16 May 2013
EMA/PRAC/332071/2013 Corr.
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 8-11 April 2013

Chair: June Raine – Vice-Chair: Almath Spooner

Explanatory notes

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

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

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

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

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

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

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

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

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

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

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

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

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

Corr. Amendments in Annex II

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1. Introduction

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

The PRAC welcomed the newly appointed representative of healthcare professionals (member Filip Babylon) and the representative of patients organisations (alternate Marco Greco) who were nominated by the European Commission and were participating in the meeting for the first time.

The Chairperson opened the meeting and welcomed all participants to the 8-11 April 2013 meeting of the PRAC.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 23 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Adoption of agenda of the PRAC meeting on 8-11 April 2013

The agenda was adopted with the addition of the following topics upon request from the members of the Committee and the EMA secretariat: diacerein 3.2.3. ; combined hormonal contraceptives 2.2.2. ; hydroxyethyl starch 3.2.6. ; everolimus 5.2.9. and 6.1.1. ; dexamphetamine 11.3.1. .

1.3. Minutes of the previous PRAC meeting on 4-7 March 2013

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

Post-meeting note: the PRAC minutes of the meeting on 4-7 March 2013 were published on 11 April 2013 on the EMA website (EMA/248666/2013).

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

2.1. Newly triggered procedures

None

2.2. Ongoing Procedures

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

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

Regulatory details:

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

Background

A referral procedure under article 107i of Directive 2001/83/EC is ongoing for Diane 35 and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms (see minutes of PRAC 4-7 February 2013). The Rapporteurs prepared a preliminary assessment report following the responses received from the MAH to the list of questions (LoQs) agreed by the PRAC.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusions and noted the preliminary list of participants for the expert meeting to be held on the 26th of April 2013. The agenda and the list of participants were adopted. The PRAC also discussed a proposal for strategic risk communication to accompany the conclusion of the review. EMA secretariat launched a call of interest for members of the PRAC to participate in a subgroup to work on the strategy with a deadline of 9th of April 2013.

2.3. Procedures for finalisation

2.3.1. Tetrazepam (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 107i of Directive 2001/83/EC for tetrazepam-containing medicines (see minutes of the PRAC 4-7 March 2013 for background) was to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs; one oral explanation took place during the meeting. The PRAC discussed the risk of skin reactions in the context of the therapeutic effect for tetrazepam-containing medicines and in the light of the proposed risk minimisation measures. The PRAC considered that the risk minimisations measures discussed during the assessment, including reduction of duration of treatment and restricted indication, were not sufficient to reduce the risk of serious cutaneous reactions.

Summary of recommendation(s)/conclusions

In light of the above, the PRAC agreed, by majority vote, on the suspension of the marketing authorisations for tetrazepam-containing medicines, with conditions for lifting the suspension, and adopted a recommendation for consideration by CMDh for agreement of a position – see Q&A EMA/225675/2013 and assessment report EMA/279100/2013).

Nineteen members/alternates, out of 32 eligible to vote, voted in favour of the suspension together with Iceland and Norway, while thirteen members/alternates[1] had divergent views (see EMA/279100/2013 Assessment report for tetrazepam containing medicinal products).

Post-meeting note: the press release 'recommendation to suspend tetrazepam-containing medicines endorsed by CMDh' EMA/256383/2013 was published on the EMA website on 29 April 2013.

2.4. Planned public hearings

None

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

3.1. Newly triggered Procedures

None

3.2. Ongoing Procedures

3.2.1. Almitrine (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for almitrine-containing medicines (see minutes of PRAC 26-29 November 2012). An assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and agreed on a list of outstanding issues to be addressed by the MAHs, who will be invited to address them in an oral explanation at the May 2013 PRAC meeting, in accordance with an updated timetable for the review. (EMA/PRAC/209863/2013).

[1] Jean-Michel Dogné (BE); Daniela Pomponiu (RO); George Aislaitner (EL); Jana Mladá (CZ); Jacqueline Genoux-Hames (LU); Jolanta Gulbinovic (LT); Amy Tanti (MT);Martin Huber (DE); Maria Popova-Kiradjieva (BG); Anna Mareková (SK) Miguel-Angel Macia (ES); Andis Lacis (LV); Filip Babylon (Representative of healthcare professionals)

3.2.2. Codeine (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for codeine-containing medicines (see minutes of PRAC 29-31 October 2012). The Rapporteurs prepared their preliminary assessment reports based on the responses provided by the MAH to the LoQs agreed by the PRAC.

Summary of recommendation(s) / conclusions

The PRAC discussed the conclusions of the preliminary assessment reports. An overview of current guidelines for acute pain management (post-operative pain relief) in children was provided. The PRAC recommended that the views on the assessment performed are gathered from the Pharmacogenomics Working Party as well as from the Paediatric Committee.

The PRAC agreed a proposal for updating the product information for codeine-containing medicines as part of a list of outstanding issues to be addressed by the MAHs, who will be invited to address them in an oral explanation at the June 2013 PRAC meeting, in accordance with an updated timetable for the review (EMA/PRAC/184919/2013).

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

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

Regulatory details:

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

Background

A referral procedure under Article 31 is ongoing for combined hormonal contraceptives (see minutes of the PRAC 4-7 February 2013).

Summary of recommendation(s) / conclusions

The PRAC was in favour of setting up an ad-hoc expert meeting in the framework of the current procedure to be held on 2nd of July 2013; an amended timetable to include this change was adopted (EMA/PRAC/122032/2013 - Rev 3). The PRAC agreed on the expertise required at the meeting. Members were invited to propose nominations from the Member States. The EMA secretariat clarified that the current provisions in terms of handling of conflicts of interest will be applied. A list of questions for the experts will be discussed at the May 2013 meeting. The PRAC noted that MAHs will be participating in the ad-hoc expert meeting in order to address questions raised by the experts.

3.2.4. Diacerein (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for diacerein-containing medicines (see minutes of the PRAC 4-7 February 2013). A request for an extension of the timetable for the review was put forward by a MAH concerned.

Summary of recommendation(s)/conclusions

The PRAC noted the request, but decided to maintain the timetable already adopted for concluding the review.

