya, a centrally authorised medicine containing fingolimod, 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 Gilenya (fingolimod) in the approved indication(s) remains favourable.
- The product information should be updated to include information on the results of an interaction study with carbamazepine and a consequent warning to avoid concomitant administration of potent CYP450 inducers. In addition, the existing information on infection under 'undesirable effects' should be revised to reflect that cases of disseminated herpes infection, some fatal, have been reported even at 0.5 mg dose. The product information should be also revised to delete the statement regarding the absence of cases of overdose reported with fingolimod. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should provide further data and in particular, a detailed review of multiple sclerosis relapse and a detailed analysis on fatal cases considering both cumulative and current periods and taking into account relevant factors such as age and gender, history of onset (in particular patients with cardiovascular conditions), risk factors, and confounding factors, time to onset. In addition, the MAH should discuss the relevance of regular dermatological examinations regarding skin cancers for patients with prior history or a family history of melanoma and treated with fingolimod.

[24] 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.
[25] Update of SmPC sections 4.4, 4.5, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

- A signal was raised with the first case of progressive multifocal leukoencephalopathy (PML) without a previous history of natalizumab treatment. As there was a doubt on the initial diagnosis of multiple sclerosis, the PRAC agreed that no change to the product information was necessary. However, the issue should continue to be closely monitored.

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.

6.1.8. Ipilimumab – YERVOY (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Ipilimumab is an antineoplastic agent indicated for the treatment of advanced (unresectable or metastatic) melanoma.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yervoy, a centrally authorised medicine containing ipilimumab, 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 Yervoy (ipilimumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add anaphylactic reactions as an undesirable effect with a very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[26].

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. Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Meningococcal group a, c, w135 and y conjugate vaccine is indicated for active immunisation of adolescents (from 11 years of age) and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W135 and Y, to prevent invasive disease.

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Menveo, a centrally authorised meningococcal conjugate vaccine, 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 Menveo (meningococcal group a, c, w135 and y conjugate vaccine) 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 variation to reflect in the product information anaphylactic reactions as an undesirable effect, and a cumulative analysis of medications errors related to reconstitution and, as appropriate, discuss possibilities to further improve the labelling and packaging.
- In the next PSUR, the MAH should provide further information, in particular, a comprehensive review of cases of whole limb swelling.

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. Mercaptopurine – XALUPRINE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Mercaptopurine is an antineoplastic agent indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xaluprine, a centrally authorised medicine containing mercaptopurine, 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 Xaluprine (mercaptopurine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on the risk of hepatosplenic T cell lymphoma (HSTCL) and lymphoproliferative disorders and to add HSTCL and lymphoproliferative disorders as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[27].

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.

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

6.1.11. Pirfenidone – ESBRIET (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Pirfenidone is an immunosuppressant agent indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Esbriet, a centrally authorised medicine containing pirfenidone, 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 Esbriet (pirfenidone) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a reference to the increases in total serum bilirubin which have been reported alongside increases in aspartate aminotransferase/alanine aminotransferase (AST/ALT) in a small number of patients. Therefore the current terms of the marketing authorisation(s) should be varied[28].

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. Telaprevir – INCIVO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Telaprevir is an inhibitor of the HCV NS3/4A serine protease indicated, in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis) under certain conditions.

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

[28] 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.

- Nevertheless, the product information should be updated to add prerenal azotemia with or without acute renal failure as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[29].
- Due to a potential increase in the risk of mortality associated with the use of telaprevir in patients with advanced/severe liver disease under triple-therapy, the MAH should submit to EMA within 30 days* a review taking into consideration the publication by *Hezode et al.*[30] and *Maasoumy et al* [31] and propose an amendment of the warning section of the product information accordingly.
- In the next PSUR, the MAH should provide a detailed review of cases of sepsis, including the number of cases which occurred on-treatment compared to off-treatment in clinical trials. The reporting rate for sepsis in the post-marketing period should be compared to the background reported rates for sepsis in similar patients on dual therapy found in literature reviews. In addition, the MAH should provide a review of cases of infections of the urinary system and discuss the need for additional risk minimisation for the prevention of renal impairment in the elderly population.

