EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 June 2013
EMA/PRAC/336080/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the 13-16 May 2013 meeting

Chair: June Raine – Vice-Chair: Almath Spooner

Explanatory notes

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

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

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

Signals assessment and prioritisation
(Item 4 of the PRAC Minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as reports of adverse events from healthcare professionals or patients (so called spontaneous reports), clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
After evaluation of a safety signal the conclusion could be that the medicine caused the adverse reaction, that a causal relationship with the adverse event was considered unlikely, or that no clear answer could be given and the signal therefore is to be further investigated. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the product information (the summary of product characteristics and the package leaflet).
For completeness the information on signals is complemented, when available, by information on worldwide population exposure.

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

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

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

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

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

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

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

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

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

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1. Introduction

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

The Chairperson opened the meeting and welcomed all participants to the 13-16 May 2013 meeting of the PRAC.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the agenda topics 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 in relation to the topics for discussion (see Annex II). No new or additional conflicts were declared.

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. 23 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 13-16 May 2013

The agenda was adopted with the addition of the following topics upon request from the members of the Committee and the EMA secretariat: codeine 3.2.1. ; pazopanib 6.2.3. ; retigabine 10.1.2. ; aprotinin 10.3.2. .

1.3. Minutes of the previous PRAC meeting on 8-11 April 2013

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting on 8-11 April 2013 were published on 5 June 2013 on the EMA website (EMA/PRAC/332071/2013).

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

2.1. Newly triggered procedures

None

2.2. Ongoing Procedures

2.2.1. **Flupirtine** (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 107i of Directive 2001/83/EC was ongoing for flupirtine-containing medicines (see minutes of PRAC 4-7 March 2013). The Rapporteurs prepared a preliminary assessment report following the responses received from the MAHs to the list of questions (LoQs) agreed by the PRAC.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusions of the Rapporteurs and agreed on a list of outstanding issues to be addressed by the MAHs, who will be invited to address them in an oral explanation at the 10-13 June 2013 PRAC meeting, in accordance with an updated timetable for the review (EMA/PRAC/137732/2013 Rev.1).

2.3. Procedures for finalisation

2.3.1. Cyproterone, ethinylestradiol – DIANE 35 & other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 mcg (NAP)

- Review of the benefit-risk balance of cyproterone 2mg / ethinylestradiol 35 mcg-containing products following notification by France of a referral under Article 107i of Directive 2001/83/EC

Regulatory details:

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

Background

A referral procedure under Article 107i of Directive 2001/83/EC for medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms -containing medicines was to be concluded (see also minutes of the PRAC 8-11 April 2013). An ad-hoc expert meeting took place at the EMA on 26 April 2013. A final assessment of the data submitted, taking in consideration the outcome of the expert meeting, was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs, the outcome of the expert meeting and heard the responses of the MAH who was invited for an oral explanation during the meeting. The PRAC discussed the risk of thromboembolism in the light of the proposed risk minimisation measures.

Summary of recommendation(s)/conclusions

The PRAC adopted, by majority vote, recommendations to be considered by CMDh for a final position – EMA/280182/2013 stating that the benefits of DIANE 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms continue to outweigh their risks for the treatment of moderate to severe acne (with or without seborrhoea) related to androgen sensitivity and/or hirsutism in women of reproductive age. In addition, the PRAC recommended that these medicines, when used for the treatment of acne, should only be used when alternative treatments have failed. Since Diane 35

and its generics act as hormonal contraceptives, they should not be used in combination with other hormonal contraceptives.

Thirty-one members/alternates voted in favour of the recommendation together with Iceland and Norway, while one member had divergent views[1] (see EMA/339116/2013 PRAC Assessment report for & other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 mcg containing medicinal products).

Post-meeting note: the press release 'Benefits of Diane 35 and its generics outweigh risks in certain patient groups - PRAC recommendation endorsed by CMDh' EMA/318380/2013 was published on the EMA website on 30 May 2013.

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

3.1. Newly triggered Procedures

3.1.1. Agents acting on the renin-angiotensin system (CAP, NAP): angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEi), direct renin inhibitors (aliskiren)

- Review of the risks of dual blockade of the renin angiotensin system through concomitant use of ARBs, ACEi or aliskiren-containing medicines following notification by Italy of a referral under Article 31 of Directive 2001/83/EC based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)
PRAC Co-Rapporteur: Martin Huber (DE), Dolores Montero (ES), Almath Spooner (IE), Menno van der Elst (NL), Margarida Guimarães (PT), Tatiana Magalova (SK), Qun-Ying Yue (SE), Julie Williams (UK)

Background

The Italian Medicines Agency (AIFA) sent a letter of notification dated 17 April 2013 of a referral under Article 31 of Directive 2001/83/EC for the review of the risks of dual blockade of the renin angiotensin system; see minutes of the PRAC 8-11 April 2013, 'signals', for background.

Discussion

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

The PRAC appointed Carmela Macchiarulo (IT) as overall Rapporteur and Martin Huber (DE), Dolores Montero (ES); Almath Spooner (IE); Menno van der Elst (NL); Margarida Guimarães (PT); Tatiana Magalova (SK); Qun-Ying Yue (SE); Julie Williams (UK) as Co-Rapporteurs for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (published on the EMA website EMA/PRAC/290692/2013) and a timetable for the procedure (EMA/PRAC/290691/2013).

[1] Isabelle Robine (FR)

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

- Review of the benefit-risk balance of strontium ranelate-containing medicines 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

The European Commission initiated, on 25 April 2013, a referral under Article 20 of Regulation (EC) No 726/2004 – following procedural steps of Article 31 of Directive 2001/83/EC - for the review of Osseor and Protelos, centrally authorised medicines containing strontium ranelate. This referral was initiated following the conclusion of the assessment of the latest PSUR procedure for Osseor and Protelos (see PRAC minutes 8-11 April 2013 for background) recommending a more in depth review of all the available data on the benefits and risks of the medicine in light of new data suggesting an increased risk of serious cardiac disorders.

Discussion

The PRAC noted the initiation of the procedure from the European Commission and discussed a list of questions to be addressed in the review as well as a timetable for conducting the review. The PRAC also agreed that an ad-hoc expert meeting should be convened to allow full understanding of the evidence and to support the PRAC in its final decision. A preliminary list of questions to be addressed by the experts, to be organised for September 2013, was discussed.

Summary of recommendation(s) / conclusions

The Committee adopted a list of questions to be addressed by the MAH (EMA/PRAC/283429/2013) and a timetable for the procedure (EMA/PRAC/283428/2013) as well as a list of questions to be addressed by the experts.

3.2. Ongoing Procedures

3.2.1. Codeine (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC was ongoing for codeine-containing medicines (see minutes of PRAC 8-11 April 2013). An extension of the scope of the procedure to include dihydrocodeine was considered.

Summary of recommendation(s) / conclusions

The PRAC discussed the possible extension of the scope and agreed that dihydrocodeine-containing medicines are not to be included in the scope of the referral procedure. Any further regulatory action for dihydrocodeine-containing medicines, if needed, would be more efficiently dealt with as a new procedure at the conclusion of the review for codeine.

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

- Review of the benefit-risk balance of combined hormonal contraceptives following the 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 was ongoing for combined hormonal contraceptives (see minutes of PRAC 8-11 April 2013). An expert meeting is planned for 2 July 2013.

Summary of recommendation(s) / conclusions

The PRAC agreed on the expertise required for the ad-hoc expert group to be convened and a list of questions to be addressed by the experts attending the meeting. The questions relate to the benefits and risks of these products including risk recognition as well as risk management. Members were invited to nominate experts from the Member States, in accordance with the expertise required, to participate to the meeting. EMA clarified that the current provisions in terms of the handling of conflicts of interest will be applied.

3.2.3. Diclofenac (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC was ongoing for diclofenac-containing medicines (see minutes of PRAC 4-7 March 2013). An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. Moreover a request for an extension of the timetable was proposed by one of the MAHs.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and agreed a proposal for updating the product information for diclofenac-containing medicines as part of a list of outstanding issues to be addressed by the MAHs. The MAHs will be invited to address the outstanding issues in an oral explanation at the 10-13 June 2013 PRAC meeting, in accordance with the updated timetable for the review (EMA/PRAC/264325/2013).

During the discussion the PRAC was informed of the results of a collaborative meta-analysis of individual participant data from all randomised trials with at least one unconfounded comparison involving a selective cyclo-oxygenase-2 inhibitor (coxib) or a traditional non-steroidal anti-inflammatory drug (tNSAID) performed by the CNT (Coxib and traditional NSAID Trialists' Collaboration) from the clinical trial service unit and epidemiological studies unit of the University of Oxford (UK). Some of the main investigators[2] were invited to present at the meeting. Finally the PRAC agreed to conclude the procedure in June 2013 as per agreed timetable.

Post–meeting note: the results presented at the meeting were published in The Lancet on 30 May 2013[3].

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

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for HES-containing products (see minutes of PRAC 8-11 April 2013). An updated assessment of the data submitted by the MAH was produced by the Rapporteurs according to the agreed timetable. An ad-hoc expert group on the referral took place on the 19 of April 2013.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and heard the outcome of the ad-hoc expert meeting. Based on the conclusion and the updated assessment report the PRAC agreed a list of outstanding issues to be addressed by the MAHs, who will be invited to address these in an oral

[2] Professor Colin Baigent, Dr Jonathan Emberson; via TC Professor Carlo Patrono
[3] Coxib and traditional NSAID Trialists' (CNT) Collaboration Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials - The Lancet 30 May 2013(Article in Press DOI: 10.1016/S0140-6736(13)60900-9).

explanation at the 10-13 June 2013 PRAC meeting, in accordance with the updated timetable for the review (EMA/PRAC/751078/2012 Rev.1).

Upon request of the Rapporteur and of the Co-Rapporteur, the PRAC also confirmed that the terms of the notification covers all licensed indications.

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

- Review of the benefit-risk balance of short-acting beta agonists-containing products in the management of tocolysis and other obstetric indications following notification by Hungary of a referral under Article 31 of Directive 2001/83/EC based on pharmacovigilance data

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for short-acting beta agonist containing products in the management of tocolysis and other obstetric indications (see minutes of PRAC 26-29 November 2012). An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and discussed preliminary proposals for the product information and agreed on a list of outstanding issues to be addressed by the MAHs, who will be invited to address these in an oral explanation at the 8-11 July 2013 PRAC meeting, in accordance with the updated timetable for the review (EMA/PRAC/744203/2012 – rev 1). The PRAC agreed to finalise the procedure in a short timeframe given that there has been previous regulatory consideration of this issue and the current referral procedure sought to ensure that the final agreed regulatory action covers all appropriate products and obstetric indications. A preparatory discussion on the communication strategy will be planned for the June 2013 PRAC meeting.

3.3. Procedures for finalisation

3.3.1. Almitrine (NAP)

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

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)
PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

A referral procedure under Article 107i of Directive 2001/83/EC for almitrine-containing medicines (see minutes of the PRAC 26-29 November 2012 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. The PRAC discussed the evidence on the risks of peripheral neuropathy and weight loss in the context of the current clinical management of chronic hypoxemia in chronic obstructive pulmonary disease (COPD). It was agreed that risk minimisation measures that had previously been put in place had not reduced the reporting of peripheral neuropathy and unwanted weight loss.

Furthermore, the PRAC noted the absence of clinically meaningful data demonstrating a favourable benefit-risk balance in an identifiable population. The MAH did not propose to generate evidence to demonstrate a positive benefit-risk balance in any patient population. Considering that no conditions for lifting a suspension of the MA could be envisaged, the PRAC agreed that a revocation of the MA would be appropriate.

Summary of recommendation(s)/conclusions

The PRAC adopted, by consensus, the revocation of the marketing authorisations for almitrine-containing medicines and adopted a recommendation to be considered by CMDh – see Q&A EMA/286565/2013. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

Post-meeting note: the press release 'Oral almitrine to be withdrawn by EU Member States' representing the agreement reached by the CMDh EMA/313994/2013 was published on the EMA website on 31 May 2013.

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

None

4. Signal assessment and prioritisation[4]

4.1. New signals detected from EU spontaneous reporting systems

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

- Signal of QT prolongation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

[4] 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 if any regulatory action is required.

Background

Agomelatine is an antidepressant used in the treatment of major depressive episodes.

The exposure for Valdoxan, a centrally authorised medicine containing agomelatine, is estimated to have been more than 5,800,000 patient-months worldwide, in the period from its first authorisation in 2009 until 2012.

During routine signal detection activities, a signal of QT prolongation was identified by the EMA, based on 7 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported and considered that the evidence supporting an association between agomelatine and QT-prolongation was relatively limited. However, since QT prolongation is a potentially serious event further review of the signal was warranted.

Summary of recommendation(s)

- The MAH for Valdoxan/Thymanax (agomelatine) should submit to the EMA, within 60 days, a cumulative review of the signal of QT prolongation and related adverse reactions.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Capecitabine – XELODA (CAP)

- Signal of convulsions

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Capecitabine is an antineoplastic agent used in the treatment of colorectal, colon, stomach and breast cancer.