3.2.5. Diclofenac (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for diclofenac-containing medicines (see minutes of PRAC minutes 29-31 October 2013). The Rapporteurs prepared their preliminary assessment reports based on the responses provided by the MAHs to the LoQs agreed by the PRAC.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusions of the preliminary assessment reports. Further discussion will take place at the May 2013 PRAC meeting once comments are received from concerned MAHs and by the members of the PRAC.

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

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for HES-containing products (see minutes of the PRAC 4-7 March 2013). The Rapporteurs prepared their preliminary assessment reports based on the responses provided by the MAH to the list of questions (LoQs) agreed by the PRAC.

Summary of recommendation(s)/conclusions

The PRAC discussed a list of questions for the experts participating in the ad hoc-expert meeting to be held on the 19th of April 2013 before finalisation of the procedure. A report from the meeting will be provided to PRAC before the May 2013 meeting. A list of questions for the authors of some recently published studies previously considered by the PRAC (see PRAC minutes 4-7 February 2013) was also agreed.

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

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

Regulatory details:

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

Background

For background, see minutes of the PRAC 4-7 February 2013. A request for an extension of the timetable for the review was put forward by one of the MAHs involved in the procedure.

Summary of recommendation(s)/conclusions

The PRAC noted the request, but decided to maintain the previously adopted timetable.

3.3. Procedures for finalisation

None

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

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

- Review of findings on pancreatic risks following notification by the European Medicines Agency (EMA) under Article 5(3) of Regulation (EC) 726/2004

Regulatory details:

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

Background

A review under Article 5(3) of Regulation 726/2004 is ongoing for GLP-1 based therapies (glucagon-like-peptide-1 (GLP-1) agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors) (see EMA/178662/2013).

The review was triggered by a publication looking at tissue samples from Type II diabetic patients who had died from other causes, suggesting an increased risk of pancreatitis and pancreatic-duct metaplasia[2].

Summary of recommendation(s)/conclusions

The PRAC had an initial discussion on the findings based on a preliminary assessment provided by the Rapporteur. The PRAC agreed that an expert meeting should be organised to better understand the strengths and limitations of the histological findings and recommended enhanced exchange of information with other international competent authorities, the MAHs and research groups in the field (EU project SAFEGUARD). PRAC members were encouraged to elaborate on questions to be addressed at the expert meeting.

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Adalimumab – HUMIRA (CAP)

- Signal of ulcers

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Adalimumab is a monoclonal antibody used in the treatment of ankylosing spondylitis, rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, axial spondyloarthritis, polyarticular juvenile idiopathic arthritis and ulcerative colitis.

The patient exposure for Humira, a centrally authorised medicine containing adalimumab, has been estimated to be more than 1.4 million patient-years worldwide in the period from 2003 until 2010.

During routine signal detection activities, a signal of ulcer was identified by the UK, based on reports of cases of skin ulcers, infected skin ulcers and other cases reported as ulcers retrieved from the UK database and 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 ulcers reported and agreed that, despite the fact that some reports were heterogeneous and their interpretation challenging, it was possible to identify a common pattern and concerns were raised over worsening of ulcers in patients treated with adalimumab. The PRAC noted that impaired healing had already been reported and is currently listed in

[2] Diabetes. 2013 Mar 22. [Epub ahead of print]
Marked Expansion of Exocrine and Endocrine Pancreas with Incretin Therapy in Humans with increased Exocrine Pancreas Dysplasia and the potential for Glucagon-producing Neuroendocrine Tumors.
Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC.

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

the product information for adalimumab-containing medicines. Therefore the PRAC agreed the signal needed further investigation.

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should submit to the EMA a cumulative review of cases of spontaneous or worsening of ulcers (with particular focus on cases raising suspicion of spontaneously emerging ulcers during adalimumab treatment) in the next PSUR, with data lock point (DLP) 31 December 2013.
- This review will be assessed in the framework of the next PSUR assessment procedure; the timing of the PRAC recommendation following this review and the accompanying PSUR will be in accordance with the published EMA PSUR timetable.

4.1.2. Adalimumab – HUMIRA (CAP)

- Signal of glioblastoma and brain neoplasms

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Adalimumab is a monoclonal antibody used in the treatment of ankylosing spondylitis, rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, axial spondyloarthritis, polyarticular juvenile idiopathic arthritis and ulcerative colitis.

The patient exposure for Humira, a centrally authorised medicine containing adalimumab, has been estimated to be more than 1.4 million patient-years worldwide in the period from 2003 until 2010.

During routine signal detection activities, a signal of glioblastoma was identified by the UK, based on 5 cases reported in the UK; 7 cases of other brain neoplasms were also reported. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of glioblastoma and brain neoplasms and noted that the current product information reports solid organ neoplasms under 'undesirable effects'. The PRAC agreed that based on the information available it was not possible to draw any conclusion on causality and agreed that the signal needed further investigation.

Moreover the PRAC noted that EudraVigilance contained a few cases of glioblastoma and brain neoplasms reported in association with other tumour necrosis factor alpha (TNF-α) inhibitors (infliximab and etanercept). Therefore the PRAC concluded that the signal should also be further investigated for these substances.

Summary of recommendation(s)

- The MAHs for Humira (adalimumab), Embrel (etanercept), Remicade (infliximab) should submit to the EMA a cumulative review of the signal of glioblastoma and other malignant brain neoplasms within 60 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Brentuximab vedotin – ADCETRIS (CAP)

- Signal of pulmonary toxicity

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Brentuximab vedotin is an antineoplastic agent used in the treatment of patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) and for patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Exposure data for Adcetris, a centrally authorised medicine containing brentuximab, are being gathered since the medicine was authorised only recently, in late 2012.

During routine signal detection activities, a signal of pulmonary toxicity was identified by the EMA, based on 20 cases obtained following a search in EudraVigilance with the MedDRA terms 'pneumonitis', 'interstitial lung disease', 'pulmonary haemorrhage', and 'pulmonary toxicity' and from the published literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported and noted that all cases, except one literature case, were clinical trials cases. The diagnosis of pulmonary toxicity was confirmed by imaging techniques and histology and two cases were fatal. The PRAC was of the view that the role of a previous treatment with bleomycin should be further characterised. Based on the information available the PRAC agreed that the signal warranted further investigation.

