10 January 2012
EMA/36832/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

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Minutes of the Meeting – 26-29 November 2012

Explanatory notes

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

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

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

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

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

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

The RMP describes what is known and not known about the safety of a medicine and states how the side effects will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects.

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RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

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

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

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

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

Product-related pharmacovigilance inspections
(Item 8 of the PRAC Minutes)
These are inspections carried out by regulatory agencies to ensure that marketing authorisation holders have systems in place that enable them to comply with their obligations to closely follow the safety of a medicine after authorisation.

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

Table of Contents

Chair: June Raine – Vice-Chair: Almath Spooner

1. Introduction

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

The Chairperson opened the meeting and welcomed all participants to the 26-29 November 2012 meeting of the PRAC.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Adoption of the agenda of the PRAC meeting on 26-29 November 2012

The agenda was adopted with the addition of the following topics upon request from the members of the Committee and the EMA secretariat: 3.1.1. almitrine; 3.1.2. diacerein; 7.1.2. angiotensin receptor blockers; 9.1.2. dabigatran; 7.1.3. ivacaftor; 7.1.4. trimetazidine.

1.3. Adoption of the minutes of the previous PRAC meeting on 29-31 October 2012

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

Post-meeting note: the minutes were published on 3 December 2012 on the EMA website (EMA/PRAC/771924/2012).

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

None

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

3.1. Newly triggered Procedures

3.1.1. **Almitrine** (NAPs)

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

Regulatory details:

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

Background

The French Medicines Agency (ANSM) sent a letter of notification dated 27 November 2012 of a referral under Article 31 of Directive 2001/83/EC for the review of almitrine-containing medicines indicated for the treatment of chronic respiratory diseases.

Discussion

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

The PRAC appointed Margarida Guimarães (PT) as Rapporteur and Evelyne Falip (FR) as Co-Rapporteur for the procedure.

Recommendation(s)

The Committee adopted a list of questions (published on the EMA website EMA/PRAC/747321/2012) and a timetable for the procedure (EMA/PRAC/747322/2012).

3.1.2. Diacerein (NAPs)

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

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)
PRAC Co-Rapporteur: Evelyne Falip (FR)

Background

The French Medicines Agency (ANSM) sent a letter of notification dated 22 November 2012 of a referral under Article 31 of Directive 2001/83/EC for the review of diacerein-containing medicines for oral administration in the symptomatic treatment of osteoarthritis of the knee and the hip.

Discussion

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

The Committee appointed Miguel-Angel Macia (ES) as Rapporteur and Evelyne Falip (FR) as PRAC Co-Rapporteur.

Recommendation(s)

The Committee adopted a list of questions (published on the EMA website EMA/PRAC/759123/2012) and a timetable for the procedure (EMA/PRAC/747322/2012).

3.1.3. **Hydroxyethyl starch (HES), solutions for infusion** (NAPs)

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

Regulatory details:

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

Background

For further background please refer to the Minutes of PRAC meeting of PRAC 29-31 October 2012.

Following discussion at the 29-31 October 2012 PRAC meeting, the German Medicines Agency (BfArM) sent a letter of notification dated 20 November 2012 of a referral under Article 31 of Directive 2001/83/EC for the review of HES-containing solutions for infusion used in hypovolaemia and hypovolaemic shock in patients who are critically ill or in intensive care units, particularly patients with sepsis.

Discussion

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

The Committee appointed Qun Ying Yue (SE) as Rapporteur and Martin Huber (DE) as PRAC Co-Rapporteur.

Recommendation(s)

The Committee adopted a list of questions (published on the EMA website EMA/PRAC/751078/2012) and a timetable for the procedure (EMA/PRAC/750422/2012).

3.1.4. **Short-acting beta agonists**: **hexoprenaline, fenoterol, ritodrine, salbutamol, terbutaline and isoxsuprine** (NAPs)

- Review of the benefit-risk balance of medicines containing short-acting beta agonists based on pharmacovigilance data following notification by Hungary of a referral under Article 31 of Directive 2001/83/EC

Regulatory details:

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

Background

For further background please see PRAC minutes 29-31 October 2012.

Following discussion at the 29-31 October 2012 PRAC meeting, the Hungarian Medicines Agency (GYEMSZI) sent a letter of notification dated 27 November 2012 of a referral under Article 31 of Directive 2001/83/EC for a review of medicinal products containing short-acting beta agonists authorised in the management of tocolysis and other obstetric indications.

Discussion

The PRAC noted the notification letter from the Hungarian 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 Julie Williams (UK) as Rapporteur and Julia Pallos (HU), Jean-Michel Dogne (BE) Jana Mlada (CZ) and Carmela Macchiarulo (IT) as Co-Rapporteurs.

Recommendation(s)

The Committee adopted a list of questions (published on the EMA website EMA/PRAC/74483/2012) and a timetable for the procedure (EMA/PRAC/744203/2012).

3.2. Ongoing Procedures

None

3.3. Procedures for finalisation

None

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

None

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

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

- Signal of angioedema

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

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 first authorisation in 2009 to 2012.

During routine signal detection activities, a signal of angioedema was identified by the EMA, based on 28 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 angioedema and requested a cumulative review of angioedema with a view to amending the product information for agomelatine-containing medicines.

Summary of recommendation(s)

- The MAH for Valdoxan/Thymanax (agomelatine) should submit within 60 days a cumulative review of the signal, including an analysis of all case reports of angioedema (narrow SMQs) and related terms, and a proposal for amending the product information.
- A type II variation was suggested as an appropriate regulatory procedure to address the signal.

4.1.2. **Atanazavir – REYATAZ** (CAP)

- Signal of angioedema

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

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

Reyataz, a centrally authorised medicine containing atazanavir, is estimated to have been used by more than 1,200,000 patients worldwide, in the period from 2003 to 2012.

During routine signal detection activities, a signal of angioedema was identified by the EMA, based on 29 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 angioedema and emphasised that none of the cases had been associated with respiratory symptoms or laryngeal oedema, and therefore were not considered severe. However, for some of them, there was a pattern suggesting a likely or very likely temporal relationship (positive re-challenge) with atazanavir treatment. Furthermore some cases of anaphylactic reactions were also reported. The PRAC agreed to request a cumulative review of angioedema and anaphylactic reaction with a view to amending the product information for atazanavir-containing medicines.

Summary of recommendation(s)

- The MAH for Reyataz (atazanavir) should submit within 60 days a cumulative review consisting of an analysis of all case reports of angioedema (narrow SMQs) and related terms and anaphylactic reaction (narrow SMQs), and a proposal for updating the product information.
- A type II variation was suggested as an appropriate regulatory procedure to address the signal.

4.1.3. **Capsaicin** patch – **QUTENZA** (CAP)

- Signal of severe burns

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pego (PT)

Background

Capsaicin is used as a local anaesthetic in the treatment of neuralgia.

Qutenza, a centrally authorised medicine available as a patch containing capsaicin, is estimated to have been used by more than 15,000 patients worldwide, in the period from first authorisation in 2009 to 2012.

During routine signal detection activities, a signal of severe burns was identified by the EMA, based on 4 cases retrieved from EudraVigilance associated with capsaicin patches. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of severe burns in the context of the PSUR assessment for Qutenza (see also Qutenza – Assessment of PSURs: 6.1.4.) and agreed with the addition to the product information of 'burns second degree'.

Summary of recommendation(s)

- The product information for Qutenza (capsaicin) should be amended in the context of the ongoing PSUR assessment procedure.

4.1.4. Leflunomide – ARAVA (CAP)

- Signal of myositis

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Leflunomide is an immunosuppressant medicine used in the treatment of rheumatoid arthritis and psoriatic arthritis.