The exposure for a centrally authorised medicines containing capecitabine is estimated to have been more than 570,000 patients worldwide, in the period from 2010 to 2012.

During routine signal detection activities, a signal of convulsions was identified by the EMA, based on about 160 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported and noted that despite the relatively high absolute number of reports, the reporting rate was low considering the extensive worldwide exposure in comparison with other substances. However some cases were well described, severe and also published in the literature[5,6]. Furthermore, drug-induced hyponatraemia, encephalopathy and

[5] Fantini M, Gianni L, Tassinari D, Nicoletti S, Possenti C, Drudi F, Sintini M, Bagli L, Tamburini E, Ravaioli A. Toxic encephalopathy in elderly patients during treatment with capecitabine: literature review and a case report. J Oncol Pharm Pract. 2011 Sep;17(3):288-91.

dehydration (all known adverse reactions of capecitabine containing medicines) could provide a biological mechanism. Therefore the PRAC agreed that the signal warranted further investigation.

Summary of recommendation(s)

- The MAH for Xeloda (capecitabine) should submit to the EMA, within 60 days, a cumulative review of the signal of convulsion. The request will be included in the current PSUR assessment procedure – see 6.1.4. .
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Bevacizumab – AVASTIN (CAP)

- Signal of anaphylactic shock

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Bevacizumab is a monoclonal antibody used in combination with other antineoplastic agents in the treatment of different types of cancer.

The exposure for Avastin a centrally authorised medicine containing bevacizumab, is estimated to have been more than 1,300,000 patients worldwide in the period from first authorisation in 2004 until 2011.

During routine signal detection activities, a signal of anaphylactic shock (MedDRA preferred term) was identified by the EMA, based on 88 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of anaphylactic shock and noted that in the majority (85%) of the cases, the patients were treated for colon, rectal, colorectal or large intestinal carcinoma. Ten of these cases had no other explanation for the reaction that occurred after or during the infusion of bevacizumab. Severe anaphylactic reactions and cytokine release reactions including fatalities have been already reported in patients treated with other monoclonal antibodies and the product information for Avastin (bevacizumab) was recently updated to communicate the risk of developing infusion and hypersensitivity reactions. The different biological mechanisms underlying infusion reactions remain not fully characterised; however, the PRAC agreed that this new evidence warranted further review.

Summary of recommendation(s)

- The MAH for Avastin (bevacizumab) should submit to the EMA, within 30 days, a variation for an update of the product information which reflects the most recent information identified in Eudravigilance.
- Furthermore the MAH should provide information regarding the status for development of an assay aiming at diagnosing anaphylaxis due to IgE hypersensitivity.

[6] Niemann B, Rochlitz C, Herrmann R, Pless M. Toxic encephalopathy induced by capecitabine. Oncology. 2004;66(4):331-5.

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

4.1.4. Duloxetine – ARICLAIM (CAP), CYMBALTA (CAP), XERISTAR (CAP), YENTREVE (CAP)

- Signal of interaction with linezolid leading to serotonin syndrome

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Background

Duloxetine is an antidepressant used in the treatment of major depression, diabetic peripheral neuropathic pain, generalised anxiety disorder and stress urinary incontinence.

The exposure for centrally authorised medicines containing duloxetine, is estimated to have been more than 43,000,000 patients worldwide, in the period from first authorisation in 2004 to 2012.

Linezolid is an antibiotic indicated for the treatment of community acquired pneumonia and nosocomial pneumonia caused by susceptible Gram positive bacteria, as well as for the treatment of complicated skin and soft tissue infections only when known or suspected to be caused by susceptible Gram positive bacteria. Linezolid is the first member of oxazolidinone antibiotics with non-selective, reversible monoamine oxidase (MAO) inhibitory action.

During routine signal detection activities, a signal of interaction with linezolid leading to serotonin syndrome was identified by the EMA, based on 6 cases retrieved from EudraVigilance for duloxetine. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of serotonin syndrome reported with concomitant use of linezolid - two of which had been published in the literature - and concluded that the evidence indicated a plausible pharmacodynamic interaction. The PRAC agreed that it would be important to adequately inform clinicians that linezolid exhibits reversible MAO inhibitory action and that the duloxetine product information should be updated accordingly.

Summary of recommendation(s)

- The MAH for centrally authorised duloxetine medicines should submit to the EMA, within 60 days, a proposal for amending the product information regarding interaction with linezolid possibly leading to serotonin syndrome, in the framework of a variation[7].

[7] SmPC: section 4.4 Special warnings and precautions for use
~~Use with antidepressants~~
~~Caution should be exercised when using <name> in combination with antidepressants. In particular the combination with selective reversible MAOIs is not recommended.~~
Serotonin syndrome
As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with duloxetine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs , tricyclic antidepressants or triptans), with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.5).
Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

4.1.5. Efavirenz – **STOCRIN** (CAP), **SUSTIVA** (CAP)

- Signal of interaction with *Ginkgo biloba*

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Background

Efavirenz is a non-nucleoside reverse transcriptase inhibitor used in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1).

The exposure for Stocrin and Sustiva, centrally authorised medicines containing efavirenz, is estimated to have been more than 1,800,000 patients worldwide, in the period from first authorisation in 1998 to 2012.

During routine signal detection activities, a signal of interaction with Ginkgo biloba was identified by the EMA, based on 2 cases published in the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of interaction between efavirenz and Ginkgo biloba published in the literature[8]. While the frequency of reporting of a pharmacokinetic interaction between Ginkgo biloba extracts and efavirenz was low given the high worldwide exposure, data from the two published cases were considered convincing. Although the biological mechanism for this interaction remains unclear, a possible induction of CYP3A4, CYP2B6 or glycoprotein P by the terpenoids contained in Gingo biloba was suggested, leading to a decrease in efavirenz plasma concentrations and possible subsequent virological failure. The PRAC agreed that the product information of efavirenz-containing medicinal products should reflect this possible interaction. The PRAC also suggested that this possible interaction should be brought to the attention of the Committee on Herbal Medicinal Products (HMPC).

Summary of recommendation(s)

- The MAH for efavirenz-containing medicinal products (Stocrin/Sustiva, Atripla) should submit to the EMA, within 60 days, a variation[9] to update the product information relating the interaction of efavirenz with Ginkgo biloba.

If concomitant treatment with duloxetine and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Section 4.5 Interaction with other medicinal products and other forms of interaction
Monoamine oxidase inhibitors (MAOIs)

[8] Wiegman DJ, Brinkman K, Franssen EJ. Interaction of Ginkgo biloba with efavirenz. AIDS. 2009 Jun 1;23(9):1184-5.
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.

[9] SmPC: section 4.3 Contraindications
Herbal preparations containing St. John's wort (Hypericum perforatum) or Ginkgo biloba must not be used while taking efavirenz due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).
4.5 Interaction with other medicinal products and other forms of interaction
Contraindications of concomitant use
Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).
St. John's wort (Hypericum perforatum): co-administration of efavirenz and St. John's wort or herbal preparations containing St. John's wort is contraindicated. Plasma levels of efavirenz can be reduced by concomitant use of St. John's wort due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John's wort and the dose of efavirenz may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

4.1.6. Mirabegron – BETMIGA (CAP)

- Signal of urinary retention

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Background

Mirabegron is a beta 3-adrenoceptor agonist used in the treatment of symptomatic treatment of urgency and increased micturition frequency and / or urge incontinence in some patients.

Betmiga, a centrally authorised medicine containing mirabegron, is estimated to have been used by more than 5000 patients. Since the medicine has been authorised in 2012 this is based on the exposure calculated form clinical trials, pending availability of further data.

During routine signal detection activities, a signal of urinary retention was identified by the EMA, based on 43 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of urinary retention and agreed that further information on the role of benign prostatic hyperplasia as an underlying condition was needed to clarify any possible role of mirabegron in the development of the reaction. The PRAC noted that this signal was not apparent during the clinical trials performed with mirabegron. Since in the clinical development phase of Betmiga (mirabegron) the study of the elderly population, in particular of patients of 75 years of age and older, was limited, the PRAC also suggested that a stratified analysis by age group of all the cases of urinary retention could be helpful in further assessing the signal.

Summary of recommendation(s)

- The MAH for Betmiga (mirabegron) should submit to the EMA a cumulative review of the signal, including an analysis of all case reports of urinary retention and related terms.
- This review should be submitted in the context of the next PSUR with data lock point (DLP) on 30 June 2013.

Ginkgo biloba extracts: co-administration of efavirenz and Ginkgo biloba extracts is contraindicated. Plasma levels of efavirenz may be reduced by concomitant use of Ginkgo biloba extracts (see section 4.3).
Package Leaflet
2. What you need to know before you take <efavirenz>
Do not take <efavirenz>
(….)
if you are currently taking any of the following medicines:
astemizole or terfenadine (used to treat allergy symptoms)
bepridil (used to treat heart disease)
cisapride (used to treat heartburn)
ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraine and cluster headaches)
midazolam or triazolam (used to help you sleep)
pimozide (used to treat certain mental conditions)
St. John's wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety)
Ginkgo biloba extracts (a herbal remedy)
If you are taking any of these medicines, tell your doctor immediately. Taking these medicines with <efavirenz> could create the potential for serious and/or life-threatening side-effects or stop <efavirenz> from working properly.
(…)
Other medicines and <efavirenz>
You must not take <efavirenz> with certain medicines. These are listed under Do not take <efavirenz>, at the start of Section 2. They include some common medicines and a herbal remedyies (St. John's wort and Ginkgo biloba extracts) which can cause serious interactions.

4.1.7. Nicardipine (NAP)

- Signal of acute pulmonary oedema in off-label use during pregnancy

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Nicardipine is a calcium channel blocker (CCB) used in the treatment of hypertension as well as for the prophylaxis and therapy of coronary insufficiency of chronic angina.

Nationally authorised medicines containing nicardipine have been very widely used worldwide and have been marketed since the late 1980s. In the period from 2007 until 2010 the global exposure has been calculated to be over 239,000,000 patient years.

Nicardipine and the other CCBs, given their muscle relaxant effects against smooth muscle cells of the genitourinary system, are used off-label as tocolytics.

During routine signal detection activities, a signal of acute pulmonary oedema was identified by IT, based on 36 cases retrieved from EudraVigilance. IT confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of acute pulmonary oedema reported and noted that as many as 35 out of 36 total cases concerned use in pregnant women, where nicardipine was used off-label as a tocolytic agent. The PRAC agreed that further information on the signal and on the usage of nicardipine across the EU as a tocolytic agent was needed.

The PRAC appointed Carmela Macchiarulo (IT) for follow-up of this signal.

Summary of recommendation(s)

- The MAH for the innovator nicardipine-containing medicines should submit to the Rapporteur, within 60 days, a cumulative review of the signal.
- The PRAC Rapporteur should transmit a NUI (non-urgent request of information) to the MSs to collect information on the existing contraindications/warnings regarding pregnancy contained in the product information of nicardipine medicines currently authorised in the EU.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.8. Orlistat – **ALLI** (CAP), **XENICAL** (CAP)

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

Regulatory details:

PRAC Rapporteur: *to be appointed*

Background

Orlistat is an inhibitor of gastrointestinal lipases used in the treatment of obesity in adults who are overweight (body mass index, BMI, ≥28 kg/m^2) and should be taken in conjunction with a mildly hypocaloric, low-fat diet.

The exposure for centrally authorised medicines containing orlistat, is estimated to have been more than 50 million patients/consumers worldwide, in the period from first authorisation in 1998 to 2012.

During routine signal detection activities, a signal of pharmacokinetic drug interaction with highly active antiretroviral therapy (HAART) was identified by EMA based on two literature reports[10][11] suggestive of drug interaction leading to loss of HAART efficacy and on 7 cases retrieved from EudraVigilance reporting concurrent use of orlistat and any HAART. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases described in the literature and agreed that the reactions were suggestive of a biologically plausible, potential pharmacokinetic interaction. The PRAC recognised that weight gain could be frequently encountered in HIV treated patients and co-administration with orlistat could be expected and that limited data is available on potential drug-drug interaction between orlistat and HAART. Therefore the PRAC agreed that the signal needed further investigation.

The PRAC appointed Isabelle Robine as overall rapporteur for follow-up of this signal.

Summary of recommendation(s)

The MAHs for Alli, Xenical (orlistat), Sustiva (efavirenz), Stocrin (efavirenz), Atripla (emtricitabine, tenofovir, efavirenz), Reyataz (atazanavir), Prezista (darunavir), Kaletra (lopinavir, ritonavir) and Truvada (tenofovir, emtricitabine) should submit to the EMA, within 60 days, a cumulative review of cases reporting concomitant administration of orlistat and HAART (regardless of events reported). This cumulative review should include a specific thorough analysis and discussion of all cases suggestive of a pejorative impact of orlistat on the virologic suppression under antiretroviral agents.