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.

*Post-meeting note: a request from the MAH providing justified grounds for a 30 day extension of this period was received on 22 October 2013. The Rapporteur agreed on such grounds.

6.1.13. Tenofovir disoproxil fumarate – VIREAD (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Tenofovir disoproxil is a nucleoside and nucleotide reverse transcriptase inhibitor indicated in adults and children, for the treatment of HIV-1 infected and for the treatment of chronic hepatitis B.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Viread, a centrally authorised medicine containing tenofovir disoproxil, 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 Viread (tenofovir disoproxil) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.

[29] 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.
[30] Hezode C et al. Safety and efficacy of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in 455 cirrhotic non responders. Week 16 analysis of the French early access program (ANRS CO20-CUPIC) in real-life setting. Hepatology. Conference Abstract. 2012; 56: 217A-8A
[31] Maasoumy B et al. (2013) Eligibility and Safety of Triple Therapy for Hepatitis C: Lessons Learned from the First Experience in a Real World Setting. PLoS ONE 8(2): e55285. doi:10.1371/journal.pone.0055285.

- In the next PSUR, the MAH should provide the total number of cases and specify the total number of medically and non-medically confirmed cases by system organ class (SOC) and include a specific section regarding the number of fatal cases, together with a discussion on the drug causality and short narratives. The MAH should also provide further details on severe renal cases with a rapid time to onset, in particular whether or not patient had renal risk factors at baseline.

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.

6.1.14. Trastuzumab – HERCEPTIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody indicated for the treatment of patients with human epidermal growth factor receptor 2 (HER2) positive early or metastatic breast cancer and for the treatment, in combination with capecitabine or 5-fluorouracil and cisplatin, of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Herceptin, a centrally authorised medicine containing trastuzumab, 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 Herceptin (trastuzumab) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.

The PRAC noted the ongoing CHMP review of a variation procedure to further strengthen the treatment duration recommendation following the results of the HERA[32] study to make clear that extending dosing beyond 1 year is not recommended. In this context, the PRAC supported the dissemination of a DHPC.

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. Voriconazole – VFEND (CAP)

- Evaluation of a PSUR procedure

[32] Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer, Piccart-Gebhart et al, N Engl J Med 2005; 353:1659-1672, October 2005, DOI: 10.1056/NEJMoa052306

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Voriconazole is triazole antifungal agent indicated for the treatment of invasive aspergillosis, candidemia in non-neutropenic patients, fluconazole-resistant serious invasive Candida infections (including *C. krusei*) and serious fungal infections caused by *Scedosporium spp. and Fusarium spp*.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vfend, a centrally authorised medicine containing voriconazole, 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 Vfend (voriconazole) 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 review of cases of medication error and propose an amendment of the product information as appropriate to improve the recommendation for administration of the powder for oral suspension presentation.
- In the next PSUR, the MAH should continue to carefully evaluate any cases of skin abnormalities in paediatric patients and is requested to interact with paediatric centres to discuss the feasibility of a prospective survey. In addition, the MAH should discuss the publication by *Van Hasselt et al.*[33] on a potential interaction between voriconazole and methotrexate causing severe skin reactions. The MAH should also keep under close monitoring cases of drug reaction with eosinophilia and systemic symptoms (DRESS) and consider the need to update the product information 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.

6.2. Follow-up to PSUR procedures[34]

6.2.1. **Saquinavir – INVIRASE** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Harald Herkner (AT)

Background

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the MAH submitted some further clarifications (see PRAC Minutes June 2013) to the previously assessed PSUR.

[33] Severe skin toxicity in paediatric oncology patients treated with voriconazole and concomitant methotrexate, Van Hasselt et al., Antimicrobial agents and chemotherapy, American Society for Microbiology, 2013

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

The PRAC concluded that the information presented did not affect the conclusions and recommendation for the PSUR procedure finalised at the level of PRAC in June 2013. As per agreed criteria, the Committee endorsed the conclusions of the Rapporteur without further plenary discussion.