Arava, a centrally authorised medicine containing leflunomide, is estimated to have been used by more than 2,100,000 patients worldwide, in the period from its marketing authorisation in 1999 to 2011.

During routine signal detection activities, a signal of disproportionate reporting of myositis was identified by the EMA, based on 15 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the reported cases of myositis. It was highlighted that in some cases the patients used a concomitant medication which can be considered a potential confounder and that polymyositis can accompany rheumatic arthritis. However, given the seriousness of the reaction, the PRAC agreed to investigate the signal further and to include related conditions such as dermatomyositis and polymyositis in its review. The PRAC also recommended that the co-administration of statins should be investigated.

Summary of recommendation(s)

- The MAH for Arava (leflunomide) should submit within 60 days a cumulative review and analysis of all case reports of myositis, dermatomyosits and polymyositis and a proposal for updating the product information. The review should include a detailed critical analysis of the epidemiology of risk factors in the patient population as well as other criteria including any potential relationship to concomitant medication and concurrent clinical conditions.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

To support the Rapporteur, the EMA secretariat will explore the possibility of providing further data on the epidemiology of risk factors of patients treated with leflunomide, with special focus on concomitant medication, in particular the use of statins in patients treated with leflunomide.

4.1.5. **Nicardipine** (NAPs)

- Signal of thrombocytopenia

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Nicardipine is a calcium channel blocker used in the treatment of hypertension.

Nationally authorised medicines containing nicardipine have been very widely used worldwide and have been marketed since the late 1980's.

During routine signal detection activities, a signal of thrombocytopenia was identified by the Italian Medicines Agency, based on 61 cases retrieved from EudraVigilance. IT as lead Member State for signal detection activities for nicardipine-containing medicines confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases and the biological plausibility of the reaction and concluded that the risk of thrombocytopenia should be considered together with other haematological disorders possibly associated with nicardipine.

Furthermore, the PRAC noted that this signal provided additional information on a known risk, since thrombocytopenia is already included in the product information of nicardipine-containing medicines in some EU Member States. Therefore, the PRAC agreed on the importance of having harmonised information on this risk in the product information of all nicardipine-containing medicines in the EU.

Summary of recommendation(s) [1]

- The MAHs for nicardipine-containing medicines should submit within 60 days a variation to update the product information by adding 'thrombocytopenia'[2] in the products information of medicines marketed in EU MS where this information is not mentioned.
- The MAHs for nicardipine-containing medicinal products are requested to monitor the haematological disorders possibly associated with the use of nicardipine in the next PSURs.

4.2. New signals detected from other sources

None

4.3. Signal follow-up and prioritisation

4.3.1. **Adalimumab – HUMIRA** (CAP)

- Signal of dermatomyositis

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

For further background information please see PRAC Minutes 3-5 September 2012. See also infliximab 4.3.3.

As requested, the MAHs submitted a cumulative review of the signal which was assessed by the Rapporteur. The EMA secretariat also performed a further search for cases of dermatomyositis reported to EudraVigilance in association with pharmacologically related substances, including certolizumab, golimumab and etanercept.

Discussion

The PRAC discussed the cumulative review and analysis performed by the MAH for the signal of dermatomyositis and recommended the strengthening of the product information in relation to dermatomyositis, including the worsening of symptoms of dermatomyositis.

At the September 2012 PRAC meeting, the Committee discussed whether the signal of dermatomyositis should also be investigated for other pharmacologically related substances: certolizumab, golimumab and etanercept. The EMA secretariat informed the Committee that a preliminary search in EudraVigilance did not reveal any cases for golimumab and certolizumab, whereas a number of reports were retrieved for etanercept. The PRAC concluded that these cases should be further assessed.

[1] In line with Article 16(2) of Regulation No (EU) 726/2004 and Article 23(2) 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). It is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to

[2] Section 4.8 of the Summary of Product Characteristics

Summary of recommendation(s)

- The MAH for Humira (adalimimab) should submit within 60 days a variation to update the product information as regards as dermatomyositis, including the worsening of symptoms of dermatomyositis.

Cases reported in association with etanercept retrieved from EudraVigilance should be further discussed at the PRAC meeting on 7-10 January 2013.

4.3.2. Hormonal contraceptives: norelgestromin / ethinylestradiol - EVRA (CAP); etonogestrel; etonogestrel and ethinylestradiol; drospirenone and ethinylestradiol (NAPs)

- Signal of arterial thrombotic events

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

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

The Member States responded to a NUI (Non Urgent Information) request made by the NL to collect information on the existing warnings regarding the risk of arterial thrombotic events contained in the product information of hormonal contraceptive products currently authorised in the EU.

Discussion

The PRAC discussed the responses to the NUI and noted that, based on the responses received, the product information of most combined hormonal contraceptives include a statement on the risk of arterial thrombotic events. The exact wording varies across MSs and across products. Some members suggested confirming whether, for the hormonal contraceptives included in the Liedegaard et al.[3] study, relevant information is reflected in the labelling.

Summary of recommendation(s)

- The Rapporteur will review the product information in relation to the information included on the known risk of arterial thrombotic events.
- This outcome will be discussed at the PRAC 7-10 January 2013 meeting leading to a further PRAC recommendation.

4.3.3. Infliximab – REMICADE (CAP)

- Signal of dermatomyositis

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Background

For further background please see PRAC Minutes 3-5 September 2012.

[3] Lidegaard O, Lokkegaard E, Jensen A, Skovland CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012;366:2257-2266

As requested, the MAHs submitted a cumulative review of the signal which was assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review and analysis performed by the MAH for the signal of dermatomyositis and recommended the strengthening of the product information in relation to dermatomyositis, including the worsening of symptoms of dermatomyositis.

Summary of recommendation(s)

- The MAH for infliximab (Remicade) should submit within 60 days a variation to update the product information in relation to dermatomyositis, including worsening of symptoms of dermatomyositis.

4.3.4. Seasonal influenza vaccines - (NAPs)

- Signal of extensive limb swelling (ELS)

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

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

The Member States responded to a NUI (Non Urgent Information) request made by the NL to collect information on extensive limb swelling (ELS) currently included in the product information of seasonal influenza vaccines authorised in the EU.

Discussion

The PRAC discussed the responses to the NUI request circulated in October 2012. Given that ELS is a rare, but known reaction that may occur with any vaccine and that swelling is already included in the product information, the PRAC agreed that regulatory action targeting specifically influenza vaccines would not be appropriate.

Summary of recommendation(s)

On the basis of the responses to the NUI request from the MSs no regulatory action is considered necessary at this time.

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.

5.1.1. Autologous Cultured Chondrocytes

5.1.2. Autologous Peripheral Blood Mononuclear Cells Activated With Pap-Gm-Csf

5.1.3. Bosentan

5.1.4. Dabrafenib

5.1.5. Delamanid

5.1.6. Dimethyl Fumarate

5.1.7. Diphtheria, Tetanus, Pertussis (Acellular, Component)

5.1.8. Enzalutamide

5.1.9. Hepatitis B, Surface Antigen

5.1.10. Human Coagulation Factor VIII / Von Willebrand Factor

5.1.11. Imatinib

5.1.12. Modified Vaccinia Ankara Virus

5.1.13. Telmisartan

5.2. Medicines already authorised

5.2.1. Abatacept – ORENCIA (CAP)

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

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)
PRAC Co-Rapporteur: Julia Pallos (HU)

Background

Abatacept is a monoclonal antibody used in the treatment of rheumatoid arthritis.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP proposed to cover the surveillance of the potential risk of immunogenicity for Orencia, a centrally authorised medicine containing abatacept.