Summary of recommendation(s)

- The MAH for Adcetris (brentuximab) should submit to the EMA a cumulative review of the signal of pulmonary toxicity and related ADRs, giving consideration to the possible effect of previous treatment with bleomycin, and should consider any necessary amendment of the product information or to the RMP, within 60 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.4. Exenatide – BYDUREON (CAP)

- Signal of injection site abscess and cellulitis

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Exenatide belongs to the class of glucagon-like peptide-1 (GLP-1) receptor agonists, used in the treatment of type II diabetes.

The exposure for centrally authorised medicines containing exenatide is estimated to have been more than 2 million patient-years respectively worldwide, in the period from its first authorisation (2006) until 2012.

Exenatide in a formulation for twice daily administration has been authorised as Byetta in the EU since 2006. Exenatide formulation for once weekly administration has been authorised as Bydureon since 2011.

During routine signal detection activities, a signal of injection site abscess and cellulitis was identified by the EMA, based on disproportional reporting observed for Bydureon (exenatide) for most of the injection site reactions contained in EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted the disproportional reporting estimates for Bydureon regarding injection site abscess and injection site cellulitis, and discussed further information from post-marketing cases received in EudraVigilance reporting abscess and cellulitis at the injection site. Based on the available evidence the PRAC agreed that the signal warranted further investigation.

Summary of recommendation(s)

- The MAH for Bydureon (exenatide) should submit to the EMA a cumulative review of the signal, and consider any necessary amendment of the product information or to the RMP.
- This review will be assessed in the framework of the next PSUR assessment procedure with data lock point 30 March 2013; the timing of the PRAC recommendation following this review and the accompanying PSUR will be in accordance with the published EMA PSUR timetable.

4.2. New signals detected from other sources

4.2.1. Agents acting on the renin-angiotensin system (CAP, NAP)

- Signal from the literature of efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials

Regulatory details:

PRAC Rapporteur: *n/a*

Background

In the framework of signal detection activities the EMA identified a recently published meta-analysis by Makani[4] on the dual blockade of the renin angiotensin system with angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEis) or direct renin inhibitors (aliskiren). Results from 33 randomised controlled trials involving 68 405 patients (mean age 61 years, 71% men) with a mean duration of treatment of 52 weeks.

IT as Rapporteur for the centrally authorised telmisartan- and aliskiren-containing medicines agreed that the signal needed initial analysis and prioritisation by the PRAC.

[4] Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomized trials. BMJ. 2013 Jan 28;346:f360. doi: 10.1136/bmj.f360.

Discussion

The PRAC noted the conclusion of the meta-analysis and the preliminary review performed suggesting 'an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy'. The PRAC noted also that for aliskiren-containing medicines, the results were in line with the previously performed review under Article 20 of Regulation (EC) No 726/2004, which concluded with a recommendation not to combine aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) and a contraindication against the use of aliskiren in combination with ARBs or ACEIs in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see also EMA/113677/2012; the outcome of this review will also be reflected in the product information for the combinations telmisartan-amlodipine, telmisartan/amlodipine, and other combinations with telmisartan). Having considered the new available evidence from the scientific literature and given the seriousness of the signals of harm associated with a dual blockade of the renin angiotensin system, the PRAC agreed on the need to further assess all information as regards to the safety of the blockade of the renin-angiotensin system.

Summary of recommendation(s)

The MSs should in the interests of the European Union consider the need for a formal benefit-risk review of the concomitant use of angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEis) or direct renin inhibitors (aliskiren) producing a dual blockade of the renin-angiotensin system. Post-meeting note: the Italian Medicines Agency (AIFA) sent a letter of notification dated 17 April 2013 of a referral under Article 31 of Directive 2001/83/EC for a review of the benefit-risk of the dual blockade of the renin-angiotensin system (RAS), involving angiotensin receptor blockers, angiotensin converting enzyme inhibitors and direct renin inhibitors (aliskiren).

4.3. Signals follow-up

4.3.1. Azithromycin (NAP)

- Signal of potentially fatal cardiac events

Regulatory details:

PRAC Rapporteur*: to be appointed*

Background

Azythromycin is a macrolide antibiotic used to treat infections caused by susceptible bacteria.

In 2012 the Pharmacovigilance Working Party discussed a signal of potentially fatal arrhythmias following the administration of oral or intravenous azithromycin and reviewed a study published in May 2012 by Ray et al[5] regarding the risk of cardiovascular death. The worldwide exposure between 2003 and 2011 for the nationally authorised azithromycin-containing innovator medicine Zithromax, Zithromax IV, for which FI is the reference Member State (RMS), is estimated to have been over 300 million prescriptions.

[5] Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.S., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B. Azithromycin and the Risk of Cardiovascular Death - N Engl J Med 2012; 366:1881-1890May 17, 2012DOI: 10.1056/NEJMoa1003833

Following discussion at the PhVWP the MAH for the innovator product, was requested – in the framework of a PSUR Work Sharing procedure - to provide a further analysis and an assessment of the above mentioned publication.

More recently, on 12 March 2013, the FDA published a Drug Safety Communication on azithromycin and the risk of potentially fatal heart rhythms.

FI provided an overview of latest responses of the MAH and agreed that the signal needed follow-up discussion and prioritisation by the PRAC.

Discussion

The PRAC discussed whether based on the available evidence the current product information for azithromycin containing medicines was still appropriate and whether an update of the product information earlier than the timeliness established by the PSUR Work Sharing procedure was considered necessary. The PRAC also noted that the MAH had proposed performing a feasibility assessment of undertaking an observational study using large electronic healthcare records in US and EU databases with the aim of examining the acute effect of azithromycin on cardiac deaths, including sudden cardiac deaths as compared to the appropriate comparison groups. The most appropriate regulatory framework for conducting the post-authorisation safety study to further examine the safety of azithromycin was discussed. The PRAC agreed that this signal and the proposal for a study should be investigated in greater detail and on the basis of a full assessment of the data.

The PRAC appointed Terhi Lehtinen as Rapporteur for the follow-up of the signal.