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

4.1.9. Sertraline (NAP)

- Signal of growth retardation in children and adolescents

Regulatory details:

PRAC Rapporteur: *Sabine Straus (NL)*

Background

Sertraline is a selective serotonin re-uptake inhibitor (SSRI) used in the treatment of various conditions including depressive episodes, panic disorder, obsessive compulsive disorder (OCD), social

[10] Kent S. Loss of Control of HIV Viremia Associated with the Fat Malabsorption Drug Orlistat. AIDS RESEARCH AND HUMAN RETROVIRUSES 2012, 28(9):961-962.
[11] De Truchis P. Orlistat/lopinavir/ritonavir interaction: decreased lopinavir CSF concentration leading to HIVrelated meningo-encephalitis: case report. Reactions Weekly 2011; 1350:36

anxiety disorder, post-traumatic stress disorder (PTSD). Sertraline should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with obsessive compulsive disorder aged 6-17 years old.

The exposure for medicines containing sertraline, nationally authorised, is estimated to have been more than 12,500,000 patient-years worldwide from 2008 until 2011 including approximately 5% of usage was in children between 12-17 years old.

During routine signal detection activities, a signal of growth retardation in children and adolescents was identified by the Danish Medicines Agency, based on 3 cases reported in Denmark. Netherlands as lead Member State for the signal detection activities for sertraline confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of growth retardation reported. Currently, the product information for sertraline-containing medicines includes a statement regarding the use in children and adolescents under 18 years of age that long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking and that physicians must monitor paediatric patients on long term treatment for abnormalities in these body systems.

The PRAC noted that a PASS entitled SPRITES (Sertraline Paediatric Registry for the Evaluation of Safety) aiming at assessing the long term effects of sertraline on cognition, emotional and physical development, and pubertal maturation in children / adolescents was currently being conducted as per condition of the marketing authorisation following conclusion of an Article 31 of Directive 2001/83/EC for Zoloft (sertraline) (see Annex IV). Therefore the PRAC agreed that this signal should be further investigated in the framework of the results of this study.

The PRAC appointed Sabine Straus (NL) as Rapporteur for follow-up of this signal.

Summary of recommendation(s)

- The MAH for Zoloft (sertraline) and associated names should submit to the Rapporteur a cumulative review of the signal. This review should be submitted in the context of the next PSUR with data lock point (DLP) on 31 March 2014.

  The PRAC Rapporteur will circulate an assessment of the first interim report for the SPRITES study for information to the PRAC members.

Post-meeting note: the assessment of the first interim report for the SPRITES study was circulated for information to the PRAC members on 6 June 2013.

4.1.10. **Tapentadol** (NAP)

- Signal of suicidal ideation

Regulatory details:

PRAC Rapporteur: *Martin Huber (DE)*

Background

Tapentadol is a centrally acting analgesic used in the management of severe chronic pain in adults.

During routine signal detection activities, a signal of suicidal ideation was identified by the UK Medicines Agency, based on cases reported nationally and others reported outside Europe accounting for a total of 14 cases. DE as reference MS for Palexia (a nationally authorised product containing tapentadol) confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of suicidal ideation reported and agreed that confounding by indication - since chronic pain syndromes are often directly or indirectly associated with an increased risk of suicidal behaviour and depressive symptoms – must be taken into account in the assessment of the signal. The product information for Palexia (tapentadol) already states that the risk of suicidal ideation and suicide attempt is known to be higher in patients suffering from chronic pain. Currently, the product information also states data from clinical trials and post-marketing reports for tapentadol do not provide evidence for an increased risk. Therefore the PRAC agreed this signal needed to be further reviewed, to ensure that the current product information is still appropriate. The PRAC stated that a further analysis of clinical trial data using the Columbia Suicide Severity Rating Scale could be useful in assessing the signal as well as data on the use of tapentadol as a means of intentional overdose.

The PRAC appointed Martin Huber (DE) for follow-up of this review.

Summary of recommendation(s)

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

4.2. New signals detected from other sources

4.2.1. **Clarithromycin** (NAP)

- Signal of cardiovascular events

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Clarithromycin is a macrolide antibiotic used to treat various types of infections including infections of the upper and lower respiratory tract, skin and soft tissue infections and in the eradication treatment of Helicobacter Pylori.

The exposure for nationally authorised medicines containing clarithromycin is estimated to have been more than 6,600,000,000 patient-days worldwide, in the period from first authorisation in 1996 to 2012.

A signal of cardiovascular events after clarithromycin use in lower respiratory tract infections was identified by the Irish Medicines Agency, triggered by the results of a recently published study[12]. IE confirmed that the signal needed initial analysis and prioritisation by the PRAC.***Discussion***

The PRAC discussed the finding of the published study from Schembri et al describing an analysis of two prospective cohort studies in UK hospitals. After multivariate adjustment, clarithromycin use in acute exacerbations of COPD was associated with an increased risk of cardiovascular events and acute coronary syndrome (HR 1.5; 95% confidence interval 1.13-1.97) and 1.67 (1.04-2.68) and in the community acquired pneumonia (CAP) cohort, clarithromycin use was associated with an increased risk of cardiovascular events (HR 1.68; 95% confidence interval 1.18-2.38) but not with acute coronary syndrome (HR 1.65; 95% confidence interval 0.97-2.80). A statistically significant association was found between clarithromycin use and cardiovascular mortality (HR 1.52; 95% confidence interval 1.02-2.26) but not all cause mortality (HR 1.16; 95% confidence interval 0.9-1.51) in acute exacerbations of chronic obstructive pulmonary disease (COPD) but not in the CAP cohort. The PRAC discussed the strengths and limitations of the study, but also took in to consideration the results of the previous CLARICOR[13] study, a double-blind randomised placebo controlled multicentre trial conducted in 2006 to determine if clarithromycin affected mortality and CV morbidity in patients with stable CHD(coronary heart disease).

While it was acknowledged that there are a number of limitations to the recently published observational study, taking into consideration the other available evidence (such as the CLARICOR trial), it was agreed that a full review of all relevant data should be undertaken.

The PRAC nominated Almath Spooner (IE) as Rapporteur for follow-up assessment of the signal.

Summary of recommendation(s)

- The MAH for the originator clarithromycin containing medicine is requested to discuss the published study by Schembri et al (10) in light of previously published literature for example the CLARICOR study (11). The MAH should supplement this discussion with an evaluation of all available data with relevance to this concern and if justified, should discuss any options for further strategies to identify and characterise possible risk groups for increased risk of cardiac mortality with clarithromycin use. In the context of the most recent publication, the review should consider not only the arrhythmogenic effects of clarithromycin but also any possibility for long-term ischaemic cardiac events. A response should be submitted to the Rapporteur within 60 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signal follow-up

4.3.1. **Adalimumab – HUMIRA** (CAP)

- Signal of dermatomyositis

[12] 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 Mar 20;346

[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. 2006 Jan 7;332(7532):22-7.

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

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

The MAH submitted additional data in reply to the PRAC recommendation to update the product information with regards to dermatomyositis, including the worsening of symptoms of dermatomyositis. The responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the additional information received on dermatomyositis and adalimumab use. Since in a number of reports dermatomyositis was present before initiation of treatment with adalimumab and could have been present but not yet diagnosed in others, the PRAC agreed that data was overall currently insufficient to support a conclusion of new onset dermatomyositis as being caused by adalimumab. However there is sufficient evidence to support a possible association between adalimumab and worsening of symptoms of dermatomyositis.

For future cases, the PRAC emphasised the importance to gather as much information as possible in order to be able to fully assess whether adalimumab may also be associated with any increased risk of new onset dermatomyositis.

Summary of recommendation(s)

- The MAHs for Humira (adalimumab) should be requested to submit a variation to the EMA to update the product information in relation to 'worsening of symptoms of dermatomyositis'[14], within 60 days.

4.3.2. Azithromycin (NAP)

- Signal of potentially fatal heart events

Regulatory details:

PRAC Rapporteur: Terhi Lehtinen (FI)

Background

For background information, see PRAC minutes of 8-11 April 2013.

The PRAC rapporteur circulated the signal assessment report to PRAC members. The assessment report was updated with late-breaking information in the newly published article [15].

Discussion

The PRAC discussed the updated assessment and noted the newly published article by Svanström et al describing a nationwide historical cohort study involving Danish adults (18 to 64 years of age), which

[14] SmPC: section 4.8: "worsening of symptoms of dermatomyositis"; frequency: unknown
[15] Henrik Svanström, M.Sc., Björn Pasternak, M.D., Ph.D., and Anders Hviid, Dr.Med.Sci.Use of Azithromycin and Death from Cardiovascular Causes N Engl J Med 2013; 368:1704-1712May 2, 2013DOI: 10.1056/NEJMoa1300799

concluded that the earlier reported increased risk of cardiovascular death by Ray WA et al.[16] may not be generalizable to clinical population, but does not contradict the possibility that there could be an increased risk among patients with pre-existing high cardiovascular risk.

In light of emerging data suggesting possible longer term effects of clarithromycin on cardiovascular morbidity/mortality of possible ischaemic origin (see clarithromycin above 4.2.1.) and the possibility that this could be a class effect common to other macrolides, the PRAC considered that a broader consideration of the cardiovascular risks of azithromycin was warranted.

Summary of recommendation(s)

- The MAHs for the originator azithromycin-containing medicine should be requested to discuss the published study on azithromycin and cardiac mortality by Svanström et al ([12]): in light of the previously published literature ([16]); to discuss possible future strategies to identify and characterize possible risk groups for increased risk of cardiac mortality with azithromycin use; to discuss possible future strategies to identify and characterize possible risk groups for increased risk of cardiac mortality with azithromycin use. The focus should not only be in the arrhythmogenic effects but also long-term ischaemic cardiac events. A response should be provided to the Rapporteur by 60 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.3. Basiliximab – SIMULECT (CAP)

- Signal of cardiovascular instability resulting in fatal outcome following off-label use in heart transplantation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

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

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

Discussion

The PRAC discussed the assessment of the cumulative review of the signal including all cases reporting cardiac failure or cardiac insufficiency, cardiac-thromboembolic events and rhythm disorders with basiliximab, as well as a summary of preclinical cardio-toxicity studies.

Moreover the PRAC was informed that seven completed clinical trials in cardiac transplantation had been conducted, but not submitted as an application for extension of indication. The main observation from the review of the events reported in these clinical trials was an apparent higher rate of cardiac adverse events in the basiliximab group, after 3 and 12 months, compared to the other induction group (mainly treated with antithymocyte immunoglobulin (ATG)) and a similar level of cardiac events

[16] Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881-1890

compared to a no induction group. The PRAC noted that literature data as well as data from studies of basiliximab in renal transplantation were reassuring.

However, the findings of these clinical trials did not explain the characteristics of the three case reports from Sweden previously discussed by the PRAC. A further analysis focusing on acute events with onset within 24 h- 48 h following administration of basiliximab was considered necessary.

In conclusion, the evidence available did not allow any firm conclusion to be drawn on causality of the reaction and a further refined analysis was needed. Since the events arose in a population outside the labelled indication and literature data as well as data from studies in renal transplantation have not revealed any concern with regard to cardiac events/ thromboembolic events, the review was considered non urgent.

Summary of recommendation(s)

- The MAH for Simulect (basiliximab) should be requested to submit to the EMA, within 6 months, an additional analysis with regard to cardiac events reported in active and passive surveillance which occurred within 48 h after basiliximab administration and a refined analysis of safety and efficacy in heart transplantation from all available clinical trials.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.4. **Tiotropium** (NAP)

- Signal of increased mortality from cardiovascular disease and all-cause mortality for tiotropium Respimat mist inhaler raised by an editorial in the British Medical Journal (BMJ).

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

For background information, see PRAC minutes of 7-11 January 2013.

The MAH replied to the request for information relevant to the concerns raised by the BMJ publication[17] including findings of pharmacokinetic studies and this information was assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the data confirming that all the trials mentioned in the publication by Beasley R et al. included data that had not been previously assessed by NL, the Reference Member State for Spiriva Respimat (tiotropium bromide solution for inhalation), and that the mortality imbalance versus placebo observed in the Spiriva Respimat COPD clinical trial database is already reflected in the current product information for Spiriva Respimat.

The PRAC discussed the increased risk of mortality observed in the meta-analyses[18] [19] referred to in the publication by Beasley et al. None of these analyses used the complete set of data available and

[17] Beasley R ,Singh S ,Loke YK ,Enright P ,Furberg CD. Call for worldwide withdrawal of tiotropium Respimat mist inhaler. BMJ 2012;345:e7390

[18] Dong YH, Lin HH, Shau WY, Wu YC, Chang CH, Lai MS. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomized controlled trials. Thorax 2012;

[19] Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ 2011;342:d3215.

when all the available 6 trials are taken into account in a pooled analysis, the increased risk of mortality is not statistically significant for the marketed dose of 5 µg.

A recent publication using the Dutch Integrated Primary Care Information database also showed a 27% increase in mortality with Spiriva Respimat (tiotropium bromide solution for inhalation) when compared to Spiriva Handihaler (tiotropium bromide inhalation powder) (HR 1.27, 95% CI 1.03-1.57). However the authors stated that it is unclear whether this association is causal or due to residual confounding by COPD severity.