Summary of advice

- The updated RMP version 14 for Orencia (abatacept) was considered acceptable.

5.2.2. Boceprevir – VICTRELIS (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Boceprevir is an antiviral used in the treatment of chronic hepatitis C (CHC) genotype 1 infection.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following finalisation of the report for the 'Healthcare Professionals Educational Material (on risk, monitoring and management of haematological disorders) impact study'.

Summary of advice

- The RMP version 4.1 for Victrelis (boceprevir) was considered acceptable.
- The next update of the RMP should take into account some additions proposed by the PRAC relating to editorial issues and clarifications regarding the 'Health Care Professionals Educational Materials Impact Study'.

See also 6.1.3.

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

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Denosumab is a monoclonal antibody used in the treatment of bone diseases, such as postmenopausal osteoporosis and bone loss associated with hormone ablation in men.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the latest PSUR for Prolia and Xgeva, centrally authorised products containing denosumab.

Summary of advice

- The updated RMPs version 3 for Prolia and Xgeva (denosumab) were considered acceptable.
- The next update of the RMP Xgeva should be aligned with the RMP for Prolia.

See also 6.1.5.

5.2.4. Dibotermin Alfa - **INDUCTOS** (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)
PRAC Co-Rapporteur: Kirsti Villikka (FI)

Background

Dibotermin alfa is a bone morphogenetic protein used in the treatment of tibial fractures, spinal fusion and internal fracture fixation.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following the second renewal of the marketing authorisation for InductOs, a centrally authorised medicine containing dibotermin alfa.

Summary of advice

- The updated RMP version 6 for InductOs (dibotermin alfa) was considered acceptable.
- The next update of the RMP should take into account some additions proposed by the PRAC such as the inclusion of a DVD and a brochure on the preparation of the product as additional risk minimisation activities and the inclusion of data on post-marketing use.

5.2.5. Duloxetine - **ARICLAIM** (CAP), **CYMBALTA** (CAP), **XERISTAR** (CAP), **YENTREVE** (CAP)

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

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)
PRAC Co-Rapporteur: Qun-Ying Yue (SE)

Background

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

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for centrally authorised medicine containing duloxetine to include results from completed paediatric double-blind trials and of a drug utilisation study.

Summary of advice

- The updated RMP version 10 for Ariclaim, Cymbalta, Xeristar, Yentreve (duloxetine) was considered acceptable.
- The next update of the RMP should take into account some editorial changes proposed by the PRAC, some clarification regarding the presentation of paediatric data and the results of the Study on the Utilization of Duloxetine (SUDULOX) as well as an update of the 'missing information' section of the RMP.

5.2.6. Eslicarbazepine acetate - ZEBINIX (CAP)

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

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)
PRAC Co-Rapporteur: Jana Mlada (CZ)

Background

Eslicarbazepine is an antiepileptic medicine.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP concerning pharmacovigilance activities related to an increased susceptibility to cutaneous reactions in particular genotypes observed with the structurally related compound carbamazepine, following

inclusion of this information in the labelling of centrally authorised medicines containing eslicarbazepine acetate.

Summary of advice

- The updated RMP version 8 for Zebinix (eslicarbazepine acetate) was considered acceptable.
- The next update of the RMP should take into account some amendments proposed by the PRAC, including a proposal for genotyping to better characterise the risk of developing severe cutaneous reactions in some patients with certain HLA alleles.

5.2.7. Everolimus – VOTUBIA (CAP)

- Evaluation of an RMP in the context of a line-extension procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (ES)
PRAC Co-Rapporteur: Julie Williams (UK)

Background

Everolimus is an immunosuppressant used in the treatment of tuberous sclerosis complex (TSC).

The CHMP is evaluating an extension of the therapeutic indication for Votubia, a centrally authorised product containing everolimus, to include use in patients less than 3 years of age, to provide new information relating to use in these patients, and to revise the starting dose for patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA). 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 5 for Votubia (everolimus) in the context of the extension of indication under evaluation by the CHMP was considered acceptable provided that an update is submitted in response to a Request for Supplementary Information to be adopted by CHMP.
- The update should take into account some additions proposed by the PRAC such as the effect on brain growth and development, and other effects in patients less than 3 years old.

5.2.8. Fosamprenavir - TELZIR (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
PRAC Co-Rapporteur: Jacqueline Genoux-Hames (LU)

Background

Fosamprenavir is an antiviral used in the treatment of HIV infection.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Telzir, a centrally authorised medicine containing fosamprenavir, following the submission of the final

report of a study in adults with HIV with hepatic impairment and availability of the 48-week data analysis for clinical paediatric studies.

Summary of advice

- The updated RMP for Telzir (fosamprenavir calcium) was considered acceptable, provided that the ongoing assessment of a variation being evaluated in parallel by CHMP does not identify any new safety concern requiring additional pharmacovigilance activities.
- The next update of the RMP should take into account some additions and clarifications proposed by the PRAC, including estimation of clinical trial exposure in relevant special populations and potential for harm from overdose in patients with hepatic impairment.

5.2.9. Imatinib – GLIVEC (CAP)

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

Regulatory details:

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

Background

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

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

Summary of advice

- The RMP version 6 for Glivec (imatinib) could not be considered acceptable until a consolidated version with changes agreed by the PRAC at the 29-31 October 2012 meeting for the RMP presented in support of a parallel procedure is submitted.

See also 6.1.8.

5.2.10. Insulin human – INSUMAN (CAP)

- Evaluation of an RMP in the context of a line-extension procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogne (BE)
PRAC Co-Rapporteur: Sabine Straus (NL)

Background

Insuman is a human insulin produced by recombinant DNA technology used in the treatment of diabetes.

The CHMP is evaluating a line extension to add Insuman Implantable 400 IU/ml solution for infusion, a formulation with a higher concentration of insulin which has been developed for use exclusively with an implantable insulin pump.

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

Summary of advice

- The RMP for Insuman Implantable (recombinant human insulin) submitted in the context of the line extension under evaluation by the CHMP could be considered approvable provided that an updated RMP and satisfactory responses to questions relating to the safety specification, the pharmacovigilance plan and risk minimisation measures are submitted.

5.2.11. Lopinavir / ritonavir – KALETRA (CAP), ALUVIA (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
PRAC Co-Rapporteur: Jacqueline Genoux-Hames (LU)

Background

The combination of lopinavir with ritonavir, two protease inhibitors, is used in the treatment of HIV infection.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Kaletra (lopinavir) and Aluvia (ritonavir) following the conclusion of a study in adults with HIV with hepatic impairment and the availability of the 48-week data analysis for clinical paediatric studies.

Summary of advice

- The updated RMP version 6 for Kaletra and Aluvia (lopinavir / ritonavir) was considered acceptable.
- The next update of the RMP should take into account some additions and clarifications proposed by the PRAC, including about the risk of immune reconstitution syndrome (IRIS) and about drug interaction between ritonavir and hepatitis C virus protease inhibitors (telaprevir and boceprevir).

5.2.12. Natalizumab - TYSABRI (CAP)

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)
PRAC Co-Rapporteur: Carmela Macchiarulo (IT)

Background

Natalizumab is a monoclonal antibody used in the treatment of multiple sclerosis.

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

In line with the adopted revised Rules of Procedure, Brigitte Keller-Stanislawski (DE) was appointed as Rapporteur with the agreement of the previously appointed Rapporteur Martin Huber (DE).