Summary of recommendation(s)

- The PRAC Rapporteur should circulate an assessment report on this signal to the PRAC members leading to a PRAC recommendation at the 13-16 May 2013 meeting.

4.3.2. Docetaxel – TAXOTERE (CAP), DOCETAXEL WINTHROP (CAP) and NAPs

- Signal of thrombotic microangiopathy

Regulatory details:

PRAC Rapporteur*:* Isabelle Robine (FR)

Background

Docetaxel is an antineoplastic agent used in the treatment of breast cancer, non small-cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer.

The patient exposure for Taxotere, a centrally authorised medicine containing docetaxel, has been estimated to be more than 1.6 million patient-years worldwide in the period from 2007 until 2010.

Before the institution of the PRAC in 2012, the EMA had identified a signal of thrombotic microangiopathy based on cases contained in EudraVigilance, and a cumulative review of the signal was requested from the MAH. The MAH replied to the request for information on the signal and the responses were assessed by the Rapporteur who agreed that the signal needed follow-up discussion by the PRAC.

Discussion

The PRAC noted that among all cases cumulatively reviewed, those that had sufficient documentation of thrombotic microangiopathy also had alternative aetiologies as confounders, and no case was reported in which there was evidence of a positive re-challenge after re-exposure to docetaxel.

Summary of recommendation(s)

- The available data do not currently justify recommending any regulatory action. However, the MAHs for Taxotere and Docetaxel Winthorp (docetaxel) are requested to continue monitoring cases of thrombotic microangiopathy, haemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and microangiopathic haemolytic anaemia and to provide an update in the next PSUR (data lock point (DLP) 1 March 2015).

4.3.3. Docetaxel – TAXOTERE (CAP), DOCETAXEL WINTHROP (CAP)

- Signal of serious and fatal drug interactions involving CYP3A4 inhibitors (grapefruit juice and dronedarone)

Regulatory details:

PRAC Rapporteur*:* Isabelle Robine (FR)

Background

Docetaxel is an antineoplastic agent used in the treatment of breast cancer, non-small-cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer.

The patient exposure for Taxotere, a centrally authorised medicine containing docetaxel, has been estimated to be more than 1.6 million patient-years worldwide in the period from 2007 until 2010.

Before the institution of the PRAC in 2012, the EMA had identified a signal of serious and fatal drug interactions involving cytochrome P450-3A4 (CYP3A4) inhibitors resulting in increased docetaxel toxicity (neutropenia and mucositis). The signal was identified following publications by Vodovar D et al[6] and Valenzuela et al.[7].

The cases had been reviewed by the Rapporteur who agreed that the signal needed follow-up analysis by the PRAC.

Discussion

The PRAC discussed the literature cases of clinically significant pharmacokinetic drug interactions between docetaxel and CYP3A4 inhibitors (grapefruit juice, dronedarone) that were considered well documented. The PRAC noted that the product information for Taxotere (docetaxel) advises caution for concomitant use of products which induce, inhibit or are metabolised by cytochrome P450-3A4. However, neither grapefruit juice, nor dronedarone are included in the list of interacting substances for Taxotere and the interaction with docetaxel is not mentioned in the product information of Multaq, a centrally authorised medicine containing dronedarone.

[6] Vodovar D, Mongardon N, Moachon L, Arnaout M, Beuzeboc P, Lokiec F, Rezai K, Pène F; Severe docetaxel overdose induced by pharmacokinetic interaction with dronedarone. J Clin Oncol. 2011 Aug 20;29(24):e694-5. doi: 10.1200/JCO.2011.35.8002. Epub 2011 Jul 5.

[7] Valenzuela B, Rebollo J, Pérez T, Brugarolas A, Pérez-Ruixo JJ. Effect of grapefruit juice on the pharmacokinetics of docetaxel in cancer patients: a case report. Br J Clin Pharmacol. 2011 Dec;72(6):978-81. doi: 10.1111/j.1365-2125.2011.04052.x

Summary of recommendation(s)

- The MAHs for the reference, centrally authorised[8] docetaxel containing medicines (Taxotere and Docetaxel Winthrop) should be requested to submit to the EMA within 60 days a variation to update the product information with regard to this signal[9].
- The MAHs of generics products should subsequently align their product information to that of the originator in accordance with current procedures.
- No mention of dronedarone needs to be specifically reported in the product information since general advice to avoid concomitant use with substances that inhibit or are metabolised by cytochrome P450-3A4 is already provided.

4.3.4. Fingolimod – GILENYA (CAP)

- Signal of haemophagocytic syndrome

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

For background information, see PRAC minutes of 29-31 October 2012. The MAH replied to the request for information on the signal and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the responses provided by the MAH and agreed that, whilst some minor clarifications still needed to be provided, it was important to raise awareness about the occurrence of the two fatal cases of haemophagocytic syndrome reported. Therefore the product information should provide information on this. Moreover, accompanying communications should be issued to raise awareness on haemophagocytic syndrome including information on its challenging diagnosis and the risk of a worse outcome when a diagnosis is delayed.

Summary of recommendation(s)

- The MAHs for Gilenya (fingolimod) should be requested to submit to the EMA within 60 days a variation to provide some further clarification on the signal, including a proposal for an update

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

[9] Summary of product characteristics (SmPC) - section 4.4 should be updated to contain a warning: 'Grapefruit (fruit or juice) consumption should be avoided (see section 4.5)'.
Section 4.5, two warnings should be added as follows: 'In case of grapefruit consumption as fruit or juice, the occurrence of docetaxel side-effects may increase, as a result of increased intestinal bioavailability. Therefore, as long as docetaxel is given, grapefruit should be avoided (see section 4.4)'.
'In case of combination with dronedarone or with CYP3A4 inhibitors (boosted PIs with ritonavir, azole antifungals and some macrolides) the occurrence of docetaxel side-effects may increase, as a result of reduced metabolism. A close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during the treatment with dronedarone or the CYP3A4 inhibitor'.
The package leaflet should be updated accordingly in section 2 - What you need to know before you take Taxotere/Docetaxel Winthrop - Taxotere/Docetaxel Winthrop with food and drink: 'Grapefruit (fruit or juice) consumption should be avoided while taking Taxotere/Docetaxel Winthrop. It can interfere with the usual effect of your medicine'.

of the product information with regards to haemophagocytic syndrome[10] as well as a proposal for a DHPC and communication plan.