In addition the PRAC discussed the results of different pharmacokinetic studies comparing tiotropium HandiHaler with tiotropium Respimat. These show inconsistent findings with no robust evidence of significant difference in absorption rate or systemic exposure per formulation. The full results of one of these studies - study 205.458 - are still awaited.

The PRAC concluded that although the signal of increased risk of mortality for tiotropium Respimat remains to be fully addressed, there is at the moment no new evidence supporting a change in the previous conclusions on its benefit-risk balance. Furthermore, as anticipated in January 2013, the results of the Tiotropium Safety and Performance in Respimat (205.452 study TIOSPIR), a large-scale, prospective, randomised PASS comparing tiotropium Respimat and tiotropium HandiHaler in 17.000 patients focusing on all-cause mortality and COPD exacerbations as primary endpoints, will provide new information. The results will be available by July 2013.

Summary of recommendation(s)

- No regulatory action is considered necessary at this time. However, the MAH for Spiriva Respimat (tiotropium bromide solution for inhalation) is requested to submit the results of the TIOSPIR study to the Rapporteur no later than 1 October 2013.

4.3.5. **Trazodone** (NAP)

- Signal of postural hypotension and somnolence at high starting dose

Regulatory details:

PRAC Rapporteur: Jolanta Gulbinovic (LT)

Background

For background information, see PRAC minutes of 1-3 October 2013.

The MAHs (brand leaders) replied to the request for information on the signal and the responses were assessed by the Rapporteur. EudraVigilance, THIN and BIFAP databases were also reviewed (see below).

Discussion

The PRAC discussed the available pharmacokinetic and pharmacodynamic data, the information arising from spontaneous reports from EudraVigilance, the scientific literature and the supporting evidence including the results of a drug utilisation study for trazodone performed in the Base de datos para la Investigacion Farmacoepedemiologica en Atencion Primaria (BIFAP) database of the Spanish Agency

Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012;7:CD009285.

for Medicines and Health Products, as well as an analysis for trazodone performed using The Health Improvement Network (THIN) database. Based on an evaluation of these data, the PRAC confirmed the need for reinforcement of warnings regarding the potential for orthostatic effects in the elderly particularly in the context of polypharmacy and comorbidities. Accordingly, warnings in the product information concerning the potential for orthostatic hypotension, somnolence, and other anticholinergic effects of trazodone in elderly patients should be strengthened with regards to concomitant medication use, concomitant diseases and drug interactions.

Summary of recommendation(s)

- The MAHs for the nationally authorised trazodone-containing medicines[20] should be requested to submit to the NCAs of the MSs, within 60 days, a variation to update the product information[21] to include warnings regarding the potential for orthostatic hypotension, somnolence and other anticholinergic effects in elderly patients particularly with concomitant medication use, concomitant diseases and drug interactions.

4.3.6. Vitamin K antagonists: warfarin, phenprocoumon (NAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

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

The MAHs replied to the request for information on the signal and the responses were assessed by the Rapporteur together with the results of the non-urgent request of information (NUI) to the Member States.

Discussion

The PRAC discussed the assessment of the information provided and noted that no additional cases were identified compared to those discussed by the PRAC at the stage of initial analysis and prioritisation, i.e. four case reports, including three published in the literature[22]. According to some

[20] 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

[21] SmPC, suggested additional wording are in italics and underlined. Section 4.2. Add cross-reference to Section 4.4
"For very elderly or frail patients, the recommended initial dose is reduced to 100 mg a day administered in divided doses or as a single night time dose ***(See Section 4.4).*** This may be incrementally increased as described under Adults, under supervision, according to tolerance and efficacy"
Section 4.4 – Suggest separate paragraph for elderly patients.
"Elderly patients ~~**are more often more sensitive to antidepressants, in particular**~~ **may more often experience** ~~**to**~~ orthostatic hypotension, ***somnolence***, and other anticholinergic effects **of trazodone**. ***Careful consideration should be given to the potential for additive effects with concomitant medication use such as with other psychotropics or antihypertensives or in the presence of risk factors such as comorbid disease, which may exacerbate these reactions. It is recommended that the patient/carer is informed of the potential for these reactions and monitored closely for such effects following initiation of therapy, prior to and following upward dose titration.***" ;Relevant sections of patient leaflet should be updated accordingly.

[22] Lam AY, Elmer GW, Mohutsky MA: Possible interaction between warfarin and Lycium barbarum - Ann Pharmacother. 35, 1199-1201 (2001)

hypotheses the interaction seemed probably pharmacokinetic and based on a possible inhibition of the hepatic drug metabolising enzymes, CYP2C9 and CYP3A4. The flavonoid components of Goji (e.g. quercetin, luteolin, apigenin) have shown antiplatelet properties in vitro and in vivo. Other mechanisms suggest that the anticoagulant effect of warfarin might be potentiated by chitosan or inhibition of vitamin K absorption. The PRAC agreed that, whereas a possible interaction cannot be excluded, there is limited data describing this interaction. Therefore, no amendment of the current product information was required.

In addition, according to the compilation of the responses to the NUI circulated by the PRAC Rapporteur, the majority of the Member States specified that the current product information on drug-food interactions is sufficient for warfarin, phenprocoumon and other vitamin K antagonists.

Summary of recommendation(s)

- No regulatory action is considered necessary at this time. However, given the seriousness of the reactions reported, including the risk of bleeding, the MAHs for warfarin and phenprocoumon containing medicines are requested to keep this signal under close surveillance in the frame of the signal detection activities, including discussion in the next related PSURs. The NCAs of the MSs should be notified by the MAHs if the signal is strengthened by new case reports or studies suggestive of drug-herbal interaction between warfarin/phenprocoumon and Goji berries (Lycium barbarum).

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the CHMP on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

Leung H, Hung A, Hui ACF, Chan TYK: Warfarin overdose due to the possible effects of Lycium barbarum – Food Chem Toxicol. 46, 1860-1862 (2008)
Rivera CA, Ferro CL, Bursua AJ, Gerber BS: Probable interaction between Lycium barbarum (goji) and warfarin – Pharmacotherapy. 32 (3), e50-3 (2012 Mar)

5.1.1. Afatinib

5.1.2. Alemtuzumab

5.1.3. Atosiban

5.1.4. Sipuleucel-T

5.1.5. Brimonidine

5.1.6. Cobicistat

5.1.7. Dexamethasone

5.1.8. Dolutegravir

5.1.9. Fenofibrate, **simvastatin**

5.1.10. Filgrastim

5.1.11. Florbetaben (**18F**)

5.1.12. Glycopyrronium bromide, **indacaterol**

5.1.13. Human coagulation Factor VII, **human von Willebrand factor**

5.1.14. Human fibrinogen, **human thrombin**

5.1.15. Infliximab

5.1.16. Lomitapide

5.1.17. Memantine

5.1.18. Mercaptine

5.1.19. Misoprostol

5.1.20. Mixture of polynuclear iron (III)-oxyhydroxide, sucrose and starches

5.1.21. Modified vaccinia Ankara virus

5.1.22. Pomalidomide

5.1.23. Radium-223

5.1.24. Serelaxin – SERELAXIN (CAP MAA)

5.1.25. Somatropin

5.1.26. Tilmanocept

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

5.1.27. Travoprost

5.1.28. Umeclidinium bromide, vilanterol

5.2. Medicines already authorised

RMP in the context of a PSUR procedure

5.2.1. Capecitabine – XELODA (CAP)

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

Regulatory details:

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

See also 6.1.4.

5.2.2. Eribulin – HALAVEN (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 2 of the RMP for the above mentioned medicine.

See also 6.1.12. .

5.2.3. Eslicarbazepine acetate – ZEBINIX (CAP)

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

Regulatory details:

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

See also 6.1.13.

5.2.4. Fidaxomicin – DIFICLIR (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 3 of the RMP for the above mentioned medicine.

5.2.5. Linagliptin – TRAJENTA (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 7 of the RMP for the above mentioned medicine.

See also 6.1.26.

5.2.6. Mannitol – **BRONCHITOL** (CAP)

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

Regulatory details:

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

See also 6.1.27.

5.2.7. Melatonin – **CIRCADIN** (CAP)

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

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pêgo (PT)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 4 of the RMP for the above mentioned medicine.

See also 6.1.28.

5.2.8. Meningococcal group **a**, **c**, **w135 and y conjugate vaccine – NIMENRIX** (CAP)

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

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 2 of the RMP for the above mentioned medicine.

See also 6.1.29.

5.2.9. Miglustat – **ZAVESCA** (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version X of the RMP for the above mentioned medicine.
See also 6.1.31.

5.2.10. Prucalopride succinate – **RESOLOR** (CAP)

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

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 10 of the RMP for the above mentioned medicine. See also 6.1.41.

5.2.11. Sodium oxybate – XYREM (CAP)

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

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pêgo (PT)

Background

Sodium oxybate is a central nervous system depressant used in the treatment of narcolepsy with cataplexy.

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

Summary of advice

- The updated RMPs version 5 for Xyrem (sodium oxybate) was considered acceptable.
- However, the next update of the RMP to be provided with the following PSUR (see also 6.1.44.), should take into account some recommendations and clarifications requested by the PRAC. These include planned actions to address the 'important safety concerns' and milestones for assessment of risk minimisation measures. In particular the update of the RMP should take into account new data of use in children and the results from a study that indicated an increase in growth hormone secretion.

See also 6.1.44.

5.2.12. Sulphur hexafluoride – SONOVUE (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Sulphur hexafluoride is a diagnostic agent used with ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal to noise ratio.

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

Summary of advice

- The updated RMPs version 6 for SonoVue (sulphur hexafluoride) was considered acceptable.

- However, the next update of the RMP to be provided with the next PSUR, should take into account some recommendations and clarifications requested by the PRAC.
- The RMP should mention the update of the educational brochure to add the warning about the risk of concomitant treatment with beta-blockers, and the occurrence of anaphylactic reactions. Moreover, the current methods proposed to measure effectiveness of risk minimisation should be improved; the MAH should also propose measures that will inform if the risk is reduced.
- In the context of the next regulatory procedure amending the Annexes to the Commission Decision, the MAH should align the Annex II with the latest QRD template with a view to reflect the key elements of existing additional risk minimisation measures for the safe and effective use of the product, as described in the RMP.
- The updated educational brochure should be submitted to NCAs for validation without delay. See also 6.1.45.

5.2.13. Thalidomide – THALIDOMIDE CELGENE (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 14 of the RMP for the above mentioned medicine. See also 6.1.47.

RMP in the context of a variation

5.2.14. Atazanavir – REYATAZ (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 6 of the RMP for the above mentioned medicine in support of a variation to include the adverse drug reaction angioedema, as a result of a cumulative review, in the product information.

5.2.15. Crizotinib – XALKORI (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Crizotinib is an antineoplastic medicine used for the treatment of adults with previously treated anaplastic-lymphoma-kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC).

The CHMP is evaluating a variation procedure for Xalkori, a centrally authorised product containing crizotinib, to include efficacy and safety data from some recently concluded studies. 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 4 for Xalkori (crizotinib), in the context of the variation under evaluation by the CHMP, was considered acceptable provided that supplementary information requested by the PRAC on various aspects, including the classification of additional pharmacovigilance activities, is included before finalisation of the variation procedure by the CHMP.
- In particular the PRAC recommended that the MAH considers the relevance of updating the risk management plan (i.e. each concerned sections) in light of the ongoing discussion on the clinical safety assessment of the ongoing variation.

5.2.16. Darunavir – PREZISTA (CAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version X of the RMP for the above mentioned medicine provided in support of a variation for an extension of indication to HIV infected treatment naive patients of different age groups.

5.2.17. Emtricitabine, rilpivirine, tenofovir – EVIPLERA (CAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 17 of the RMP for the above mentioned medicine provided in support of a variation for an extension of indication in antiretroviral treatment-naïve adult patients with a predetermined viral load.

5.2.18. Everolimus – VOTUBIA (CAP)

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

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 7/5 of the RMP for the above mentioned medicine provided in support of a variation for a line extension to add a new pharmaceutical form and new strengths for a paediatric indication.

5.2.19. Fampridine – FAMPYRA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 5.2 of the RMP for the above mentioned medicine provided in support of a variation to include information regarding hypersensitivity reactions (including anaphylaxis).

5.2.20. Insulin human – INSUMAN (CAP)

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

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 1.1 of the RMP for the above mentioned medicine provided in support of a variation for a line extension to introduce a presentation a new strength, pharmaceutical form and route of administration for intraperitoneal use.

5.2.21. Natalizumab – TYSABRI (CAP)

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Tysabri (natalizumab) is a monoclonal antibody indicated as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis (RRMS) in selected patient groups.