Summary of advice

- The updated RMP version 14 for Tysabri (natalizumab) was considered acceptable.
- The next update of the RMP should provide clarification regarding the timelines for the analysis of pregnancy data related to exposure to natalizumab (from drug registries and post-marketing data), and a proposal for a method for the analysis of these data.
- Since a more recent version of the RMP has been submitted with another variation currently under evaluation by the CHMP, the MAH should address the above within the ongoing variation.

See also related PSUR 6.1.10.

5.2.13. Pazopanib – VOTRIENT (CAP)

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

Regulatory details:

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

Background

Pazopanib is a protein-kinase inhibitor used in the treatment of renal cell carcinoma.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in relation to an ongoing type II variation to add safety information on posterior reversible encephalopathy syndrome (PRES), reversible posterior leukoencephalopathy syndrome (RPLS) and thrombotic microangiopathy (TMA) to the product information for Votrient, a centrally authorised product containing pazopanib.

Summary of advice

- The RMP version 9 for Votrient (pazopanib) submitted in the context of the type II variation under evaluation was considered acceptable provided that supplementary information relating to pancreatitis is included before finalisation of the variation procedure by the CHMP.

5.2.14. Pregabalin – LYRICA (CAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
PRAC Co-Rapporteur: Maria Alexandra Pego (PT)

Background

Pregabalin is a gamma-aminobutyric acid analogue used in the treatment of epilepsy, anxiety disorders and neuralgia.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP for Lyrica, a centrally authorised medicine containing pregabalin, to include the final report of a Drug Utilisation Study examining prescribing patterns for pregabalin from two different patient databases in EU (The Health Improvement Network (THIN) in the United Kingdom and the Swedish Prescribed Drug Register (SPDR)) and to address some editorial issues identified in a previous version.

Summary of advice

- The updated RMP version 8 for Lyrica (pregabalin) was considered acceptable.
- The next update of the RMP should provide further clarification as well as measures to minimise the potential risk of abuse, misuse and drug dependence. This is currently included in the product information.

5.2.15. Pandemic influenza vaccine (H5N1) A/Vietnam/1194/2004 NIBRG-14 (H5N1) (split virion, inactivated, adjuvanted) – ADJUPANRIX (CAP)

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

Regulatory details:

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

Background

Adjupanrix is an adjuvanted H5N1 pandemic influenza vaccine.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR.

Summary of advice

- The updated RMP version 9 for Adjupanrix (Pandemic influenza vaccine (H5N1)) was considered acceptable.

See also 6.1.11.

5.2.16. Prepandemic influenza vaccine (H5N1) A/Indonesia/05/2005 PR8 IBCDC-RG2 (H5N1) (split virion, inactivated, adjuvanted) – PREPANDRIX (CAP)

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

Regulatory details:

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

Background

Prepandrix is an adjuvanted H5N1 pandemic influenza vaccine.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following assessment of the accompanying PSUR submitted.

Summary of advice

- The updated RMP version 9 for Prepandrix (Pandemic influenza vaccine (H5N1)) was considered acceptable.
- The next update of the RMP should take into account some additions proposed by the PRAC such as the inclusion of narcolepsy amongst the potential risks, and clarification of the optimal design and methodology for safety and effectiveness studies, including proposals to test the logistical and implementation challenges in a mass immunisation/emergency situation.

See also 6.1.12.

5.2.17. Ranibizumab – LUCENTIS (CAP)

- Evaluation of an RMP in the context of a 90-day type II variation – extension of indication

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)
PRAC Co-Rapporteur: Dolores Montero (ES)

Background

Ranimizumab is a monoclonal antibody used in the treatment of age-related macular degeneration.

The CHMP is evaluating an extension of the therapeutic indication for Lucentis, a centrally authorised product containing ranimizumab, to include the treatment of choroidal neovascularisation secondary to pathologic myopia. 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 11 for Lucentis (ranimizumab) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable provided that an update of the RMP taking into account some additions and clarifications regarding the PRAC's proposal on consistency of the educational material is submitted before finalisation of the variation procedure by the CHMP.

5.2.18. Tenofovir disoproxil fumarate – VIREAD (CAP)

- Evaluation of an RMP in in the context of a 90-day type II variation – extension of indication

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
PRAC Co-Rapporteur: Miguel Angel Macia (ES)

Background

Tenofovir disoproxil fumarate is a nucleotide analogue reverse transcriptase inhibitor (NRTI) used in the treatment of HIV infection.

The CHMP is evaluating an extension of the therapeutic indication for Viread, a centrally authorised product containing tenofovir disoproxil fumarate, to add the treatment of HIV-infection in selected populations of paediatric and adolescent patients.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of the indication. The update of the RMP will also include the updates resulting from the evaluation of two other variations under evaluation by the CHMP to add safety information to the product information of Viread.

Summary of advice

- The updated RMP for Viread (tenofovir disoproxil fumarate) submitted in the context of the extension of indication under evaluation by the CHMP was considered acceptable.
- The next update of the RMP should take into account additions and clarifications proposed by the PRAC regarding the epidemiology of resistance to lamivudine, relevant non-clinical data related to bone toxicity and clinical exposure in patients with chronic hepatitis B who are resistant to lamivudine.

5.2.19. Tolvaptan – SAMSCA (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Carmela Macchiarulo (IT)

Background

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

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following the assessment of the accompanying PSUR submitted for Samsca, a centrally authorised medicine containing tolvaptan.

Summary of advice

- The updated RMP version 9 for Samsca (tolvaptan) was considered acceptable.

See also 6.1.18.

5.2.20. Ulipristal – ELLAONE (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)
PRAC Co-Rapporteur: Ulla Wändel-Liminga (SE)

Background

Ulipristal is a hormonal oral contraceptive used in emergency contraception.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following the assessment of the accompanying PSUR submitted for Ellaone, a centrally authorised medicine containing ulipristal.

Summary of advice

- The RMP version 11 for Ellaone (ulipristal) was considered acceptable.

See also: 6.1.19.

5.2.21. Varenicline – CHAMPIX (CAP)

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

Regulatory details:

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

Background

Varenicline is a nicotinic receptor partial agonist used for smoking cessation.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP following the assessment of the accompanying PSUR submitted for Champix, a centrally authorised medicine containing varenicline.

Summary of advice

- The updated RMP version 8 for Champix (varenicline) was considered acceptable.
- The next update of the RMP should take into account additions and clarifications proposed by the PRAC regarding the latest information on cardiovascular risk as well as other risks being evaluated in parallel regulatory procedures under evaluation.

See also: 6.1.20.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1.1. Apixaban – ELIQUIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Apixaban is an inhibitor of coagulation factor Xa used to prevent venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery.

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

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

6.1.2. Azacitidine – VIDAZA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Azacitidine is an antineoplastic used in the treatment of myelodysplastic syndromes.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Vidaza (azacitidine) in the approved indication(s) remains favourable.
- Some adverse drug reactions should be kept under close monitoring and acute febrile neutrophilic dermatosis should be added to the product information. In addition, the risk of cardiac events could not be excluded and should be reflected in the product information. The risk of cardiac events should be added to the RMP as a potential risk. Therefore, the current terms of the marketing authorisation should be varied[4].

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

6.1.3. Boceprevir – VICTRELIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

See also 5.2.2. .

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

[4] The PRAC Assessment Report and PRAC recommendation will be transmitted to the CHMP for adoption of an opinion.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Victrelis (boceprevir) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- In the next PSUR, the MAH should address some remaining issues, including a review of cases of angioedema, Drug Reaction with Eosinophilia and Systemic Symptoms DRESS and Stevens Johnson Syndrome (SJS), and should take into account some safety aspects to be kept under close monitoring.