4.3.5. Fluoroquinolones: ciprofloxacin (NAP), enoxacin (NAP), flumequine (NAP), lomefloxacin (NAP), levofloxacin (NAP), moxifloxacin (NAP), ofloxacin (NAP), pefloxacin (NAP), prulifloxacin (NAP), rufloxacin (NAP), norfloxacin (NAP)

- Signal of retinal detachment

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

For background, see PRAC minutes 4-7 March 2013.

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

Discussion and summary of recommendation(s)

Based on the available evidence, the PRAC was in favour of the EMA conducting a self-controlled case series (SCCS) analysis in The Health Improvement Network (THIN) database, taking into account the potential methodological issues that have been identified. With the collaboration of the PRAC Rapporteur, a protocol will be drafted within 3 months. Follow-up discussion will be planned accordingly.

4.3.6. Mirtazapine (NAP)

- Signal of pancreatitis

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

For background information see PRAC minutes 1-3 October 2012. The MAH replied to the request for information on the signal of pancreatitis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the cumulative review provided and noted that pancreatitis occurred with a low incidence in the mirtazapine-treatment arm during clinical trials. The low incidence did not allow an increased risk to be estimated from clinical trial data. However, the cumulative analysis of post-marketing cases, including well-documented published reports, provided sufficient evidence to confirm that mirtazapine can be associated with pancreatitis. In addition, the pre-clinical data show dose-related steatosis and possibly increased acinar atrophy in the highest dose male rats.

[10] Section 4.8 of the SmPC: information about the occurrence of two fatal cases of HPS

Therefore, the PRAC agreed to update the product information of mirtazapine-containing medicine to include pancreatitis as rare adverse reaction

Summary of recommendation(s)

- The MAHs for the reference, nationally authorised [11] mirtazapine–containing medicine should be requested to submit to the National Competent Authorities (NCAs) of the MSs within 60 days a variation to update the product information to include "pancreatitis"[12] as an undesirable effect with the frequency "rare" (as observed in clinical trials).
- The MAHs of generics products should subsequently be requested to align their product information with that of the originator in accordance with current procedures.

4.3.7. Pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a) – PANDEMRIX (CAP)

- Signal of narcolepsy: further information following conclusion of the data review of Pandemrix and narcolepsy under Article 20 of Regulation (EC) No 726/2004

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

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

The Swedish medicines agency published on their website the results of a registry study carried out in Sweden, investigating the association of narcolepsy with Pandemrix (pandemic influenza vaccine (H1N1)). The registry involved nearly six million individuals and compared people who were vaccinated with Pandemrix with those who were not. The Rapporteur confirmed that this new information on the previously discussed signal should be brought to the attention of the PRAC as a follow-up.

Discussion

The PRAC discussed the new results investigating the association of narcolepsy with Pandemrix (pandemic influenza vaccine (H1N1)). The results suggested a two-fold increased risk of narcolepsy in young adults between 21 and 30 years of age (hazard ratio 2.92; 95% CI 1.78-4.79) and a three-fold increased risk of narcolepsy in people aged 20 years and younger, with a trend towards a decline in the excess risk with increasing age at vaccination. The PRAC also discussed some methodological strengths and limitations of the study - such as uncertainty around how the diagnoses of incident cases were validated.

The PRAC agreed that these data indicated a signal of increased risk within the 21-30 years age group, and therefore that it is important that this new information is reviewed in depth in an expedited manner. Since the text on narcolepsy in the product information for Pandemrix currently states that 'this risk increase has not been found in adults (older than 20 years)', the appropriateness of retaining

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

[12] Section 4.8 of the Summary of Product Characteristics - under the SOC Gastrointestinal disorders - frequency "rare"

this text should be considered during the further review. However SE expressed the opinion that the results from this study are sufficient as basis for revising this statement in the product information.

The PRAC also noted that it was possible that further data would become available from an ongoing French study, which had previously been considered by PRAC (Etude NarcoFlu-VF (NarcoFlu VAESCO-France)). There is also an ongoing study involving identification of adult narcolepsy cases from UK sleep centres that would provide further data on this issue – the results of this study are likely to become available by autumn 2013. The PRAC agreed that it is essential that the Committee obtains further information from the French study results before reaching any conclusion.

Summary of recommendation(s)

- A thorough evaluation of the Swedish study results and exploration of further data from the French study by the Rapporteur is warranted and follow-up discussion is planned for the June 2013 meeting.

4.3.8. Valproate (NAP)

- Signal of neurodevelopmental effects following in utero exposure

Regulatory details:

PRAC Rapporteur: *to be appointed*

Background

Valproate is a well-known anti-epileptic substance. In most EU Member States nationally authorised medicines containing valproate (as valproic acid, sodium valproate and, valproate semisodium) are also authorised for the treatment of patients with bipolar disorder. Some valproate-containing medicines are also approved for the prophylactic treatment of migraine.

In 2012 the Pharmacovigilance Working Party discussed a literature review prepared by the Danish Medicines Agency of studies of the neurodevelopmental effects of antenatal exposure to sodium valproate (or valproic acid) in children of women with epilepsy and the responses provided by the concerned MAH on the same matter. Key principles for the SmPC wording for use of valproate for treatment of epilepsy during pregnancy had already been agreed by the PhVWP in 2004. Also a referral under Article 31 of Directive 2001/83/EC on the use of valproate in bipolar disorder was concluded in 2010 (see Q&A). The referral included some recommendations on the wording in section 4.6 of the SmPC on pregnancy.

The PhVWP also discussed the responses received to an NUI to investigate the level of information regarding development effects reported in the SmPCs of various valproate-containing medicines marketed in the EU. The PhVWP concluded on the need to further review the issue and to collect information on the follow-up of cases as well as to clarify confounding factors relating to maternal exposure. DK proposed the issue for follow-up discussion and further analysis by the PRAC.