The CHMP had been evaluating 'grouped' variations for Tysabri consisting of an extension of indication in RRMS population without high disease activity for those patients who are negative for anti- John Cunningham virus (JCV) antibodies, and extension of indication in the RRMS population with high disease activity with the introduction of glatiramer acetate as an additional example of treatment failure. Subsequently the former extension of indication request was withdrawn by the MAH, whereas the latter is under evaluation by the CHMP. 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 16.1 for Tysabri (natalizumab) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable provided that an updated risk management plan is submitted and all references to the withdrawn indication are removed before finalisation of the variation procedure by the CHMP.

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

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 15 of the RMP for the above mentioned medicine provided in support of a variation to update the specific obligations related to narcolepsy currently included in Annex II for Pandemrix.

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

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 6 of the RMP for the above mentioned medicine provided in support of a variation for an extension of the indication to include adults.

5.2.24. Pramipexole – OPRYMEA (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 1 of the RMP for the above mentioned medicine provided in support of a variation for a line extension to add a new pharmaceutical form.

5.2.25. Ranibizumab – LUCENTIS (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 11.2 of the RMP for the above mentioned medicine provided in support of a variation for an extension of indication to include visual impairment due to choroidal neovascularisation secondary to pathologic myopia.

5.2.26. Rituximab – MABTHERA (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 9.1 of the RMP for the above mentioned medicine provided in support of a variation for a line extension to add subcutaneous route of administration.

5.2.27. Sugammadex – BRIDION (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Background

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

The CHMP is evaluating a variation procedure for Bridion, a centrally authorised product containing sugammadex, to include information about marked bradycardia and bradycardia with cardiac arrest and to introduce new precautions relevant to the prescriber in the product information. 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 6 for Bridion (sugammadex) in the context of the variation under evaluation by the CHMP was considered acceptable.

5.2.28. Tocilizumab - ROACTEMRA (CAP)

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 14 of the RMP for the above mentioned medicine provided in support of a line extension to register the subcutaneous route of administration, a new pharmaceutical form, a new strength and new presentations.

5.2.29. Trastuzumab - HERCEPTIN (CAP)

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Trastuzumab is a monoclonal antibody used in the treatment of breast cancer and metastatic gastric cancer.

The CHMP is evaluating a variation consisting of a line extension for Herceptin, a centrally authorised medicine containing trastuzumab, available as a solution for infusion. The extension of the trastuzumab consists of a subcutaneous (SC) formulation in the approved breast cancer indication.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of the indication.

Summary of advice

- The updated RMP Version 11.2 for Herceptin (trastuzumab) in the context of the extension of indication under evaluation by the CHMP was considered acceptable, provided that an updated RMP is submitted with the next PSUR taking into account some points raised by the PRAC.
- These concern a request to conduct a Phase IV clinical trial concerning safety of 100 mg/m^2 docetaxel and sc Herceptin (trastuzumab) in patients with metastatic breast cancer with a specific focus on active cardiac monitoring.
- Clear milestones should be provided by the company for some studies mentioned in the Pharmacovigilance Plan of the RMP.

5.2.30. Voriconazole – VFEND (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the MAH's responses on the PRAC Rapporteur Assessment Report endorsed during the April 2013 PRAC meeting for the above mentioned medicine provided in support of a variation, regarding abnormal liver function tests and monitoring of hepatic function.

The PRAC noted that the proposed RMP updates regarding the risk of serious cutaneous reactions, to include a recommendation for regular dermatologic evaluation (variation II-95), will be assessed during a subsequent PRAC meeting.

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

None

RMP in the context of a stand-alone RMP procedure

5.2.31. Capsaicin – QUTENZA (CAP)

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

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pêgo (PT)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 15 of the RMP for the above mentioned medicine.

5.2.32. Ulipristal – ESMYA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 9 of the RMP for the above mentioned medicine.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[23]

6.1.1. Abiraterone – ZYTIGA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Background

Abiraterone is an androgen biosynthesis inhibitor indicated for the treatment of metastatic castration resistant prostate cancer in adult men under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Zytiga (abiraterone) in the approved indication(s) remains favourable.
- The product information should be updated to include a warning relating to skeletal muscle effects as well as the undesirable effects diarrhoea (with a frequency very common) and rhabdomyolysis and myopathy (with a frequency uncommon). Therefore the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide cumulative reviews of cases of pancytopenia, leukopenia/neutropenia/agranulocytosis, thrombocytopenia, adrenal insufficiency, serious cutaneous reactions including DRESS, as well as hypothyroidism. In addition, the MAH should comment on the rate of respiratory failure leading to death in the early access protocol (EAP) study. Finally, the MAH should submit an updated RMP to reflect rhabdomyolysis/myopathy as an important identified risk.

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.

6.1.2. Bazedoxifene – CONBRIZA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

[23] 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.

[24] 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.

Background

Bazedoxifene is a selective oestrogen receptor modulator (SERM) indicated for the treatment postmenopausal osteoporosis in women at increased risk of fracture.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Conbriza, a centrally authorised medicine containing bazedoxifene, 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 Conbriza (bazedoxifene) in the approved indication(s) remains favourable.
- The product information should be updated to include palpitations, rash and pruritus as undesirable effects with a frequency unknown. Therefore the current terms of the marketing authorisation should be varied[25].

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.

6.1.3. **Bortezomib – VELCADE** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Velcade, a centrally authorised medicine containing bortezomib, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.4. **Capecitabine – CAPECITABINE ACCORD** (CAP), **ECANSYA** (CAP), **XELODA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate functioning as an orally administered precursor of 5-fluorouracil (5-FU) and is indicated for the treatment of metastatic colorectal cancer as well as for the adjuvant treatment of patients following surgery for stage III (Dukes' stage C) colon

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

cancer. Capecitabine is also indicated for first-line treatment of advanced gastric cancer as well as for the treatment of patients with locally advanced or metastatic breast cancer under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Capecitabine Accord, Ecansya and Xeloda, centrally authorised medicines containing capecitabine, 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 Capecitabine Accord, Ecansya and Xeloda (capecitabine) in the approved indication(s) remains favourable and the current terms of the marketing authorisation(s) should be maintained.
- However, in relation to the metastatic colorectal cancer indication, the MAH for Xeloda should submit to EMA within 60 days a variation to update the product information in line with the efficacy results of the recent publications[26] by *Souglakos et al, 2012 and Montagnani et al, 2010* respectively.
- In addition, the MAH for Xeloda should submit to EMA within 60 days a variation to reflect the risk of Stevens Johnson syndrome (SJS) and bullous dermatitis in the product information, and should discuss cases of photosensitivity reactions.
- Moreover, the MAH for Xeloda should submit to EMA within 60 days cumulative reviews of cases of convulsions and interstitial lung disease (ILD) respectively.
- In the next PSUR, the MAH(s) should closely monitor several adverse reactions, including cases of intestinal obstruction, gastrointestinal perforation/ischaemia and pancreatitis, as well as cases of severe ocular toxicity. The MAH for Xeloda should also perform a cumulative review of cases of cerebrovascular disorders as well as a review of (prophylactic) treatment of hand foot syndrome (HFS), and discuss RMP updates with additional information on prevention and treatment of HFS as well as the need for potential risk minimisation activities. Finally, the MAH for Xeloda should discuss the possible relevance of reducing the initial dose of capecitabine monotherapy in elderly patients as suggested in the publication[27] by *Venderbosch et al, 2012*, taking into account other publications (e.g. *Seymour et al, 2011*) and propose an update of the product information as needed.
- The MAH(s) for Capecitabine Accord and Ecansya should align their product information against that of Xeloda and reflect vasospasm as an undesirable effect.

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.

See also 5.2.1.

[26] Souglakos et al. Randomised phase-II trial of CAPIRI (capecitabine, irinotecan) plus bevacizumab vs FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) plus bevacizumab as first-line treatment of patients with unresectable/metastatic colorectal cancer (mCRC). Br J Cancer 2012;106(3):453–9
Montagnani et al. Differences in efficacy and safety between capecitabine and infusional 5-fluorouracil when combined with irinotecan for the treatment of metastatic colorectal cancer. Clin Colorectal Cancer 2010;9(4):243–7

[27] Venderbosch et al. Outcome of First Line Systemic Treatment in Elderly Compared to Younger Patients With Metastatic Colorectal Cancer: A Retrospective Analysis of The CAIRO and CAIRO2 Studies of the Dutch Colorectal Cancer Group (DCCG). Acta Oncol. 2012; 51(7):831-9
Seymour et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet. 2011 May 21;377(9779):1749-59

6.1.5. Conestat alfa – RUCONEST (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Ruconest, a centrally authorised medicine containing conestat alfa, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.6. Darbepoetin alfa – ARANESP (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Aranesp, a centrally authorised medicine containing darbapoetin alfa, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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. Darifenacin hydrobromide – EMSELEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Emselex, a centrally authorised medicine containing darifenacin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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. Decitabine – DACOGEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Dacogen, a centrally authorised medicine containing decitabine, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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. Deferasirox – EXJADE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Deferasirox is an iron chelating agent indicated for the treatment of chronic iron overload.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Exjade, a centrally authorised medicine containing deferasirox, 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 Exjade (deferasirox) in the approved indications remains favourable and the current terms of the marketing authorisation should be maintained.
- However, the MAH should submit within 60 days a variation to include a table summarising safety monitoring recommendations in the product information. This variation should also include a discussion on the possible risk of interaction between deferasirox and busulfan based on a recent publication[28] by *Sweiss et al* as well as the risk of pancreatic disorders based on spontaneous cases of pancreatitis. The MAH should consider the need for an update of the product information as appropriate.
- In the next PSUR, the MAH should keep a number of adverse reactions under close monitoring.

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.

6.1.10. Desirudin – REVASC (CAP)

- Evaluation of a PSUR procedure

[28] Sweiss K, Patel P and Rondelli D. Deferasirox increases busulfan blood concentrations. Bone Marrow Transplantation. 2012;47:315-316

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Revasc, a centrally authorised medicine containing desirudin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The frequency of PSUR submission should be revised from 3-yearly to 5-yearly. The next PSUR should be submitted within 90 days of the data lock point set at 11/11/2017. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.11. Doripenem – DORIBAX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Doribax, a centrally authorised medicine containing doripenem, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

Given there are several adverse reactions that need closely monitoring, the PRAC recommended revising the frequency of PSUR submission from 3-yearly to yearly. The next PSUR should be submitted within 70 days of the data lock point set at 11/10/2013. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.12. Eribulin – HALAVEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Halaven, a centrally authorised medicine containing eribulin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

See also 5.2.2.

6.1.13. Eslicarbazepine acetate – ZEBINIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Zebinix, a centrally authorised medicine containing eslicarbazepine acetate, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

See also 5.2.3.

6.1.14. **Fenofibrate**, **pravastatin – PRAVAFENIX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Pravafenix, a centrally authorised medicine containing fenofibrate/pravastatin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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. **Fidaxomicin – DIFICLIR** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Dificlir, a centrally authorised medicine containing fidaxomicin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

See also 5.2.4.

6.1.16. **Granisetron – SANCUSO** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jolanta Gulbinovic (LT)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Sancuso, a centrally authorised medicine containing granisetron (transdermal patch), 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

Due to the occurrence of some cases of lack of efficacy and product adhesion issues specific to the patch formulation, the PRAC recommended that PSUR frequency for granisetron transdermal patch-containing medicines is maintained at 6 monthly and the next PSUR should be submitted within 70 days of the data lock point set at 19/04/2013. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.17. Hepatitis B vaccine (rDNA) – HBVAXPRO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of HBVaxPro, a centrally authorised hepatitis B vaccine (rDNA) 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The next PSUR should be submitted within 90 days of the data lock point set at 28/02/2014. Subsequent 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.

6.1.18. Human hepatitis B immunoglobulin – ZUTECTRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Zutectra, a centrally authorised medicine containing human hepatitis B immunoglobulin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.19. Human normal immunoglobulin – HIZENTRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Hizentra, a centrally authorised medicine containing human normal immunoglobulin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.20. Human normal immunoglobulin – KIOVIG (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Kiovig, a centrally authorised medicine containing human normal immunoglobulin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.21. Human normal immunoglobulin – PRIVIGEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Privigen, a centrally authorised medicine containing human normal immunoglobulin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Cervarix, a centrally authorised human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed), 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.23. Hydrocortisone – PLENADREN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Plenadren, a centrally authorised medicine containing hydrocortisone (indicated for the treatment of adrenal insufficiency in adults), 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

Given that there are several adverse reactions that need close monitoring, the PRAC recommended maintaining the frequency of PSUR submission at 6-monthly. The next PSUR should be submitted within 70 days of the data lock point set at 03/05/2013. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.24. Insulin glulisine – APIDRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Apidra, a centrally authorised medicine containing insulin glulisine, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.25. Levodopa, carbidopa, entacapone – LEVODOPA/CARBIDOPA/ENTACAPONE ORION (CAP), STALEVO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Based on the assessment of the PSURs, the PRAC concluded that the benefit-risk balance of Levodopa/carbidopa/entacapone Orion and Stalevo, centrally authorised medicines containing levodopa/carbidopa/entacapone, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The frequency of PSUR submission should be revised from yearly to 3-yearly. The next PSUR should be submitted within 90 days of the data lock point set at 17/10/2015. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.26. Linagliptin – TRAJENTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Trajenta, a centrally authorised medicine containing linagliptin, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The frequency of PSUR submission should be maintained 6-monthly. The next PSUR should be submitted within 70 days of the data lock point set at 02/05/2013. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

See also 5.2.5.