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

6.1.4. Capsaicin – **QUTENZA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pego (PT)

Background

See also 4.1.3.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Qutenza (capsaicin) in the approved indication(s) remains favourable.
- Having reviewed the PSUR, the PRAC recommended the product information should be updated to advise the use of mask and protective glasses in addition to gloves (which are already recommended). The PRAC also considered that the adverse reaction of second degree burns (see Qutenza under Signal: 4.1.3.) and the risk of accidental exposure (including eye pain, eye and throat irritation and cough) should be reflected in the product information and in the RMP. The RMP should also state that Qutenza (capsaicin) should be administered under medical supervision in order to prevent off-label use and/or administration errors. Moreover risk minimisation measures and pharmacovigilance activities should be proposed in the RMP to address newly identified risk and missing information. The current terms of the marketing authorisation should be varied[5].

The frequency of submission of PSURs should be changed from the recommended 5 year period as currently included in the EURD list to once yearly and the next PSUR should be submitted within 70 days of the data lock point.

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

- Evaluation of a PSUR procedure

[5] The PRAC Assessment Report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

See also 5.2.3.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prolia and Xgeva, centrally authorised medicines containing denosumab, and issued a recommendation on the marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of data on safety and efficacy, the benefit-risk balance of Prolia and Xgeva (denosumab) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- A follow-up review of safety data should be submitted by the MAHs within 60 days.

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

6.1.6. Eribulin – HALAVEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Eribulin is an antineoplastic medicinal product used in the treatment of breast cancer.

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

Summary of recommendation(s) and conclusions

- Based on the review of data on safety and efficacy, the benefit-risk balance of Halaven (eribulin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- A follow-up review of disseminated intravascular coagulation (DIC) should be submitted by the MAH within 60 days in the context of a variation procedure.
- The next update of the RMP should take into consideration the outcome of this assessment.

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

6.1.7. Human hepatitis B immunoglobulin – ZUTECTRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

Human hepatitis B immunoglobulin is used to prevent hepatitis B virus (HBV) re-infection in HBV-DNA negative patients after liver transplantation for hepatitis B induced liver failure.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zutectra, a centrally authorised medicine containing human hepatitis B immunoglobulin, and issued a recommendation on its marketing authorisation.

In line with the adopted revised Rules of Procedure, Brigitte Keller-Stanislawski (DE) was appointed as Rapporteur with the agreement of the previously appointed Rapporteur Martin Huber (DE).

Summary of recommendation(s) and conclusions

- Based on the review of data on safety and efficacy, the risk-benefit balance of Zutectra (human hepatitis B immunoglobulin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- In the next PSUR, the MAH should present preliminary results of the ongoing studies and final results of the completed studies, and provide a comparison of sales figures and reported cases of serious adverse reactions.

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

6.1.8. Imatinib – GLIVEC (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

See also 5.2.9.

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

Summary of recommendation(s) and conclusions

- Based on the review of data on safety and efficacy, the benefit-risk balance of Glivec (imatinib) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.

The frequency of submission of PSURs should remain every 3 years and the next PSUR should be submitted within 90 days of the next data lock point.

6.1.9. Interferon Beta 1a – AVONEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Avonex, a centrally authorised medicine containing interferon beta-1a, 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 Avonex (interferon beta-1a) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- Data on pregnancy should be reviewed in the context of the results from the pregnancy registry of beta-interferons.

The frequency of submission of PSURs should remain every 3 years and the next PSUR should be submitted within 90 days of the next data lock point.

6.1.10. Natalizumab - TYSABRI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Background

See also 5.2.12.

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

In line with the adopted revised Rules of Procedure, Brigitte Keller-Stanislawski (DE) was appointed as Rapporteur with the agreement of the previously appointed Rapporteur Martin Huber (DE).

Summary of recommendation(s) and conclusions

- Based on the review of data on safety and efficacy, the risk-benefit balance of Tysabri (natalizumab) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- The MAH should be requested to provide a more thorough analysis of pregnancy data taking into account gestational age and treatment duration during pregnancy in order to determine the risk of abortion, malformations, stillbirth and premature births in pregnant women.

- In addition, the MAH should be requested to provide information on the ongoing work from the scientific consortium that was established to conduct research in the area of progressive multifocal leukoencephalopathy (PML).

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

6.1.11. Pandemic influenza vaccine (H5N1) A/Vietnam/1194/2004 NIBRG-14 (H5N1) (split virion, inactivated, adjuvanted) – ADJUPANRIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

See also 5.2.15.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Adjupanrix, a centrally authorised pandemic influenza vaccine, 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 Adjupanrix (pandemic influenza vaccine (A/Vietman/H5N1)) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.

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

6.1.12. Pandemic influenza vaccine (H5N1) A/Indonesia/05/2005 PR8 IBCDC-RG2 (H5N1) (split virion, inactivated, adjuvanted) – PREPANDRIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

See also 5.2.16.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prepandrix, a centrally authorised pandemic influenza vaccine, 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 Prepandrix (prepandemic influenza vaccine (A/Indonesia/H5N1)) in the approved indication(s) remains favourable.

- The current terms of the marketing authorisation should be maintained.

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

6.1.13. Piperaquine tetraphosphate / dihydroartemisinin – EURARTESIM (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

The combination of piperaquine tetraphosphate and dihydroartemisinin is used in the treatment of malaria.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Eurartesim, a centrally authorised medicine containing this combination, 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 Eurartesim (piperaquine tetraphosphate / dihydroartemisinin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.

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

6.1.14. Rilpivirine – EDURANT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in the treatment of HIV infection.

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

Summary of recommendation(s) and conclusions

- Based on the review of data on safety and efficacy, the risk-benefit balance of Edurant (rilpivirine) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.

- The MAH should be requested to closely monitor the adverse drug reaction of agranulocytosis, potentially an important safety risk despite the small number of cases.

The frequency of submission of PSURs should be changed from once yearly to 6 monthly and the next PSUR should be submitted within 70 days of the next data lock point.

6.1.15. Rosiglitazone – AVANDIA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Rosiglitazone is a member of the class of thiazolidinediones used in treatment of type II diabetes.

Currently the marketing authorisation for Avandia, a centrally authorised medicine containing rosiglitazone, has been suspended on the recommendation of the CHMP.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Avandia, and issued a recommendation on necessary updates of the product information, should the suspension of the marketing authorisation of Avandia be lifted.

Summary of recommendation(s) and conclusions

- The marketing authorisation for Avandia (rosiglitazone) is suspended. Based on the review of the data on safety and efficacy, the risk-benefit balance of Avandia in the approved indication(s) remains unfavourable.
- Should the conditions for the lifting of the suspension of the marketing authorisation for Avandia be fulfilled and the suspension lifted, the product information should be amended to take into account the outcome of the assessment of the PSUR.

Whilst the marketing authorisation remains suspended, the frequency of submission of PSURs should be changed from once yearly to every 3 years and the next PSUR should be submitted within 90 days of the next data lock point.

6.1.16. Tafamidis – VYNDAQEL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Tafamidis is a stabilizer of transthyretin used in the treatment of amyloidosis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vyndaqel, a centrally authorised medicine containing tafamidis, 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 Vyndaqel (tafamidis) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- Off-label use should be monitored in forthcoming PSURs.

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

6.1.17. Temsirolimus – TORISEL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Temsirolimus is an antineoplastic medicine used in the treatment of renal cell carcinoma and mantle-cell lymphoma.

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

The harmonisation of the data lock point of temsirolimus with that of tacrolimus and sirolimus (31 March 2015) is recommended. The frequency of submission of PSURs should be changed from once yearly to every 3 years and the next PSUR should be submitted within 90 days of the data lock point.