Discussion

The PRAC noted that the increased risk of potential teratogenic effects in the foetus from the use of valproate and related products during pregnancy had been previously recognised.

It has not been possible to establish whether there was a causal relationship between neurocognitive impairment and valproate exposure in utero given the neurological indications for which valproate is

being used i.e. the children of women being treated with valproate may already have an increased genetic or environmental risk of neurological impairment (confounding by indication).

However, the PRAC agreed that there was a need to confirm that the information included in the product information for the various valproate-containing medicines across the different indications adequately reflects the latest published scientific data on in utero exposure, including recent findings on the association between treatment with valproate in women with epilepsy during pregnancy and developmental delay in children.

The PRAC appointed Doris Stenver as Rapporteur for the assessment of the review.

Summary of recommendation(s)

- The Rapporteur should prepare an assessment report on this signal consolidating all available information to date (including recent study data and data for all indications) within 60 days leading to a further PRAC recommendation in June 2013.

For follow-up of other signals discussed in the past by the PRAC see also **tolvaptan** 10.1.2. and **ipilimumab** 6.1.23. .10.1.

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. Alogliptin

5.1.2. Alogliptin, metformin

5.1.3. Alogliptin, pioglitazone

5.1.4. Aripiprazole

5.1.5. Avanafil

5.1.6. Canagliflozin

5.1.7. Dabrafenib

5.1.8. Dapagliflozin, metformin

5.1.9. Enzalutamide

5.1.10. Esomeprazole

5.1.11. Flutemetamol F-18

5.1.12. Fluticasone furoate, vilanterol

5.1.13. Levetiracetam

5.1.14. Lomitapide

5.1.15. Lorcaserin

5.1.16. Modified Vaccinia Ankara virus

5.1.17. Somatropin

5.1.18. Spheroids of human autologous matrix-associated chondrocytes

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

5.2. Medicines already authorised

RMP in the context of a PSUR procedure

5.2.1. Aztreonam – CAYSTON (CAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

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

See also 5.2.1.

5.2.2. Bivalirudin – ANGIOX (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 10.1 of the RMP for the above mentioned medicine.

See also 6.1.6.

5.2.3. Cetuximab – ERBITUX (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

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

See also 6.1.7.

5.2.4. Dabigatran – PRADAXA (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

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

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

Summary of advice

- The updated RMP version 25 for Pradaxa (dabigatran) could be considered acceptable provided that the MAH submits to the EMA an updated version to address a request of the PRAC regarding off-label use in patients with prosthetic heart valves. The off-label use should be classified as an identified risk in accordance with the results of the RE-ALIGN (evaluation of the long term safety of the use of dabigatran etexilate in patients with a bileaflet mechanical heart valve).
- Furthermore a continuous update of the development of an antidote is expected with each RMP update

See also 6.1.8.

5.2.5. Daptomycin – CUBICIN (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 8 of the RMP for the above mentioned medicine.

See also 6.1.9.

5.2.6. Deferiprone – FERRIPROX (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 7 of the RMP for the above mentioned medicine.

See also 5.2.6.

5.2.7. Dexmedetomidine – DEXDOR (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

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

See also 6.1.11.

5.2.8. Etravirine – INTELENCE (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 8 of the RMP for the above mentioned medicine.

See also 6.1.14.

5.2.9. Everolimus – VOTUBIA (CAP)

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

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 8.6 of the RMP for the above mentioned medicine.

See also 6.1.1.

5.2.10. Exenatide – BYDUREON (CAP), BYETTA (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Exenatide is a glucagon like peptide-1 (GLP-1) receptor agonist used in the treatment of type II diabetes in selected patients.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMPs following assessment of the accompanying PSUR for Byetta and Bydureon, centrally authorised products containing exenatide.

Summary of advice

- The updated RMPs version 20 for Byetta and Bydureon (exenatide) were considered acceptable.

See also 6.1.16.

5.2.11. Fingolimod – GILENYA (CAP)

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

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Fingolimod is an immunosuppressant 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 Gilenya, a centrally authorised product containing fingolimod.

Summary of advice

- The updated RMP version 5 for Gilenya (fingolimod) was considered acceptable.
- In the next update of the RMP to be submitted to the EMA with the next PSUR, the MAH should address some points raised by the PRAC, including risks of skin cancer and hypotension, which are to be upgraded to 'important identified risks' and the risk of 'multiple sclerosis relapse' to be included as an 'important potential risk'.
- Furthermore the MAH should also consider the inclusion of peripheral oedema as an important identified risk; data regarding the clinical trial exposure should be presented consistently between the PSUR and the RMP.

See also 6.1.17.

5.2.12. Memantine – AXURA (CAP), EBIXA (CAP)

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

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 6.1 of the RMP for the above mentioned medicine.

See also 6.1.29.

5.2.13. Micafungin – MYCAMINE (CAP)

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

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 11 of the RMP for the above mentioned medicine.

See also 6.1.30.

5.2.14. Midazolam – BUCCOLAM (CAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

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

See also 6.1.31.

5.2.15. Orlistat – XENICAL (CAP)

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

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

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

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

Summary of advice

- The updated RMPs version 5 for Xenical (orlistat) was considered acceptable.
- However the next update of the RMP should take into consideration some minor points raised by the PRAC. In addition the PRAC noted an article regarding the effect of orlistat on carboxylesterase-2 (CES2) and possible effects on anti-cancer pro-drugs, published on-line in December 2012[13]; the MAH is requested to provide comments and additional data that may be relevant.

See also 6.1.32.

5.2.16. Oseltamivir – TAMIFLU (CAP)

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

[13] Xiao D, et al. Carboxylesterase-2 is a highly sensitive target of the antiobesity agent orlistat with profound implications in the activation of anticancer prodrugs. Biochem Pharmacol (2012), http://dx.doi.org/10.1016/ j.bcp.2012.11.026

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

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

See also 6.1.32.

5.2.17. Panitumumab – VECTIBIX (CAP)

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

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

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

See also 6.1.36.