6.2.2. Sodium oxybate – XYREM (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

Background

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

Summary of advice and conclusions

- The MAH should continue to monitor all events that could be related to brain damage and neurotoxicity, especially those occurring with repeated exposure, and present such results in future PSURs.
- The MAH should submit an updated RMP alongside the forthcoming PSUR submission (due in December 2013).

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[35]

7.1.1. Deferasirox – EXJADE (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Exjade is a centrally authorised medicine containing desferasirox, an oral iron chelator, indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major and for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the selected patient groups.

When a new indication in patients with non-transfusion-dependent thalassaemia (NTDT) syndromes aged 10 years and older was agreed it was also agreed that further safety data in addition to the Assessment of Exjade in Nontransfusion-Dependent Thalassemia THALASSA trial had to be provided by the MAH, therefore an observational cohort study was requested in NTDT paediatric patients over 10 years old, for whom deferoxamine is contraindicated or inadequate, in order to assess the long-term exposure and safety.

A protocol was submitted by the MAH which was assessed by the Rapporteur.

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

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1 - in accordance with Article 107n of Directive 2001/83/EC, considered that a revised PASS protocol should be resubmitted within 30 days to address some considerations provided by the PRAC on the study design. A 30 day-assessment timetable will be applied.

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

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Background

For background, see PRAC Minutes April 2013.

The MAH presented a revised protocol in accordance with the PRAC request which was assessed by the Rapporteur.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.25 in accordance with Article 107n of Directive 2001/83/EC, endorsed the revised protocol.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[36]

7.2.1. Aliskiren – **RASILEZ** (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Rasilez is a centrally authorised medicine containing aliskiren, a renin inhibitor indicated for the treatment of essential hypertension.

As part of the RMP for Rasilez, the MAH for was required to conduct a study in order to investigate colorectal hyperplasia and gastrointestinal cancer. The MAH submitted a protocol for the study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) on the incidence of colorectal hyperplasia and gastrointestinal cancer in treated adult hypertensive patients in the United States – a cohort study based on secondary use of health claims data - which was assessed by the Rapporteur. The PRAC was to provide advice to the CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC agreed that overall, the proposed PASS was well designed, and fulfilled the study objectives. However several issues , in particular how the lack of information on patients aged

[36] 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

65 years and older might affect the study results, should be addressed before the final conclusion on acceptability can be reached. A revised PASS protocol should be resubmitted within 1 month and will follow a 60 day review procedure.

7.2.2. Human normal immunoglobulin – HYQVIA (CAP)

- Evaluation of a PASS protocol

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

Background

HyQvia is a centrally authorised medicine containing human normal immunoglobulin, used as replacement therapy in adults (> 18 years) in primary immunodeficiency syndromes

As part of the RMP for Hyqvia, the MAH for was required to conduct a PASS on the Long-Term Safety of HyQvia. The MAH submitted a protocol for a study to acquire additional long-term data (including assessment of anti-rHuPH20 (Recombinant Human Hyaluronidase) antibodies) on safety of HyQvia and to assess the prescribed treatment regimens and product administration of HyQvia in routine clinical practice in subjects treated with HyQvia, which was assessed by the Rapporteur. The PRAC was to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC recommended that a number of points are taken in account in the final version of the protocol. In particular the MAH should support the keeping of a treatment diary for all patients who have been included in the study to ensure a sufficient documentation of any adverse event during home treatment. Moreover how the rate of adverse reactions will be calculated should be clarified. It would be acceptable for data on anti- rHuPH20 antibodies to not be collected; in this case the MAH should confirm that the proposed protocol can be classified as a non-interventional study.

7.3. Results of PASS imposed in the marketing authorisation(s)[37]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[38]

None

7.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS[39]

See ANNEX, section 16.