6.1.18. Tolvaptan – SAMSCA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

See also 5.2.19.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Samsca, a centrally authorised medicine containing tolvaptan, 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 Samsca (tolvaptan) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- In line with the outcome of the discussion on the signal of dehydration in October 2012 (see Minutes of the meeting of PRAC 29-31 October 2012), the MAH should address the concerns raised about the potential risk of more severe dehydration when tolvaptan is administered concomitantly with a diuretic. The MAH should also be requested to review the possible interaction between tolvaptan and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and risk of renal dysfunction.
- In the next PSUR, the MAH should also evaluate the effectiveness of the current risk minimisation measures for the adverse event of over-rapid correction of hyponatraemia. If risk existing minimisation measures prove insufficient the MAH is requested to propose additional risk minimisation activities and to submit an updated RMP.
- The MAH should be requested to monitor and critically analyse the use of doses of tolvaptan less than 15 mg and submit an overview of all reported cases with a lower initial dose, review data on current drug utilisation, and evaluate the impact of the lower dose on the benefit-risk balance of tolvaptan and its effectiveness in these patients.

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

6.1.19. Ulipristal – ELLAONE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

See also 5.2.20.

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

The frequency of submission of PSURs should be changed from every 6 months to every year and the next PSUR should be submitted within 70 days of the next data lock point.

6.1.20. Varenicline – CHAMPIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

See also 5.2.21.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Champix, a centrally authorised medicine containing varenicline, 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 Champix (varenicline) in the approved indication(s) remains favourable.
- The PRAC recommended updating the product information with regard to seizure-related events. Therefore the current terms of the marketing authorisation should be varied[6].
- For the next PSUR, the MAH is requested to continuously monitor the risk of suicide-related events, which is currently being evaluated in clinical trials. The MAH should also closely monitor the interaction between varenicline and opioids, and present in the next PSUR a cumulative review and a literature search on this interaction.

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

7. Post-authorisation safety studies (PASS)

7.1. Post-authorisation safety studies protocols

7.1.1. Aclidinium Bromide - EKLIRA GENUAIR; BRETARIS GENUAIR (CAP)

- Evaluation of a protocol for a PASS to evaluate the risk of cardiovascular endpoints

Regulatory details:

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

Background

Aclidinium bromide is an anticholinergic used in the treatment of chronic obstructive pulmonary disease (COPD). For further background please refer to PRAC Minutes 29 - 31 October 2012.

At the time of the centralised marketing authorisation of the aclidinium bromide-containing medicines Eklira and Bretaris Genuair, the CHMP requested the MAH to perform a drug utilisation study (DUS) and a post-authorisation safety study (PASS) to examine the risk of selected cardiovascular events.

The protocol for the DUS was discussed at the PRAC meeting of 29-31 October 2012. The protocol for the PASS was discussed by the PRAC at the current meeting.

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

Endorsement / Refusal of the protocol

Having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, the PRAC objected to the draft protocol for Eklira/Bretaris Genuair (aclinidium bromide) as the Committee considered that the design of the study did not fulfil the study objectives and that an amended protocol should be submitted.

Therefore, the PRAC recommended that the MAH should submit a revised PASS protocol within 60 days to reflect the additions recommended by the PRAC with regard to the study objectives and design. A standard 60-day assessment timetable will apply.

7.1.2. **Angiotensin receptor blockers** (ARBs): **Telmisartan - KINZALMONO, MICARDIS, PRITOR** (CAP); **Telmisartan / HCT - KINZALKOMB, MICARDISPLUS, PRITORPLUS** (CAP); **Telmisartan / amlodipine - ONDUARP, TWYNSTA** (CAP)

- Evaluation of a proposal for a PASS

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

For further background please refer to PRAC Minutes 29 - 31 October 2012.

Following the PRAC's discussion in October 2012, IT presented a proposal for an ad hoc study of the ARB class regarding the possible increase of cardiovascular risk in the diabetic population with additional cardiovascular risk factors.

The PRAC considered it necessary to review a more detailed proposal and to consider other approaches such as a patient-level meta-analysis.

Summary of advice

IT will provide a revised detailed proposal, including a plan for statistical analysis, modalities, expected deliverables and timelines. Follow-up discussion will take place when the protocol is presented.

7.1.3. **Ivacaftor – KALYDECO** (CAP)

- Letter from the EMA Paediatric Committee (PDCO) - collection of long-term data on disease progression in the 5-year post-authorisation study (PASS)

Regulatory details:

PRAC Rapporteur: Miguel Angel Macia (ES)
PRAC Co-Rapporteur: Julia Pallos (HU)

Background

The PDCO contacted the PRAC regarding a request for modification of the Paediatric Investigational Plan (PIP) for Kalydeco. The MAH requested the removal of a two-year placebo-controlled study (study D) in children with Forced Expiratory Volume in 1 second FEV1 > 90% from the PIP on the basis that the study was no longer feasible. The study was to evaluate the impact of ivacaftor on disease progression.

The PDCO adopted a positive opinion on the PIP modification request but at the same time emphasised the importance of gathering long-term data on disease progression to ensure safe and effective use of

Kalydeco in paediatric patients and recommended that the 5-year post-authorisation safety study (PASS) included in the Risk Management Plan be used to gather these data.

The PRAC discussed the PDCO letter and recommendations.

Summary of advice

The PRAC considers the lack of long-term data on disease progression (including rate of decline of lung function, diabetes mellitus and distal intestinal obstruction syndrome) to be an important knowledge gap that is of particular cause of concern in children with cystic fibrosis.

The PRAC therefore agreed on the need to amend the PASS protocol - for which a letter of objection (with recommendation for the submission of a new protocol) was agreed during the 3-5 October 2012 meeting - to include the additional objective of obtaining long-term disease progression data and specific endpoints.

A revised letter to the MAH was agreed by the PRAC requesting the MAH to further amend the PASS protocol and giving the MAH a one month extension to the deadline for submission of the revised PASS protocol.

7.1.4. **Trimetazidine** (NAPs)

- PRAC advice for a joint protocol for a PASS study to address all important, potential and identified risks – request for PRAC advice from MSs

Regulatory details:

PRAC Rapporteur: n/a

Background

The Annex IV of the Commission Implementing Decision issued on 3 September 2012 laid out the conditions to the marketing authorisations of trimetazidine-containing medicinal products, which were subject to a recently concluded referral procedure under Article 31 of Directive 2001/83/EC.

The conditions include the requirement to conduct a drug utilization study to verify the compliance of prescribers regarding the restricted indication after marketing authorisation changes. There is also a requirement to perform a PASS study to address all important, potential and identified risks, particularly Parkinsonism, the final protocol of which should be submitted to Member States/Reference Member States within 60 days of the Commission decision and agreed upon before the study is started.

PRAC advice was sought by EE on the appropriateness of encouraging the MAHs concerned to conduct a joint study and to submit a joint protocol.

Summary of advice

The PRAC noted that study protocols are submitted to Member States. On the understanding that these are non-interventional PASS that will be conducted in more than one Member State, the marketing authorisation holder should submit the study protocols to EMA/PRAC for PRAC assessment in accordance with current legal requirements.

Marketing authorisation holders should submit the study protocols to the PRAC. As there is more than one medicinal product concerned, the Member States should encourage marketing authorisation holders to submit joint protocols.

7.2. Results of post-authorisation safety studies

None

8. Product related pharmacovigilance inspections

8.1. List of planned pharmacovigilance inspections

The list of planned pharmacovigilance inspections is reviewed twice a year according to a risk based approach. The PRAC members were requested to send comments if any to EMA by 10 December 2012. After that date the current revision of the programme will be considered agreed by the PRAC.