5.2.18. Retigabine – TROBALT (CAP)

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

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

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

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

Summary of advice

- The updated RMP version 7 for Trobalt (retigabine) was considered acceptable. However, the next update of the RMP should address some points raised by the PRAC.
- Discoloration effects of nails and skin have been discovered with long term and high dose use. The PRAC noted that the issue is currently under evaluation in a variation II/14 and a revised RMP should be submitted with the next PSUR to reflect the outcome for this variation and to provide updates, as information becomes available on the findings on nail, lip and/or skin discolouration and any information relating to the case of retinitis pigmentosa, along with the results of ophthalmology consultations. A targeted follow-up questionnaire for patients on nail/skin and/or mucosal surface discolouration should be included in the revised RMP.
- 'Use in patients with haemodialysis' should remain under the missing information until data on the effects in steady state drug exposure in haemodialysis patients become available.

See also 6.1.38.

5.2.19. Strontium ranelate – OSSEOR (CAP), PROTELOS (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)
An assessment of the RMP for Osseor and Protelos (strontium ranelate) was performed by the Rapporteur. The PRAC agreed to adopt the assessment of the RMP via written procedure following conclusion of the meeting in order to allow alignment with the final recommendation on the PSUR.

See also 6.1.41.

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

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

Regulatory details:

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

See also 6.1.42.

5.2.21. Telaprevir – INCIVO (CAP)

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

Regulatory details:

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

See also 6.1.43.

5.2.22. Vinflunine – JAVLOR (CAP)

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

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)
As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 11 of the RMP for the above mentioned medicine.

See also 6.1.51.

RMP in the context of a variation

5.2.23. Certolizumab pegol – CIMZIA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version of the RMP for the above mentioned medicine, provided in support of an extension of the indication for the treatment of adult patients with active axial spondyloarthritis.

5.2.24. Human hepatitis B immunoglobulin – ZUTECTRA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version of the RMP for the above mentioned medicine, provided in support of a variation to include the final results of a PASS.

5.2.25. Telaprevir – INCIVO (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version of the RMP for the above mentioned medicine, provided in support of a variation to include information on the interaction of telaprevir with organic anion transporter polypeptides (OATPs) and other pharmacokinetic information.

5.2.26. Ulipristal acetate - ELLAONE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Ulipristal is selective progesterone receptor modulator. EllaOne, a centrally authorised product containing ulipristal, is indicated for emergency contraception within 120 hours (five days) of unprotected sexual intercourse or contraceptive failure.

The CHMP is evaluating a variation to change the classification of the medicine from a "medicinal product subject to medical prescription" to a "medicinal product not subject to medical prescription" in the EU. The PRAC is to provide advice to the CHMP on the proposed RMP to support this variation.

Summary of advice

- The updated RMP version 13 for EllaOne (ulipristal) could be considered acceptable provided that a revised version addressing some issues raised by the PRAC is submitted before finalisation of the procedure at the CHMP.

- In particular, the classification of 'missing information' should be reconsidered in light of the data gathering exercise by an ongoing pregnancy registry which has collected data on the follow-up of pregnancy cases.
- Considering the fact that some pharmacovigilance activities listed in the RMP are currently ongoing and the results are still awaited, the classification of relevant potential risks should not be revised.
- Furthermore, the proposal for additional risk minimisation measures should be clarified and justified.

5.2.27. Vardenafil – VIVANZA (CAP)

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

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 2 of the RMP for the above mentioned medicine, provided in support of a variation, line extension for the addition of a new pharmaceutical form.

5.2.28. Voriconazole – VFEND (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of this updated version 1.3 of the RMP for the above mentioned medicine, provided in support of a variation to inform prescribers of the limited safety data in patients with abnormal liver function tests and redefine the monitoring of hepatic function.

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

5.2.29. Sugammadex – BRIDION (CAP)

- Evaluation of an RMP in the context of a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

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

See also 8.1.5.

RMP in the context of a stand-alone RMP procedure

5.2.30. Cinacalcet – MIMPARA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

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

5.2.31. Dapagliflozin – FORXIGA (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

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

5.2.32. Ulipristal acetate – ELLAONE (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Ulipristal is selective progesterone receptor modulator. EllaOne, a centrally authorised product containing ulipristal is indicated for emergency contraception within 120 hours (five days) of unprotected sexual intercourse or contraceptive failure.

As part of the RMP for EllaOne (ulipristal), the MAH proposed to collect clinical follow-up information on the outcomes of pregnancies resulting from non-response to EllaOne or pregnancies inadvertently exposed to EllaOne. A pregnancy registry/study for collecting data on exposed pregnancies is available in all European countries where the product is launched. The MAH was requested to increase awareness among healthcare professionals and patients of the existence of the pregnancy registry and to improve the collection of follow-up information on pregnancy cases.

The MAH submitted an updated proposal to increase knowledge about pregnancy exposure and to optimise the collection of pregnancy exposure data through the existing pregnancy registry which had been previously assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on this updated proposal and related updates of the RMP.

Summary of advice

- The updated RMP version 12 for EllaOne (ulipristal) as well as the updated proposal regarding measures to strengthen the awareness of the pregnancy registry and improve follow up of pregnancy outcomes was considered acceptable.
- However the MAH should submit an updated version to the EMA, within 60 days, to address minor revisions suggested by the PRAC regarding post-marketing data collection.

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1.1. Adefovir dipivoxil – HEPSERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Adefovir dipivoxil is an oral prodrug of adefovir, an acyclic nucleotide phosphonate analogue of adenosine monophosphate, and is indicated for the treatment of chronic hepatitis B in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Hepsera (adefovir dipivoxil) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 30 days a cumulative review of renal and bone events and assess cases of lack of efficacy. The MAH should consider submitting a variation to EMA should these data impact on the product information.
- The MAH should submit to EMA an RMP within 90 days pursuant to Article 21(2) of Regulation (EC) No 726/2004 to address the risks of renal proximal tubulopathy, bone disorders, and Fanconi syndrome as well as the low antiviral potency and genetic barrier to resistance.
- Over the next PSUR period, the impact of rtQ215 substitutions in response to adefovir dipivoxil therapy should be closely monitored.