[37] In accordance with Article 107p-q of Directive 2001/83/EC
[38] 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
[39] In line with the revised variations regulation for any submission before 4 August 2013

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

See ANNEX, section 17.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. On-going or concluded pharmacovigilance inspection

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

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. **Fingolimod – GILENYA** (CAP)

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

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

Background

For background information see PRAC Minutes April 2013. The PRAC recommended that the MAH of Gilenya submitted a variation to the product information with regards to haemophagocytic syndrome as well as a proposal for a DHPC and communication plan. A variation including a DHPC had been submitted and was assessed by the Rapporteur. PRAC advice was requested by CHMP on the assessment of this variation.

Summary of conclusion and advice

The PRAC considered some amendments necessary to improve the readability of the overall message contained in the DHPC as well as of the detailed recommendation and background information. The PRAC agreed with the Communication Plan as proposed.

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

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. Organisation of the PRAC meetings

- PRAC meeting dates 2016 - 2018

EMA circulated the planned dates for the PRAC meetings in 2016 -2018. Dates can be subject to changes in accordance with potential variations in planning. However, the EMA scientific committee members would be kept informed in advance.

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

- Consultation on the draft List, version October 2013

The PRAC endorsed the updated EURD list, version October 2013.

Post-meeting note: following the PRAC meeting in October 2013, the updated EURD list was adopted by the CHMP at its October 2013 meeting and was published on the EMA website on 6 November 2013 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.4. Signal Management

12.4.1. Signal Management

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

The EMA received a progress report on the activity of the SMART group. On 4 October 2013 the Q&A on Signal Management EMA/261758/2013 was published on the EMA website. The Q&A is directed especially to the MAHs as it contains practical aspects of the signal management process. Furthermore a publication package containing a cumulative list of signals analysed since the start of the PRAC with recommendations made together with the exact texts of the variations requested during September 2013 PRAC was published on EMA website (see PRAC recommendations on safety signals on the EMA website - Home>Regulatory>Human medicines>Pharmacovigilance>Signal management>PRAC recommendations) and will be regularly updated.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Additional Monitoring

- Consultation on the draft List, version October 2013

The PRAC was informed of the products falling within the mandatory scope newly added to the additional monitoring list. The updated list is due publication by the end of October 2013.

Post-meeting note: The updated additional monitoring list was published on the EMA website on 28 October 2013 (see: Home>Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of risk Minimisations

None

12.8. Post-Authorisation Safety Studies

12.8.1. Post-Authorisation Safety Studies

- Q&A on the resubmission of protocols of non-imposed PASS

EMA presented an update to the Questions and Answers on post-authorisation safety studies to be published on the EMA website (Home>Regulatory>Human medicines>Post-authorisation>Post Authorisation Safety Study (PASS)) clarifying that amended protocols of non-imposed PASSs Amended protocol should normally not be resubmitted to the PRAC for review. In specific circumstances and in agreement with the PRAC Rapporteur, a revised protocol may be resubmitted voluntarily to the PRAC by the MAH.

12.9. Community Procedures

None

12.10. Risk communication and Transparency

None

12.11. Continuous pharmacovigilance

12.11.1. Notification of 'withdrawn' products by Marketing authorisation Holders

EMA reminded the PRAC that the amendments to the 2010 pharmacovigilance legislation introduced by Directive 2012/26/EC and Regulation (EU) No 1027/2012 require Marketing Authorisation Holders (MAHs) to notify the competent authorities of the reasons which lead them to temporarily or permanently cease/suspend the marketing of a medicinal product, withdraw the medicinal product from the market, request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation ("withdrawn products").

These notifications need to be sent to the European Medicines Agency for both centrally and nationally authorised medicines and also to the concerned Member State(s) for nationally authorised medicines, when the decision to withdraw the product on the basis that the medicine is harmful; the medicine lacks therapeutic efficacy; the benefit-risk balance of the medicine is not favourable; the qualitative and quantitative composition of the medicine are not as declared; manufacturing or inspection issues have been identified.

Guidance on how to notify competent authorities about these "withdrawn products" is planned to be published on the EMA website by the end of October 2013.