8.2. On-going or concluded pharmacovigilance inspections

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

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

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

9.1.1. Cinacalcet – MIMPARA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

For background information please refer to the Minutes PRAC Meeting 3-5 September 2012.

As requested the MAH responded to a list of questions agreed by the PRAC to address a signal of QT prolongation/ventricular arrhythmias. The Rapporteur assessed the MAH responses submitted in the framework of a variation procedure under evaluation by the CHMP.

Summary of advice

- The proposed variation to update the product information for Mimpara (cinacalcet) should include a revision of the wording of the product information to include information on the risk of QT prolongation/ventricular arrhythmias as a physiological consequence of hypocalcaemia as well as additional warnings for patients with known congenital long QT syndrome or patients receiving drugs known to cause QT prolongation.
- Since it is well known by health care professionals that QT-prolongation and ventricular arrhythmia can be a physiological consequence of hypocalcemia - already known risk associated with cinacalcet - a DHPC to accompany the changes to the product information was not considered useful.

- The next version of the RMP to be submitted should be updated to reflect this change.

9.1.2. Dabigatran – PRADAXA (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

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

The PRAC was requested to provide advice to the CHMP on a type II variation application by the MAH to include in the product information a new contraindication triggered by analysis of the interim results of the RE-ALIGN study (The Randomized, phase II study to Evaluate the sAfety and pharmacokinetics of oraL dabIGatran etexilate in patients after heart valve replacemeNt).

Summary of Advice

- The proposed variation to update the product information for Pradaxa (dabigatran) with a new contraindication for patients with a prosthetic heart valve was considered appropriate.
- Given that the change in the product information impacts on the conditions of appropriate use of the medicine, a DHPC to inform HCPs of the new contraindication was considered necessary.

9.1.3. Parecoxib – DYNASTAT (CAP)

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

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Parecoxib is non-steroidal anti-inflammatory drug (NSAID) used in the treatment of postoperative pain.

The PRAC was requested to provide advice to the CHMP on a type II variation application by the MAH to include in the product information a new statement about the risks of spontaneous abortion and effects on fertility with NSAIDs. This was prompted by review of a study by Nakhai-Pour et al. 2011[7]. This and two other epidemiological studies[8,9] along with post-marketing data have been submitted in support of the proposed changes.

[7] Hamid Reza Nakhai-Pour, Perrine Broy, Odile Sheehy, and Anick Bérard Use of non-aspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion CMAJ October 18, 2011 183:1713-1720; published ahead of print September 6, 2011, doi:10.1503/cmaj.110454

[8] Nielsen GL, Sørensen HT, Larsen H, Pedersen L.
Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. BMJ. 2001 Feb 3;322(7281):266-70.

[9] Li, D.K., Liu, L. and Odouli, R. (2003) Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. British Medical Journal 327(7411), 368-372

Summary of advice

- In light of the available pharmacoepidemiological data, an update of the product information for Dynastat (parecoxib) to reflect, as fully as possible, the available information on the risk of spontaneous abortion for non-aspirin NSAIDs was considered appropriate.
- However, in the framework of the current variation procedure, the MAH should be requested to comment further on the need to refine the text already included in the product information to ensure that the overall risk minimisation message is coherent and to propose more specific information on the potential risk of spontaneous abortion. The current product information for Dynastat (parecoxib) contraindicates parecoxib use in the last trimester and recommends that parecoxib should not be used during the first two trimesters of pregnancy unless clearly necessary.

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

9.2.1. Ofatumumab – ARZERRA (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Ofatumumab is a monoclonal antibody used in chronic lymphocytic B-Cell leukemia.

Arzerra, a centrally authorised product containing ofatumumab, was authorised under a conditional marketing authorisation in 2010. A request for renewal of the marketing authorisation was submitted by the MAH for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the safety data submitted and the CHMP Rapporteur assessment report, the PRAC advised on a renewal of the conditional marketing authorisation.

9.2.2. Teriparatide – FORSTEO (CAP)

- PRAC consultation on a renewal procedure of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Teriparatide is a parathyroid hormone analogue used in the treatment of osteoporosis in postmenopausal women and in men under certain conditions.

Forsteo, a centrally authorised medicine containing teriparatide, was authorised in 2003.

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

Summary of advice

Based on the review of the risk management system for Forsteo (teriparatide), and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this second renewal procedure. The PRAC recommended that the MAH continue to submit yearly PSURs.

9.2.3. Tocofersolan D-Alpha-Tocopheryl Polyethylene Glycol Succinate – VEDROP (CAP)

- PRAC consultation in an annual reassessment procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Vitamin E (in the form of tocofersolan, a pro-drug of which the active metabolite is d-alpha-tocopherol) is used to treat vitamin E deficiencies due to digestive malabsorption in children and adolescents suffering from chronic cholestasis.

Vedrop, a centrally authorised product containing tocoferol, was authorised under exceptional circumstances in 2009. 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 Vedrop could only be finalised if satisfactory clarification is given on some pending issues. These include an update on the status of the communication with each of the three additional centres that are proposed as sites for enrolment of additional patients to the Vedrop registry as well as milestones for levels of patient recruitment to be reached.

9.2.4. Vandetanib – CAPRELSA (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Vandetanib is an antineoplastic agent used in the treatment of some thyroid cancers.

Caprelsa, a centrally authorised product containing vandetanib, was authorised under conditional marketing authorisation in 2012. A request for renewal of the marketing authorisation was submitted

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

Summary of advice

Based on the review of the available information on the status of the fulfilment of Specific Obligations and safety data submitted, the PRAC agreed with the CHMP Rapporteur's conclusions and the recommendations are endorsed.

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

None

9.4. Other requests

9.4.1. Loxapine

- PRAC consultation on a drug utilisation study (DUS) protocol upon CHMP request

The PRAC provided advice on aspects related to the risk management system for a product under evaluation by the CHMP for an initial marketing authorisation application, upon specific request.

9.4.2. **Pioglitazone – ACTOS** (CAP), **GLUSTIN** (CAP), **pioglitazone / metformin - COMPETACT** (CAP), **GLUBRAVA** (CAP), **pioglitazone / glimepiride - TANDEMACT** (CAP)

- PRAC consultation on a final protocol for a Pan European Observational Study of Pioglitazone and Risk of Bladder Cancer, upon CHMP request

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Pioglitazone hydrochloride is a member of the thiazolidinedione class, used in the treatment of type II diabetes.

Centrally authorised medicines containing pioglitazone were subject to a referral procedure under Article 20 of Regulation (EC) No 726/2004.

The CHMP requested that the MAH provides a high level protocol for a pan-European study to characterise the nature and size of the risk of bladder cancer associated with pioglitazone in patients with type II diabetes. The protocol for this Pan European Observational Study of Pioglitazone and the Risk of Bladder Cancer was submitted in October 2012.

This observational study is being conducted to further assess the association between pioglitazone use and bladder cancer risk among patients with type II diabetes mellitus in four European countries: Finland, Netherlands, Sweden, and the United Kingdom.

The advice of the PRAC was sought on the protocol of the study.

Summary of advice

- The protocol of the pan-European multiple database bladder cancer risk characterisation study was considered broadly sufficient to deliver on the study objectives

- However some amendments were proposed by the PRAC regarding the methodology for analysing the results. The analysis should focus on the cohort study, with extensive sensitivity analysis to determine the robustness of the findings.

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

10.1. Renewals of the Marketing Authorisation

None

10.2. Safety related variations of the Marketing Authorisation

None

10.3. Other requests

10.3.1. **Trimetazidine** (NAPs)

- PRAC advice for a joint protocol for a PASS study to address all important, potential and identified risks – request of PRAC advice from MSs

Regulatory details:

PRAC Rapporteur: N/A

Please refer to 7.1.4.