6.1.27. Mannitol – BRONCHITOL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Bronchitol, a centrally authorised medicine containing mannitol, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

See also 5.2.6.

6.1.28. Melatonin – CIRCADIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pêgo (PT)

Background

Melatonin is a psycholeptic agent indicated as monotherapy for the short-term treatment in some patients of primary insomnia characterised by poor quality of sleep.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Circadin, a centrally authorised medicine containing melatonin, 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 Circadin (melatonin) in the approved indication(s) remains favourable.
- The product information should be updated by reinforcing that *'tablets should be swallowed whole'* to reduce the risk of medication errors and maintain the prolonged release properties. In addition, the undesirable effects nausea, galactorrhoea, hypersensitivity reaction, angioedema, oedema of mouth, and tongue oedema should be added to the product information with the corresponding frequency. Therefore the current terms of the marketing authorisation should be varied[29].

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.

See also 5.2.7.

6.1.29. Meningococcal Group A, C, W135 and Y Conjugate Vaccine – NIMENRIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Nimenrix, a centrally authorised medicine containing 6meningococcal Group A, C, W135 and Y conjugate vaccine (conjugated to tetanus toxoid carrier protein), remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

See also 5.2.8.

6.1.30. Methylthioninium chloride – METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

[29] Update of SmPC sections 4.2 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Methylthioninium Chloride Proveblue, a centrally authorised medicine containing methylthioninium chloride, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.31. Miglustat – ZAVESCA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Miglustat is an inhibitor of glucosylceramide synthase indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease and for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease under certain conditions.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Zavesca (miglustat) in the approved indication(s) remains favourable.
- The product information should be updated to reflect under Annex II 'obligation to conduct post-authorisation measures' that annual study reports of the Niemann-Pick type C (NP-C) disease registry (multicentre, prospective, observational, cohort study) should be submitted with each PSUR. Therefore the current terms of the marketing authorisation should be varied[30].

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.

See also 5.2.9.

6.1.32. Nicotinic acid, laropiprant – PELZONT, TREDAPTIVE, TREVACLYN

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
The PRAC adopted its assessment report of the PSUR and noted the marketing authorisation(s) for the concerned products had been withdrawn at the request of the MAH (see also EMEA/CHMP/21862/2013).

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

6.1.33. Pandemic influenza vaccine (H1N1) (whole virion, inactivated, prepared in cell culture) – CELVAPAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Celvapan, a centrally authorised pandemic influenza vaccine (H1N1) (whole virion, inactivated, prepared in cell culture), 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.34. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – ADJUPANRIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Adjupanrix, a centrally authorised pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted), remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.35. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Foclivia, a centrally authorised pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted), 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The frequency of PSUR submission should be revised from 6-monthly to yearly. The next PSUR should be submitted within 70 days of the data lock point set at 19/10/2013. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.36. Pasireotide – SIGNIFOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Pasireotide is an injectable somatostatin analogue indicated for the treatment for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Signifor, a centrally authorised medicine containing pasireotide, 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 Signifor (pasireotide) in the approved indication(s) remains favourable.
- The product information should be updated to correct the frequency allocated to the adverse reaction anaemia to uncommon and to refine the wording for the existing warning on hyperglycaemia. Therefore the current terms of the marketing authorisation should be varied[31].

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.

6.1.37. Pixantrone dimaleate – PIXUVRI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Background

Pixantrone dimaleate is a cytotoxic aza-anthracenedione indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL).

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

[31] 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.

- The product information should be updated to improve the expression of the strength to avoid the potential risk of dosing errors that could potentially result in an overdose. Therefore the current terms of the marketing authorisation should be varied[32]. PRAC also agreed a DHPC and communication plan due for further agreement at the CHMP level.

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.

6.1.38. Posaconazole – NOXAFIL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Noxafil, a centrally authorised medicine containing posaconazole, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

The frequency of PSUR submission should be revised from yearly to 5-yearly. The next PSUR should be submitted within 90 days of the data lock point set at 25/10/2017. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.39. Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – AFLUNOV (CAP), PREPANDEMIC INFLUENZA VACCINE (H5N1) (SURFACE ANTIGEN, INACTIVATED, ADJUVANTED) NOVARTIS VACCINES AND DIAGNOSTIC (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Aflunov and Prepandemic Influenza Vaccine (H5N1) Novartis Vaccines and Diagnostic, centrally authorised prepandemic influenza vaccines (H5N1) (surface antigen, inactivated, adjuvanted) 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The frequency of PSUR submission should be revised from 6-monthly to yearly. The next PSUR should be submitted within 70 days of the data lock point set at 19/10/2013. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

[32] Update of SmPC section 4.2. The package leaflet is updated accordingly The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

6.1.40. Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – PREPANDRIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Prepandrix, a centrally authorised prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted), remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.41. Prucalopride succinate – RESOLOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Resolor, a centrally authorised medicine containing prucalopride succinate, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

See also 5.2.10.

6.1.42. Regadenoson – RAPISCAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Rapiscan, a centrally authorised medicine containing regadenoson, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.43. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Zostavax, a centrally authorised shingles (herpes zoster) vaccine (live), 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.44. Sodium oxybate – XYREM (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pêgo (PT)

Background

Sodium oxybate is a central nervous system depressant indicated for the treatment of narcolepsy with cataplexy in adult patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xyrem, a centrally authorised medicine containing sodium oxybate, and issued a recommendation on its marketing authorisation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Xyrem (sodium oxybate) in the approved indication(s) remains favourable and the current terms of the marketing authorisation should be maintained.
- However, due to findings in a published non-clinical study investigating neurotoxicity, the MAH should submit to EMA within 60 days a critical analysis of all relevant pre-clinical data and present a cumulative evaluation of all adverse events that could be related with neurotoxicity stratified by exposure time. The MAH should submit a variation as warranted by the conclusions.
- The MAH should submit an updated RMP alongside the next PSUR to ensure planned actions to address important safety concerns, milestones for assessment of risk minimisation measures and use in the paediatric population are updated. The MAH should also consider categorising paediatric and adolescent use as an important potential risk in addition to missing information.

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.

See also 5.2.11.

6.1.45. Sulphur hexafluoride – SONOVUE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of SonoVue, a centrally authorised medicine containing sulphur hexafluoride, remained favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

See also 5.2.12.

6.1.46. Tadalafil – **ADCIRCA** (CAP), **CIALIS** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Adcirca and Cialis, centrally authorised medicines containing tadalafil, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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.

6.1.47. Thalidomide – **THALIDOMIDE CELGENE** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Thalidomide is an immunosuppressant agent indicated in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

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

- The product information should be updated to include posterior reversible encephalopathy syndrome (PRES) as an undesirable effect (see also PRAC Minutes January 2013). Therefore the current terms of the marketing authorisation should be varied[33].
- Regarding thromboembolic events (arterial thromboembolic events, venous thromboembolic events and mixed type thromboembolic events), the MAH should estimate the proportion of patients with risk factors for thromboembolic events receiving a thromboprophylaxis in the next PSUR,.

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.

See also 5.2.13.

6.1.48. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of RoActemra, a centrally authorised medicine containing tocilizumab, 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. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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. Interferon beta 1a – AVONEX (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

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 December 2012). The responses were assessed by the Rapporteur for further PRAC advice.

[33] The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.
[34] Follow up procedures as per the conclusions of PSUR procedures, assessed outside next PSUR procedures

Summary of recommendation(s) and conclusions

- The MAH should submit to EMA within 30 days a variation to include in the product information a warning regarding the risk of collapsing focal segmental glomerulosclerosis during interferon-beta treatment and reflect this as an undesirable effect.
- The MAH should submit to EMA within 30 days a cumulative review of cases of thrombotic microangiopathy, haemolytic uremic syndrome and thrombotic thrombocytopenic purpura and consider submitting a variation if changes to the product information are warranted.

6.2.2. Imatinib – **GLIVEC** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

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 December 2012). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of recommendation(s) and conclusions

- The MAH should submit to EMA within 60 days a variation to reflect in the product information cases of drug rash with eosinophilia and systemic symptoms as undesirable effects.

6.2.3. Pazopanib – **VOTRIENT** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

During the evaluation of PSUR#4 for the above mentioned medicine(s), the MAH was requested to submit further data which were assessed in the framework of the most recently assessed PSUR (see PRAC Minutes April 2013). One remaining response was assessed separately by the Rapporteur for further PRAC advice.

Summary of recommendation(s) and conclusions

- Based on the review of all clinical studies completed since the product was authorised, the risk-benefit balance of Votrient (pazopanib) in the approved indication(s) remains favourable.
- In the next PSUR, the MAH should closely monitor potential pharmacokinetic effects with combination products.

6.2.4. Sitagliptin, metformin – **EFFICIB** (CAP), **JANUMET** (CAP), **RISTFOR** (CAP), **VELMETIA** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

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 February 2013). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of recommendation(s) and conclusions

- In the next PSUR, the MAH should continue to closely monitor cases of unlisted serious skin reactions including bullous pemphigoid and should consider updating the product information where changes are warranted.
- The possible increased risk of pancreatic cancer in patients using GLP-1-based therapies (glucagon-like-peptide-1 (GLP-1) agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors is currently under review under Article 5(3) of Regulation 726/2004 (see PRAC Minutes April 2013 and EMA/178662/2013) and changes may be warranted upon completion of this referral procedure.

6.2.5. Temsirolimus – TORISEL (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

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 December 2012). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of recommendation(s) and conclusions

- The MAH for Torisel (temsirolimus) should be requested to submit to the EMA within 60 days a variation to update the product information to correct the frequency of the occurrence of interstitial lung disease (ILD) under undesirable effects and provide further study analysis to further investigate this risk in sub-populations, in particular East Asian patients.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of post-authorisation safety studies

7.1.1. Alipogene tiparvovec – GLYBERA (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

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

A revised study protocol of the 'An Observational Longitudinal Pharmacoepidemiologic Study in Lipoprotein Lipase-Deficient (LPLD) Patients, Either Treated or Not Treated with Alipogene Tipravovec (Glybera)' was submitted by the MAH following the recommendations agreed by the PRAC in February 2013. The PRAC considered the protocol not approvable and agreed on a list of questions for revision. The updated protocol was assessed by the Rapporteur.

Summary of advice

- The study protocol version 2013-2.0 for the above mentioned study was not yet acceptable and satisfactory responses to a further list of questions agreed by the PRAC needs to submitted to the EMA with 1 month. Upon submission a 30 day assessment timetable will be applied leading to a further PRAC recommendation.

7.1.2. **Ulipristal – ESMYA** (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

For background please see minutes of the PRAC 7-10 January 2013. The PRAC was requested to provide advice to CHMP on a protocol submitted by the MAH. The MAH submitted responses to the comments raised by the PRAC which were assessed by the Rapporteur.

Summary of advice

- The study protocol should be further updated and could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA before finalisation of the procedure at CHMP level. Clarification is needed on the estimated number of available gynaecologists across the participating countries in Cegedim Onekey database, since the PRAC expressed concern that this database will suffer from selection bias based on the figures provided. The MAH should provide justification on the proportion of gynaecologists included in the database in the different countries. Numbers of patients enrolled and proportion of recruited patients of the total number exposed should be included in a study report.

7.2. Results of post-authorisation safety studies

7.2.1. **Human fibrinogen thrombin – EVICEL (CAP)**

- PRAC consultation on PASS study results, upon CHMP request

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Evicel is a centrally authorised medicine containing human fibrinogen and thrombin, used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis.

As part of the RMP for Evicel, the MAH is to conduct a PASS study in vascular surgery of approximately 300 patients. The MAH provided an interim clinical study report evaluating the first 100 subjects enrolled, which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP following assessment of the study results.

Summary of advice

- Based on the clinical study report presenting results for the first 100 enrolled patients, the PRAC agreed that no new safety concerns have been identified. None of the events reported were classified as related to Evicel. None of the events were classified as a graft occlusion complication nor were they classified as potentially related to non-graft thrombotic events nor bleeding events at the anastomotic site.
- The MAH should provide clarification on potential selection bias and, for each study centre, the proportion of recruited patients of the total number of eligible.

7.2.2. Insulin glargine – LANTUS (CAP), OPTISULIN (CAP)

- PRAC consultation on PASS study results, upon CHMP request

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Insulin glargine is a human insulin analogue used for the treatment of diabetes.

The final study report for the International Study of Insulin and Incident Breast Cancer (ISICA) was assessed and discussed at the 3-7 PRAC January 2013 meeting, together with a systematic review of all studies investigating a possible association with breast cancer.

Following advice provided in January 2013 the MAH supplemented the information provided with responses to some outstanding comments of the PRAC which were assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the assessment of such responses.