Post meeting note: guidance addressed to Marketing Authorisation Holders was published on the EMA website on 31 October 2013: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/10/news_detail_001939.jsp&mid=WC0b01ac058004d5c1

12.12. Interaction with EMA Committees and Working Parties

None

12.13. Interaction within the EU regulatory network

None

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

12.14.1. European Network Centres for Pharmacoepidemiology and Pharmacovigilance (**ENCePP**)

- Nomination of Committee representatives for the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance ENCePP Steering Group

The PRAC nominated Marie Louise (Marieke) De Bruin - independent scientific expert member, nominated by the European Commission - as representative for the ENCePP Steering Group.

13. Any other business

13.1.1. EMA new organisation structure

The revised EMA organisational structure was outlined to the Committee and the input from the Committee actively sought on the review of all operations and to re-designed processes in order to give best possible support to the Committee.

13.1.2. Assessors training for sharing best practice in pharmacovigilance assessment

The proposed dates for the assessors training were discussed and it was agreed to organise a training session in November 2013 and, if possible in February 2014.

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. Brimonidine

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

14.1.2. Cabozantinib

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

14.1.3. Dolutegravir

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

14.1.4. Florbetaben (^{18}F)

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

14.1.5. Insulin degludec, liraglutide

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

14.1.6. Macitentan

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

14.1.7. Peginterferon beta–1a

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

14.1.8. Tilmanocept

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

14.1.9. Tobramycin

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

14.1.10. Travoprost

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

14.1.11. Zoledronic acid

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

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. Aztreonam – CAYSTON (CAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

14.2.2. Betaine – CYSTADANE (CAP)

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

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

14.2.3. Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins – CHONDROCELECT (CAP)

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

14.2.4. Cinacalcet – MIMPARA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

14.2.5. Dabigatran – PRADAXA (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

14.2.6. Dexmedetomidine – DEXDOR (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

14.2.7. Eculizumab – SOLIRIS (CAP)

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

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

14.2.8. Emtricitabine – EMTRIVA (CAP)

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

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

14.2.9. Emtricitabine, tenofovir disoproxil – TRUVADA (CAP)

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

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

14.2.10. Everolimus – AFINITOR (CAP), **VOTUBIA** (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.11. Fingolimod – GILENYA (CAP)

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

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

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

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

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

14.2.13. Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.14. Methylnaltrexone – RELISTOR (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.15. Mifamurtide – MEPACT (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.16. Pirfenidone – ESBRIET (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.17. Retigabine – TROBALT (CAP)

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

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

14.2.18. Tacrolimus – PROTOPIC (CAP)

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

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

14.2.19. Telaprevir – INCIVO (CAP)

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

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

14.2.20. Tenofovir disoproxil fumarate – VIREAD (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

14.2.21. Vandetanib – CAPRELSA (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

RMP in the context of a variation

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

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

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

14.2.23. 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)

14.2.24. Denosumab – XGEVA (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.25. Golimumab – SIMPONI (CAP)

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

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

14.2.26. Idursulfase – ELAPRASE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

14.2.27. Linagliptin, metformin – JENTADUETO (CAP)

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

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

14.2.28. Nilotinib – TASIGNA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.29. Omalizumab – XOLAIR (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.30. Omalizumab – XOLAIR (CAP)

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

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

14.2.31. Paclitaxel – ABRAXANE (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)
The PRAC agreed on the conclusion of the Rapporteur assessment of the RMP version 13 for Abraxane (paclitaxel) via written procedure on the 11 October 2013.

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

- Evaluation of an RMP in the context of a variation

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

14.2.33. Peginterferon alfa-2a – PEGASYS (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.34. Sorafenib – NEXAVAR (CAP)

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

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

14.2.35. Tacrolimus – ADVAGRAF (CAP), **MODIGRAF** (CAP)

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

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

14.2.36. Tocilizumab – ROACTEMRA (CAP MAA)

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

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

14.2.37. Ulipristal – ESMYA (CAP MAA)

- Evaluation of an RMP in the context of a variation

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

14.2.38. Voriconazole – VFEND (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

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

See Bazedoxifene (CONBRIZA); Eslicarbazepine (ZEBINIX), Japanese encephalitis vaccine (inactivated, adsorbed) (IXIARO), Tacrolimus (MODIGRAF) under section 8 or 16 as applicable.