11. Organisational, regulatory and methodological matters

11.1. Mandate and organisation of the PRAC

11.1.1. Rules of Procedure of the PRAC

The PRAC unanimously adopted the revised Rules of Procedures as per the proposal of the EMA Management Board. These Rules of Procedure will be in use as of the current meeting whilst awaiting a favourable opinion on the revised Rules from both the EMA Management Board and the European Commission.

Post-meeting note: the Rules of Procedure received a favourable opinion from the EMA Management Board at their 13 December meeting and from the European Commission on 20 December 2012 and entered formally into force on 21 December 2012.

11.2. Pharmacovigilance audits and inspections

None

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

11.3.1. Periodic Safety Update Reports

- Clarification on PSUR submission requirements for PSURs for generic products authorised under Article 10(1) of Directive 2001/83/EC

Following the entry into force of the new Pharmacovigilance legislation on 02 July 2012, pursuant to Article 28(2) of Regulation (EC) No 726/2004 and Article 107b(3) of Directive 2001/83/EC,PSURs for generic products authorised under Article 10(1) of Directive 2001/83/EC are no longer required to be submitted unless there is an explicit condition in the marketing authorisation or there is a request from a national competent authority or EMA or as specified in the EURD list, which will become binding on 1st April 2013. As clarified in the Questions 5.7 and 5.11 of the Questions and Answers to support the implementation of the Pharmacovigilance legislation, a standard wording on the PSUR cycle following the reference medicinal product in the Annex II, should no longer be regarded as a condition to the MA to submit routine PSURs.

11.3.2. PSURs Repository

None

11.3.3. Union Reference Date List

11.3.3.1. Consultation on the draft List, version December 2012

The PRAC was consulted on the EURD list version November 2012. It was agreed that PRAC members should give input on the few outstanding issues by 5 December 2012. The responses received will be integrated into the list for consideration and adoption by CMDh and CHMP at their December 2012 meetings. Any unresolved issues will be brought back to the PRAC at its January 2013 meeting.

11.4. Signal Management

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

The Signal Management Review Technical (SMART) Working Group will hold a virtual meeting in December 2012 and present a progress report at the plenary meeting of the PRAC in January 2013.

11.5. Adverse Drug Reactions reporting and additional reporting

None

11.6. Eudravigilance Database

None

11.7. Risk Management Plans and Effectiveness of risk Minimisations

None

11.8. Community Procedures

None

11.9. Risk communication and Transparency

11.9.1. Safety Communication

- Adapting format of EMA safety communication

EMA presented the new format that will accompany the publication of the notification of EU Referral procedures.

11.10. Continuous pharmacovigilance

None

11.11. Interaction with EMA Committees and Working Parties

11.11.1. Committees

11.11.1.1. Paediatric Committee (PDCO)

Please refer to:

7.1.3. Ivacaftor - KALYDECO

11.11.2. Working Parties

- Working Group on Quality Review of Documents (QRD): revised mandate – interaction with PRAC

EMA informed the Committee that a revised mandate of the QRD Working Group has been drafted. The revised mandate reflects all the current activities of the QRD and its interaction with stakeholders. As an EMA working party, the QRD group will liaise with PRAC on issues related to the safe use of medicines and, particularly, in the area of prevention of medication errors when elements of product information are involved.

Information is needed from some Member States regarding the national ADR reporting details to be included in the QRD product information template. Member States were requested to send confirmation/amendments.

11.11.3. Other

- Summary of Product Characteristics (SmPC) Advisory Group – Revision of webpage and member list update

EMA informed PRAC of the launch of the revised EudraSmPC webpage (http://eudrasmpc.eudra.org/) and asked for confirmation of the PRAC representatives in the SmPC Advisory Group. The previously appointed Members from the Pharmacovigilance Working Party were confirmed. Nominations for additional Members were welcomed by 7 December 2012. The list of Members of the Group will be published on the EMA website.

11.12. Interaction within the EU regulatory network

None

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

11.13.1. Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

None

11.13.2. Other

- Proposals for drug safety priorities for EC DG Research Framework Programme 8 (FP8) funding in Work Programme 2014

The EMA presented an outline of a number of drug safety topics as potential proposals for Drug Safety Research Priorities for European Commission (EC) DG RTD Eighth Framework (FP8) funding in the 2014 Work Programme. The topics related to potential safety risks associated with use of calcium supplements, smoking cessation therapies and anti-hypertensive agents. The PRAC agreed with the proposed topics and suggested they be further developed as scientific fiches including re-circulation among the PRAC members for their input. Following adoption by the PRAC the proposals will be transmitted to the CHMP and then to the EC.

12. Any other business

- Management and circulation of documents

This topic was deferred to future meetings.

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 26-29 November 2012 meeeting.*

PRAC member / PRAC alternate	*Country*	*Outcome restriction following evaluation of e-DoI for the current meeting*	*Topics on the current Committee Agenda for which restriction applies* *Product/ substance*
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Full involvement	
Yuliyan Eftimov	Bulgaria	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Eva Jirsova	Czech Republic	Full involvement	
Jana Mlada	Czech Republic	Full involvement	
Doris Stenver	Denmark	Full involvement	
Katrin Kiisk	Estonia	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Brigitta Kütting - apologies	Germany	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer-reviewer for:	Pregabalin, Varenicline, Apixaban, Tafamidis, Temsirolimus, Parecoxib
Julia Pallos	Hungary	Full involvement	
Gudrun Kristin Steingrimsdottir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Fernanda Ferrazin	Italy	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 current meeting*	*Topics on the current Committee Agenda for which restriction applies* *Product/ substance*
Alexandra Pego - apologies	Portugal	Full involvement	
Daniela Pomponiu	Romania	Full involvement	
Tatiana Magalova	Slovakia	Full involvement	
Milena Radoha-Bergoč	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
June Munro Raine	Chair	Full involvement	
Julia Dunne	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 current 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		Cannot act as Rapporteur or Peer-reviewer for:	Dabrafenib, Pazopanib, Pandemic Influenza vaccines, Prepandemic influenza vaccines, Ofatumumab Pregabalin,Varenicline, Apixaban, Tafamidis, Temsirolimus, Parecoxib
Stephen Evans		Cannot act as Rapporteur or Peer-reviewer for:	Dabrafenib, Pazopanib, Pandemic Influenza vaccines, Prepandemic influenza vaccines, Ofatumumab
Brigitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Involvement in discussions only with respect to procedures involving the following products (i.e. no part in final deliberations and voting as appropriate as regards these medicinal products) - Cannot act as Rapporteur or Peer	Agomelatine Trimetazidine

Independent scientific experts nominated by the European Commission	Country	Outcome restriction following evaluation of e-DoI for the current meeting:	Topics on the current Committee Agenda for which restriction applies *Product/ substance*
		reviewer for these products	

Additional European experts participating at the meeting for specific Agenda items	Country	
Jamila Hamdani	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for the discussion on the specific agenda items
Veerle Verlinden	Belgium	
Benedicte Lunddahl Rasmussen	Denmark	
Yvonne Buggy	Ireland	
Helene Plein	Ireland	
Guiseppe Rosano	Italy	
Wilhelmina Elisabeth Hoogendoorn	Netherlands	
Ursula Vetter	Netherlands	
Ita Walsh	Netherlands	
Agneta Aust Kettis	Sweden	
Charlotte Backman	Sweden	
Charlotta Bergquist	Sweden	
Rebecca Chandler	Sweden	
Kristina Dunder	Sweden	
Jane Woolley	United Kingdom	