Summary of advice

- The PRAC concluded that, overall, this study (and the totality of the available data) did not allow a conclusion that the use of insulin glargine is associated with an increased risk of breast cancer.
- However, since the results are not fully consistent across different studies, the MAH should be asked to present systematically in future PSURs any newly available data regarding the risk of breast cancer and discuss these in the context of the overall available data. Furthermore, if the investigators of the Kaiser Permanente study decide to prolong the study, the MAH should present the results to the regulatory authorities.

7.2.3. Oseltamivir – TAMIFLU (CAP)

- PRAC consultation on PASS study results, upon CHMP request

Regulatory details:

PRAC Rapporteur: Kirsti Villika (FI)

Background

Tamiflu is a centrally authorised medicine containing oseltamivir, an inhibitor of influenza virus neuraminidase enzymes, indicated in the treatment and prevention of influenza in individuals 1 year of age or older and during a pandemic influenza outbreak, also for treatment and post-exposure prevention of influenza in infants less than 1 year of age.

As part of the RMP for Tamiflu, the MAH conducted a PASS to evaluate the safety of Tamiflu in pregnancy: "Assessing the safety of oseltamivir exposure in pregnant women in Denmark and Sweden (NV25577)". The MAH submitted the results of the study which were assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP following assessment of the study results. The summary of the interim data compilation of the Japanese Tamiflu Pregnancy Survey (TAM0902) and the company's Drug Safety Report 1053031 (Pregnancy and Lactation) were also assessed by the Rapporteur and presented at the meeting.

Summary of advice

- Taking into consideration the limitations of the current Swedish-Danish registry study, discussed in the context of interim results of the Japanese study, the available literature, and a further pregnancy drug safety report provided by the MAH, the data do not suggest an increased risk for congenital anomalies or other adverse pregnancy outcomes after exposure to oseltamivir. However, the PRAC considered that the exposure during pregnancy should be followed-up by the MAH. PRAC recommended that the registery study should be continued to gather a further two years data.
- The PRAC confirmed previous advice agreed at the 8-11 April 2013 meeting (see PSUR) that an annual review of pregnancy reports should be provided.

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

8.1.1. Amifampridine – FIRDAPSE (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Amifampridine is a voltage-dependent potassium channel blocker indicated for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

Firdapse, a centrally authorised product containing amifampridine, was authorised in 2009 under exceptional circumstances. The benefit-risk is reviewed on a yearly basis by the CHMP based on the

additional post-authorisation data (i.e. specific obligations) submitted. The PRAC is responsible for providing advice to the CHMP on this annual re-assessment with regard to safety and risk management aspects.

Summary of advice

Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, the PRAC considered that the annual re-assessment procedure for Firdapse could only be finalised if satisfactory clarification is given on some pending issues. These include an update on the progression of the QT study.

8.1.2. Azacitidine – VIDAZA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Azacitidine is an antineoplastic agent indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with intermediate-2 and high-risk myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) or acute myeloid leukaemia (AML) under certain conditions.

Vidaza, a centrally authorised medicine containing azacitidine, was authorised in 2008.

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

Summary of advice

Based on the review of the risk management system for Vidaza (azacitidine), and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could be finalised, pending some clarification relating to the treatment of secondary myelodysplastic syndromes. Further PRAC advice will be provided as applicable

8.1.3. .Iloprost – VENTAVIS (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Iloprost is a synthetic prostacyclin analogue indicated for the treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.

Ventavis, a centrally authorised medicine containing iloprost, was authorised in 2003.

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

Summary of advice

Based on the review of the risk management system for Ventavis (iloprost), and the CHMP Rapporteur's assessment report, the PRAC considered that this second five year renewal procedure could be finalised, provided, in particular, that the use of iloprost during pregnancy and lactation is kept as important missing information in the RMP. Further PRAC advice will be provided as applicable

8.1.4. Lacosamide – VIMPAT (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Lacosamide is an antiepileptic agent indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy.

Vimpat, a centrally authorised medicine containing lacosamide, was authorised in 2003.

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

Summary of advice

Based on the review of the risk management system for Vimpat (lacosamide), and the CHMP Rapporteur's assessment report, the PRAC considered that this second five year renewal procedure could be finalised. Further PRAC advice will be provided as applicable.

8.1.5. Olanzapine – ZYPADHERA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Terhi Lehtinen (FI)

Background

Olanzapine pamoate is an antipsychotic, antimanic and mood stabilising agent indicated for maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

Zypadhera, a centrally authorised medicine containing olanzapine pamoate prolonged release suspension for injection, was authorised in 2008.

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

Summary of advice

Based on the review of the risk management system for Zypadhera (olanzapine, suspension for injection), and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could be finalised. Further PRAC advice will be provided as applicable.

8.1.6. Vildagliptin – JALRA (CAP), XILIARX (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Vildagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated in the treatment of type 2 diabetes mellitus in adults under certain conditions.

Jalra and Xiliarx, centrally authorised medicines containing vildagliptin, were authorised in 2008.

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

Summary of advice

Based on the review of the risk management systems for Jalra and Xiliarx (vildagliptin), and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could be finalised, pending some clarifications relating to the treatment of secondary myelodysplastic syndromes. In addition, due to the potential association of thyroid and pancreatic cancer with glucagon-like-peptide-1 (GLP-1) agonists and DPP-4 inhibitors, the MAH should provide within 60 days a cumulative review of those cases (s) and should closely monitor these adverse reactions in the next PSUR. In the meantime, the review of pancreatic risks with GLP-1-based therapies for type 2 diabetes is ongoing under Article 5(3) of Regulation (EC) 726/2004 (see PRAC Minutes April 2013) and further actions will be taken as warranted upon finalisation. Further PRAC advice on the renewal procedure will be provided as applicable.

8.1.7. Vildagliptin, metformin – ICANDRA (CAP), ZOMARIST (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Vildagliptin/metformin is used in combination in the treatment of indicated in the treatment of type 2 diabetes mellitus under certain conditions.

Icandra and Zomarist, centrally authorised medicines containing vildagliptin/metformin, were authorised in 2008.

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

Summary of advice

Based on the review of the risk management systems for Icandra and Zomarist (vildagliptin/metformin), and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could be finalised. Due to the potential association of thyroid and pancreatic cancer with glucagon-like-peptide-1 (GLP-1) agonists and DPP-4 inhibitors, the MAH should provide within 60 days a cumulative review of those cases (s) and should closely monitor these adverse reactions in the next PSUR. In the meantime, the review of pancreatic risks with GLP-1-based therapies for type 2 diabetes is ongoing under Article 5(3) of Regulation (EC) 726/2004 (see PRAC Minutes April 2013) and further actions will be taken as warranted upon finalisation. Further PRAC advice on the renewal procedure will be provided as applicable.

9. Product related pharmacovigilance inspections

9.1. On-going or concluded pharmacovigilance inspection

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

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

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

10.1.1. **Pazopanib – VOTRIENT** (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

See also PRAC minutes 8-11 April 2013. Responses were received from the MAH to the comments raised by the PRAC which were assessed by the Rapporteur.

Summary of advice

The PRAC agreed that more intensive liver monitoring is needed based on the data presented and therefore supported the proposed amendment of the product information. Based on the responses received the PRAC considered a DHPC a sufficient risk minimisation tool and suggested refinements of the main messages.

10.1.2. Retigabine – **TROBALT** (CAP)

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

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

Retigabine is an antiepileptic drug. Trobalt, a centrally authorised product containing retigabine, is indicated in the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy.

At the April 2013 meeting the PRAC was informed that about two years after the authorisation of retigabine as adjunct treatment in partial epilepsy, reports of pigment changes/discolouration of the skin, lips and nails and pigment changes in ocular tissues, including the retina, have started to emerge with long term and high dose use, and that the issue was currently under evaluation in a variation by the CHMP. The indication for retigabine is proposed to be restricted to adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated. A DHCP is also proposed to inform physicians of these changes and the advice of the PRAC was sought on this procedure.

Summary of advice

The PRAC supported the dissemination of the DHPC and provided some suggestions for refinement of the key messages. The PRAC commented that the next PSUR and updated RMP when submitted should provide opportunity for full benefit-risk analysis. Therefore they should include updates on follow-up of patients and progress on the further non-clinical investigations initiated.

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

None

10.3. Other requests

10.3.1. **Epoetins**:
darbepoetin-alfa - ARANESP (CAP), **epoetin-beta - NEORECORMON** (CAP), **epoetin-zeta - RETACRIT SILAPO** (CAP), **epoetin alfa – BINOCRIT** (CAP), **ABSEAMED** (CAP), **EPOETIN ALFA HEXAL** (CAP), **epoetin theta – EPORATIO** (CAP), **methoxy polyethylene glycol-epoetin beta – MIRCERA** (CAP)

- PRAC consultation on the evaluation of a proposal for a joint post-authorisation safety study on target haemoglobin levels in chronic kidney disease (CKD) patients, upon CHMP request

Regulatory details:

PRAC Rapporteur (overall): Martin Huber (DE)
PRAC Rapporteurs: Isabelle Robine (FR), Dolores Montero Corominas (ES)

Background

In 2011, FDA announced new recommendations for erythropoiesis-stimulating agents (ESAs), which are used to stimulate the production of red blood cells (FDA Drug Safety Communication: Modified

dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease).

The recommendations called for a change in the haemoglobin target levels in patients with chronic kidney disease on dialysis, in order to reduce the risk of serious cardiovascular events. After assessment of the evidence behind the new FDA dosing recommendations, the EMA's Pharmacovigilance Working Party (PhVWP) proposed a List of Questions adopted by the CHMP in July 2011.

The MAHs concerned submitted post-hoc re-analyses of their clinical data. The MAHs were encouraged by the PhVWP and CHMP to agree on common core elements of a statistical analysis protocol that will ensure similar analysis methods are to achieve applied comparability between the results of the pooled analyses from different MAHs. To this end, the MAHs were requested to collaborate in order to prepare one proposal for a common set of statistical analyses to be applied to the relevant data for each ESA. Key points for the re-analyses of pooled data were made available to the MAHs.

The MAHs submitted both specific statistical analysis plans (SAP) and common core elements of an analysis plan (CCE) to re-analysis their clinical trial data taking into account the different recommendations in the US and the EU concerning haemoglobin levels in CKD patients. The SAPs were based on the common core elements of an analysis plan, which was agreed by all MAHs of ESAs.

The PRAC was requested to provide advice to the CHMP on these proposals.

Summary of advice

- The PRAC agreed that the 'Common Core Elements', should be revised taking the same key points into careful consideration. The SAPs of the MAHs should be adapted in line with such recommendations. Subsequently, the MAHs should start their statistical analyses at company level immediately. The MAHs should submit the reports on results within 6 months after receiving the CHMP position.
- The methods of the overall meta-analysis will be provided upon completion of the 'stage 1' analysis. The company-level results of all ESAs should be pooled and analysed in a second step.
- The SAP and the report on results should be added to the respective RMP of each medicine.

10.3.2. **Aprotinin** (NAP)

- PRAC consultation on an ongoing CHMP review of the benefit-risk balance of aprotinin under Article 31 of Directive 2001/83/EC

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
PRAC Co-Rapporteur: Ulla Wändel-Liminga (SE)

Background

Following an assessment in 2007, the CHMP suspended the EU marketing authorisations for aprotinin-containing products, due to safety concerns, in particular on the basis of the preliminary results of the 'Blood conservation using antifibrinolytics' (BART) trial. In its review, the CHMP acknowledged the need to trigger an overall review of the benefits and risks of antifibrinolytics, once sufficient data became available, including the final results of BART.

In March 2010, Germany triggered an Article 31 procedure to assess all antifibrinolytics (aprotinin, aminocaproic acid and tranexamic acid), in all their approved indications. Following the review and clarification to the EC the CHMP adopted an opinion in July 2012 recommending the lifting of the suspension for aprotinin and the variation of the marketing authorisations for aminocaproic acid, and tranexamic acid.

The CHMP requested the advice of the PRAC on the pharmacovigilance activities and risk minimisation measures proposed with this opinion.

Summary of advice

- The PRAC agreed with the risk minimisation measures and pharmacovigilance activities proposed and recommended the restricted distribution of aprotinin via the proposed registry.
- With regards to the proposed registry, the PRAC supported giving due consideration to the inclusion of a comparator group to assess main safety concerns, and to gather further data on clinically meaningful benefit.

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Meningococcal group C polysaccharide conjugate vaccine adsorbed (NAP)

- PRAC consultation on a variation, upon Member States' request

Regulatory details:

Lead member: Julie Williams (UK)

Background

NeisVac-C is a meningococcal group C polysaccharide conjugate vaccine (tetanus toxoid protein conjugate).

Baxter, the MAH for NeisVac-C was requested by the Medicines and Healthcare products Regulatory Agency (MHRA) as Reference Member State (RMS) to submit a RMP with a quality variation to transfer the manufacturing site of the drug with an update to the manufacturing process of the active substance. The MAH has submitted RMP version 4.0 with quality Type II variation which was assessed by UK who asked PRAC advice on some aspects including intensive safety monitoring strategies to be put in place by the MAH.