RMP in the context of a stand-alone RMP procedure

14.2.39. Adefovir dipivoxil – HEPSERA (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

14.2.40. Human papilloma virus [types 16, 18] (**recombinant**, **adjuvanted**, **adsorbed**) **– CERVARIX** (CAP)

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

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

14.2.41. Imiglucerase – CEREZYME (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.42. Pegfilgrastim – NEULASTA (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.43. Telbivudine – SEBIVO (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

14.2.44. Temsirolimus – TORISEL (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.45. Velaglucerase alfa – VPRIV (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

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

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines, remained 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).

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines, remained 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[40]

15.1.1. Aztreonam – CAYSTON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

15.1.2. Betaine – CYSTADANE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

15.1.3. Bevacizumab – AVASTIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

15.1.4. Certolizumab pegol – CIMZIA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

15.1.5. Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins – CHONDROCELECT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

15.1.6. Cinacalcet – MIMPARA (CAP)

- Evaluation of a PSUR procedure

[40] 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.

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

15.1.7. Colestilan – BINDREN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

15.1.8. Copper (^{64}Cu) chloride – CUPRYMINA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

15.1.9. Dabigatran – PRADAXA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

15.1.10. Dexmedetomidine – DEXDOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

15.1.11. Emtricitabine – EMTRIVA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

15.1.12. Emtricitabine, tenofovir disoproxil – TRUVADA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

15.1.13. Enfuvirtide – FUZEON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

15.1.14. Everolimus – AFINITOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

15.1.15. Everolimus – VOTUBIA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

15.1.16. Florbetapir (^{18}F) – AMYVID (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

15.1.18. Influenza vaccine (H1N1) (surface antigen, inactivated, adjuvanted) – FOCETRIA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

15.1.19. Insulin degludec – TRESIBA (CAP)
Insulin degludec, **insulin aspart – RYZODEG** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

15.1.20. Lapatinib – TYVERB (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

15.1.21. Methylnaltrexone – RELISTOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

15.1.22. Mifamurtide – MEPACT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

15.1.23. Olanzapine – ZALASTA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Terhi Lehtinen (FI)

15.1.24. Olanzapine pamoate – ZYPADHERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Terhi Lehtinen (FI)

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

15.1.26. Panitumumab – VECTIBIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

15.1.27. Raltegravir – ISENTRESS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

15.1.28. Retigabine – TROBALT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

15.1.29. Rivaroxaban – XARELTO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

15.1.30. Tacrolimus – PROTOPIC (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

15.1.31. Teduglutide – REVESTIVE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

15.1.33. Travoprost – TRAVATAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

15.1.34. Travoprost, timolol – DUOTRAV (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

15.1.35. Vandetanib – CAPRELSA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

15.1.36. Zonisamide – ZONEGRAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

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)[41]

See section 7.

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

16.2.1. Catridecog – NOVOTHIRTEEN (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

16.2.2. Dapagliflozin – FORXIGA (CAP)

- Evaluation of a PASS protocol

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

16.2.3. Insulin degludec – TRESIBA (CAP)

- Evaluation of a PASS protocol

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

16.2.4. Linaclotide – CONSTELLA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

16.2.5. Mirabegron – BETMIGA (CAP)

- Evaluation of a PASS protocol

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

16.2.6. Pegloticase – KRYSTEXXA (CAP)

- Evaluation of a PASS protocol

[41] In accordance with Article 107n of Directive 2001/83/EC
[42] 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: Martin Huber (DE)

16.2.7. Pegloticase – KRYSTEXXA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

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

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

16.2.9. Tenofovir disoproxil – VIREAD (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

16.3. Results of PASS imposed in the marketing authorisation(s)[43]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[44]

None

16.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS[45]