Summary of advice

- PRAC proposed a list of questions to be addressed by the MAH in the framework of the ongoing national variation on a web-based intensive safety monitoring study of NeisVac-C vaccination in toddlers.
- Finally the PRAC commented on the need for clear communication on the aims of the study to be presented to the parents of the children vaccinated.
- Follow-up advice by the PRAC following assessment of the replies received, will be provided upon request of the MSs.

11.2. Renewals of the marketing authorisation

None

11.3. Other requests

11.3.1. Peritoneal dialysis solutions (NAP)

- PRAC consultation on the results of an epidemiological study pursuant to an obligation imposed in accordance with Article 21a and 22a of Directive 2001/83/EC following completion of a referral procedure under Article 31 of Directive 2001/83/EC

Regulatory details:

Lead member: Julie Williams (UK)

Background

For background see 'Baxter dialysis solution' pages on the EMA website including the outcome of the procedure under Article 31 of Directive 2001/83/EC on the European Commission Decision on the EC website.

The Article 31 referral resulted in certain conditions for the marketing authorisations.

Therefore, following conclusion of the referral, UK assessed data pertaining to the Endotoxin-Associated Sterile Peritonitis Observational Study (e-STEPS) and the results of a retrospective, non-interventional clinical audit of peritonitis events across the European Union 2010-2012, in accordance with the milestones for evaluation and reporting described in the consolidated RMP presented in accordance to the conditions of the MA of the products concerned by the referral - and asked PRAC advice on the conclusion of the assessment.

Summary of advice

The PRAC considered that the results of the e-STEPS provide some reassurance that exposure to endotoxin did not appear to adversely affect peritoneal membrane function and that overall the symptoms of aseptic peritonitis were mild and short-lived. However, this does not downplay the unwanted symptoms of aseptic peritonitis, the needless exposure to antibiotics with potential unwanted side effects or a potential contribution to antibiotic resistance, and the risks involved with removing the peritoneal dialysis catheter. Furthermore the numbers evaluated in each cohort were small and therefore any conclusions drawn need to be interpreted with caution.

This part of commitment 5 is considered partially fulfilled, but the MAH is requested to provide a response to the questions agreed by the PRAC. The PRAC considered that the existing education of healthcare professionals and patients was adequate but stressed that this needs to be accompanied by ongoing rigorous and continuous monitoring by the MAH of the quality of the product.

The PRAC considered that the data presented within the clinical audit did not identify an increase in total peritonitis events, culture negative peritonitis events or aseptic peritonitis events that occurred during the period of endotoxin exposure. However, some further clarifications were suggested by the PRAC to be requested from the MAH.

Follow-up advice by the PRAC following assessment of the replies received, will be provided upon request of the MSs.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. Reporting of plenary meeting discussed procedures

- Draft figures for the first 6 months of PRAC activity

EMA circulated to the PRAC figures for the first 6 months of PRAC activity. Figures will be updated periodically.

12.1.2. Risk based criteria for adoption of PRAC output with or without plenary meeting discussion

- Proposal for PRAC adoption without further plenary meeting discussion

EMA presented to the PRAC, at the organisational matters teleconference of the PRAC on 23 May 2013, a set of risk-based criteria for adoption and finalisation of PRAC outcome documents without plenary meeting discussion for renewal, conditional renewal and annual reassessment procedures as well as for follow-up to PSUR procedures. The criteria follow the approach agreed in the past for PSURs (see minutes of the PRAC 4-7 February 2013 11.3.3.2. PSUR flowchart).

In addition EMA presented a revised proposal for adoption of the PRAC outcome for risk management plans, following experience gained so far by the Committee on the use of the criteria discussed in January 2013 (see minutes 7-10 January 2013 - 11.7.2.1. RMP Flowchart).

The revised criteria were endorsed by the PRAC.

12.2. Pharmacovigilance audits and inspections

None

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

12.3.1. Union Reference Date List

12.3.1.1. Consultation on the draft List, version May 2013

The EURD list version May 2013 was presented to the PRAC at the organisational matters teleconference of the PRAC on 23 May 2013.

Regarding herbal substances in the EURD list, the members reported comments from some stakeholders regarding PSURs for products which are by default subject to a legal derogation. The EMA had agreed to review the sub-list of herbal substances and the relevance for including such substances in the EURD list following a risk-based approach, bearing in mind that signal detection and risk minimisation obligations still apply. Following re-consideration of each herbal substance originally included in the EURD list, a proposal to reduce the number of entries in the list was presented and agreed by the Committee for Herbal Medicinal Products (HMPC), and subsequently endorsed by the PRAC. Since the EURD can be amended whenever considered necessary in response to the emergence of relevant new safety information, new herbal substances may be added in the future upon requests by National Competent Authorities. In addition, it was agreed that only products containing the substances as mono-component would be subject to PSUR submission in accordance with the EURD list.

Regarding the new format of the EURD list EMA informed PRAC that new columns on submission date and next DLP had been included in the list. A link to the published timetables for PSUR procedure through PRAC has also been added.

Finally, EMA clarified that further clarifications regarding the PSUR submission requirements to the EMA have been added following questions raised by stakeholders on the EURD list cover note.

The PRAC endorsed the updated version of the EURD list including the PRAC Rapporteurs' countries and delegates names (for PSUR single assessment of substances containing in CAPs and NAPs with a data lock point (DLP) in 2013) as identified and agreed in April 2013 (see PRAC Minutes April 2013).

Post-meeting note: following the PRAC meeting in May 2013, the updated EURD list was adopted by the CMDh and CHMP at their May 2013 meetings and is due for publication on 31 May 2013 (see Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.4. Signal Management

12.4.1. Signal Management

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

The PRAC discussed, at the organisational matters teleconference of the PRAC on 23 May 2013, a revised proposal for implementing necessary updates of product information arising from the assessment of signals and best practice for exchanging information with the CMDh in order to facilitate harmonised implementation across the EU. Roles and responsibilities for EMA and for the Members States were clarified. A revised proposal will be discussed in June 2013.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. List of medicines under additional monitoring

The PRAC discussed, at the organisational matters teleconference of the PRAC on 23 May 2013, some updates needed to the list of medicines under additional monitoring in the published list for April 2013. The list will be revised periodically and made available on the EMA website.

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of risk Minimisations

None; see 12.1.2.

12.8. Post-authorisation Safety Studies

12.8.1. Patient Registries

- Proposal to initiate the process of encouraging and supporting joint disease based-registries

Discussion on this item was deferred to the June 2013 meeting of the PRAC.

12.9. Community Procedures

None

12.10. Risk communication and Transparency

12.10.1. Public Participation in Pharmacovigilance

- Concept paper on public hearings

The PRAC discussed a concept paper on public hearings at the organisational matters teleconference of the PRAC on 23 May 2013. The paper aims to establish a definition and an agreed vision for public hearings in order to underpin the drafting of rules of procedure.

The PRAC supported the definition of public hearings in principle but also suggested the need for more focus on the clarity of purpose for public hearings and where they fit best into the pharmacovigilance process. EMA will take into consideration the comments received in updating the paper to be discussed at the 13 June meeting of the EMA Management Board.

12.11. Continuous pharmacovigilance

None

12.12. Interaction with EMA Committees and Working Parties

None

12.12.1. Human Scientific Committees Working Party with Healthcare Professionals' Organisations (HCPWP) and Patients' and Consumers' Working Party (PCWP)

- Revised mandate, objectives and rules of procedures
- Nomination of PRAC representative at the HCPWP and PCWP

The mandate of the newly created Human Scientific Committees Working Party with Healthcare Professionals' Organisations (HCPWP) was presented at the PRAC for adoption at the organisational matters teleconference of the PRAC on 23 May 2013. The PRAC adopted the mandate and agreed that the member and alternate nominated by the EC to represent the healthcare professional at the PRAC should be PRAC representatives at the HCPWP. The revision of the mandate of the Patients and Consumers Working Party (PCWP) which had been aligned with that of the HCPWG was also adopted. The PRAC agreed that the member and alternate nominated by the EC to represent patient organisations at the PRAC should be PRAC representatives at the PCWP. Nominations will be confirmed at the June 2013 meeting of the PRAC.

12.13. Interaction within the EU regulatory network

12.13.1. Heads of Medicines Agencies (HMA)

- Call for participation in the Pharmacovigilance Audit Facilitation Group (PAGF)

A new working subgroup, the Pharmacovigilance Audit Facilitation Group (PAFG), has been organised within the Heads of Medicines Agencies (HMA) Working Group of Quality Managers (WGQM) in order to foster a common approach to pharmacovigilance audits.

At the organisational matters teleconference of the PRAC on 23 May 2013, Julia Pallos – one of the two members of the PRAC nominated to participate in the PAFG – introduced the mandate, working methods and communication to the PRAC. The Committee discussed expected deliverables and exchange of information with the PAFG. The communication and the way of cooperation between the different stakeholders were also addressed. The PRAC representatives will periodically update the PRAC on the progress of PAFG's program of work which will be completed over 3 years. Consultations on draft guidance will be performed regularly. The next update is planned for the September 2013 meeting.

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

12.14.1. Novel influenza strain (H7N9) in humans

- Preparatory activities

At the organisational matters teleconference of the PRAC on 23 May 2013, EMA gave an update on current activities in relation to the recent outbreak of novel influenza A(H7N9) following identification in 3 patients in China. An existing 'flu taskforce' comprising Directorate General for Health & Consumers, Directorate-General for Research & Innovation, European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and EMA have started meeting to ensure adequate preparedness, communication and coordination. The Agency liaison with international regulatory partners and the World Health Organization (WHO) are underway. Updates to the PRAC will be given as appropriate.

13. Any other business

13.1.1. Medication errors workshop

- Final report from the workshop

The PRAC was informed of the publication of the medication errors workshop on the EMA website (EMA/144458/2013).

ANNEX I – List of abbreviations

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

www.ema.europa.eu

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

ANNEX II – List of participants

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 13-16 May 2013 meeting.

PRAC member PRAC alternate	*Country*	*Outcome restriction following evaluation of e-DoI for the meeting*	*Topics on the current Committee Agenda for which restriction applies*
			Product / substance
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogne	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	Cyproterone, ethinylestradiol, Radium-223, iloprost
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Eva Jirsova	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Terhi Lehtinen	Finland	Cannot act as Rapporteur or Peer-reviewer for:	Duloxetine, umeclidinium bromide, vilanterol, nicardipine
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
George Aislaitner	Greece	Full involvement	
Julia Pallos	Hungary	Full involvement	
Gudrun Kristin Steingrimsdottir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjorg Buajordet	Norway	Full involvement	
Pernille Harg	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimaraes	Portugal	Full involvement	

PRAC member PRAC alternate	*Country*	*Outcome restriction following evaluation of e-DoI for the meeting*	*Topics on the current Committee Agenda for which restriction applies* *Product / substance*
Alexandra Pego	Portugal	Full involvement	
Daniela Pomponiu	Romania	Full involvement	
Anna Marekova	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Ulla Wandel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Julia Dunne	United Kingdom	Full involvement	
June Munro Raine	United Kingdom	Full involvement	
Julie Williams	United kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting:**	**Topics on the current Committee Agenda for which restriction applies** *Product / substance*
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise (Marieke) De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer-reviewer for:	Umeclidinium bromide, vilanterol, Meningococcal group a, c, w135 and y conjugate vaccine, Pandemic influenza vaccine, Human papillomavirus vaccine, pazopanib, prlistat
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Cannot act as Rapporteur or Peer-reviewer for:	Strontium ranelate, Agomelatine
Lennart Waldenlind		Full involvement	

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
Benedicte Lunddahl Rasmussen	Denmark	
Kim Bouillon	France	
Alban Dhanani	France	
Nivéditha Lebonheur	France	
Bich-Hang Pham	France	
Christine Diesinger	Germany	
Jutta Krappweis	Germany	
Fabio Facchinetti	Italy	
Giuseppe Rosano	Italy	
Anna-Marie Coleman	Ireland	
Lies van Vlijmen	Netherlands	
Johan Aulin	Sweden	
Charlotte Backman	Sweden	
Rolf Gedeborg	Sweden	
Hans Sjögren	Sweden	
Lars Ståhle	Sweden	
Inga Bellahn	United Kingdom	
Claire Davies	United Kingdom	
Alisa Gebbie	United Kingdom	
Bridget King	United Kingdom	
Nicola Parkinson	United Kingdom	
Jonathan Ross	United Kingdom	
Andrew Thomson	United Kingdom	
Catherine Tregunno	United Kingdom	
Jane Woolley	United Kingdom	

Oxford Group	
Colin Baigent	No restrictions were identified for the participation of Oxford Group attending the PRAC meeting for discussion on specific agenda items
Jonathan Emberson	
Carlo Patrono	

Health care professionals and patients observers	
Flip Babylon	No restrictions were identified for the participation of health care professionals and patients observers attending the PRAC meeting for discussion on specific agenda items
Marco Greco	

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

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