16.5.1. Certolizumab pegol – CIMZIA (CAP)

- Evaluation of interim PASS results

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

16.5.2. Golimumab – SIMPONI (CAP)

- Evaluation of interim PASS results

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

16.5.3. Golimumab – SIMPONI (CAP)

- Evaluation of interim PASS results

[43] In accordance with Article 107p-q of Directive 2001/83/EC
[44] 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
[45] In line with the revised variations regulation for any submission before 4 August 2013

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

16.5.4. Vidagliptin – GALVUS (CAP), **JALRA** (CAP), **XILIARX** (CAP)
Vidagliptin, metformin – EUCREAS (CAP), **ICANDRA** (CAP), **ZOMARIST** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (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. Bazedoxifene – CONBRIZA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

17.1.2. Bortezomib – VELCADE (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

17.1.3. Catumaxomab – REMOVAB (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

17.1.4. Eslicarbazepine – ZEBINIX (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

17.1.5. Galsulfase – NAGLAZYME (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

17.1.6. Japanese encephalitis vaccine (inactivated, adsorbed) – IXIARO (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

17.1.7. Ribavirin – RIBAVIRIN TEVA (CAP), RIBAVIRIN TEVA PHARMA (CAP)

- PRAC consultation on renewals of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

17.1.8. Tacrolimus – MODIGRAF (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

17.1.9. Vandetanib – CAPRELSA (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

ANNEX II – List of participants:

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 7-10 October 2013 meeting.

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***
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	Octocog alfa, combined hormonal contraceptives, aflibercept, sorafenib, rivaroxaban
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Eva Jirsová	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Terhi Lehtinen	Finland	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
George Aislaitner	Greece	Full involvement	
Julia Pallos	Hungary	Full involvement	
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Ruchika Sharma	Ireland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Kamila Czajkowska	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero Corominas	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	

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*
Julie Williams	United Kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies *Product / substance*
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise (Marieke) De Bruin		Full involvement	
Stephen J. W. Evans		Cannot act as Rapporteur or Peer-reviewer for:	Human papillomavirus vaccine, Pandemic H1N1 and seasonal trivalent influenza vaccines
Brigitte Keller-Stanislawski		Full involvement	
Hervé Le Louet		Full involvement	
Lennart Waldenlind		Full involvement	

Health care professionals and patients observers	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies *Product / substance*
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
Torbjörn Callreus	Denmark	
Gedske Thomsen	Denmark	
Camille Thomassin	France	
Béatrice Porokhov	France	
Kim Bouillon	France	
Leo Niskanen	Finland	
Yvonne Buggy	Ireland	
Ria Mahon	Ireland	
Maarten Simoons	Netherlands	
Lies van Vlijmen	Netherlands	
Roman Zahorec	Slovakia	
Charlotte Backman	Sweden	
Rolf Gedeborg	Sweden	
Bengt Ljungberg	Sweden	
Elina Ronnemaa	Sweden	
Tomas Salmonsson	Sweden	
Patrick Batty	United Kingdom	
Elena Elliot-Smith	United Kingdom	
Sarah Mee	United Kingdom	
Alison Shaw	United Kingdom	
Catherine Tregunno	United Kingdom	
Jane Woolley	United Kingdom	

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

European Medicines Agency
Peter Arlett – Head of Department, Pharmacovigilance
Christelle Bouygues – Scientific Administrator, Regulatory Affairs
Roberto De Lisa – Scientific Administrator, PRAC Secretariat
Corinne De Vries – Head of Service, Risk Management Review
Georgy Genov – Head of Service, Signal Management
Kasia Kmiecik – Assistant, PRAC Secretariat
Sheila Kennedy – Head of Service, Committees Secretariat
Geraldine Portier – Scientific Administrator, PRAC Secretariat
Tanya Sepehr – Assistant, PRAC Secretariat
Tania Teixeira – Head of Service, Referral Procedures

ANNEX III – List of abbreviations

For a List of the acronyms and abbreviations used in the PRAC (Pharmacovigilance Risk Assessment Committee) Minutes used in the PRAC minutes, see:

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