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

6.1.2. Aliskiren – RASILEZ (CAP), RIPRAZO

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Aliskiren is a renin inhibitor indicated for the treatment of essential hypertension.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Rasilez (aliskiren) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should monitor cases of drug-drug interaction with non-steroidal anti-inflammatory drugs (NSAIDs) and discuss the need to update SmPC sections 4.4 and 4.5 as well as the package leaflet to reflect the risk of gastrointestinal haemorrhage. The MAH should also monitor cases of chyloperitoneum and severe hyperkalaemia in patients with pre-existing cardiac disease, pre-existing renal disease and pre-existing diabetes. In addition, the MAH should discuss cases of hypotension events and consider updating the product information accordingly. Finally the MAH should discuss the increased reporting rate of fatal cases observed in the period covered by the last PSUR and provide a description of the characteristics of the relevant patients (i.e. concomitant pathologies and concomitant treatments).

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

6.1.3. Anagrelide – XAGRID (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

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

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

6.1.4. Aztreonam – CAYSTON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

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

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 11 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list

of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.5. Belimumab – BENLYSTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

Belimumab is a human monoclonal antibody used as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Benlysta (belimumab) in the approved indication(s) remains favourable.
- The product information should be updated to reflect the risk of opportunistic infections associated with the use of belimumab. Therefore the current terms of the marketing authorisation(s) should be varied[14].
- The MAH should address in the next PSUR all risks identified in the RMP.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 8 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.6. Bivalirudin – ANGIOX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Bivalirudin is a thrombin inhibitor used as an anticoagulant in adult patients under certain conditions.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Angiox (bivalirudin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should re-evaluate appropriately the role of the activated clotting time (ACT) to assess bivalirudin activity during administration and submit to EMA within 30 days a variation to update SmPC section 4.2 and the package leaflet.
- In the next PSUR, the MAH should address the results of three recent publications comparing durations of treatment with bivalirudin and consider updating the product information accordingly. In addition, the MAH should provide a cumulative review of haemorrhage cases where a history of head trauma or balloon aortic valvuloplasty has been reported, focussing on the reported risk factors and making recommendations for possible action where appropriate. Finally the MAH is requested to comment on whether the product information wording on the continuation of the infusion dose post-percutaneous coronary intervention (PCI) should be strengthened to recommend that the infusion should be continued post-procedure.

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

6.1.7. Cetuximab – ERBITUX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

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

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

6.1.8. Dabigatran – PRADAXA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Dabigatran is a direct thrombin inhibitor indicated for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Pradaxa (dabigatran) in the approved indication(s) remains favourable.
- The product information should be updated to contraindicate the use of Pradaxa in patients with a lesion or condition considered to be a significant risk factor for major bleeding. Therefore the current terms of the marketing authorisation should be varied[15].
- The MAH should submit to EMA within 60 days a summary of all available data on the P-glycoprotein inhibitory potential of posaconazole and of tacrolimus. The MAH should discuss whether a caution or recommendation against concomitant use of dabigatran with posaconazole or tacrolimus is warranted. In the case of tacrolimus, it should also discuss whether the current contraindication should be kept. In addition, in view of the interaction with rifampicin (and other P-gp inducers) and the reduction in dabigatran exposure when used concomitantly, the MAH should consider whether a contraindication is appropriate.
- In the next PSUR, the MAH should discuss whether more extensive information should be provided to prescribing physicians in view of the significant off-label use and the increase in bleeding events.
- Finally, the MAH should submit along with the next PSUR an updated RMP reflecting the recruitment for study 1160.129 and provide an update on the development of an antidote.
- The MAH should provide an update on the implementation of the patient alert card as part of the labelling (IIIA) and provide updated data on implementation on the effectiveness of this measure.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 18 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.9. Daptomycin – CUBICIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

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

[15] Update of SmPC section 4.3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

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

6.1.10. Deferiprone – FERRIPROX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

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

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

6.1.11. Dexmedetomidine – DEXDOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

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

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 15 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.12. Eculizumab – SOLIRIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

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

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

6.1.13. Eltrombopag – REVOLADE (CAP)

- Evaluation a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

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

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 30 September 2013. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal should be updated accordingly.

6.1.14. Etravirine – INTELENCE (CAP)

- Evaluation a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

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

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 27 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.15. Everolimus – VOTUBIA (CAP)

- Evaluation a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Everolimus is a protein kinase inhibitor used for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) and for the treatment of patients

with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Votubia (everolimus) in the approved indication(s) remains favourable.
- The product information should be updated to include drug-drug interactions with imatinib and with dronedarone. Therefore the current terms of the marketing authorisation should be varied[16].
- In the next PSUR, the MAH should continue to closely monitor several conditions, including cholelithiasis and the paediatric population subgroups in detail.
- The MAH should be requested to submit an updated RMP to address the drug-drug interactions of everolimus with imatininb and dronaderone and to further describe the drug-drug interaction of everolimus with enzyme-inducing antiepileptic drugs (EIAEDs).

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 30 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.16. Exenatide – BYDUREON (CAP), BYETTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist and is used for the treatment of type 2 diabetes mellitus.

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

Summary of recommendation(s) and conclusions

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

[16] Update of SmPC sections 4.3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

- The product information for Bydureon should be updated to add acute pancreatitis as an undesirable effect with a frequency 'not known'. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- The PRAC recommendation following the assessment of the current PSUR is without prejudice to the outcome of the ongoing Article 5(3) referral procedure (see 3.4.1.).
- In the next PSUR, the MAH should discuss reports of acute renal failure associated with exenatide once weekly and the need to update the product information for Bydureon where necessary. The MAH should also monitor serious bullous conditions and serious skin reactions and should continue to monitor cases of hepatic disorders.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 30 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.17. Fingolimod – GILENYA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Gilenya (fingolimod) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) for Gilenya (fingolimod) should be maintained.
- In the next PSUR, the MAH should provide a complete description of reported cases of skin cancers and malignant melanoma in double-blind controlled trials. The MAH should also provide information on the duration of exposure and phototype of patients included in clinical trials. In addition, the MAH should reflect on the need for additional pharmacovigilance activities regarding the risk of skin cancers and propose risk minimisation measures. To this end, the MAH should make proposals for an update of the SmPC sections 4.4 and 4.8 and to the package leaflet. Finally the MAH should address cases of posterior reversible encephalopathy syndrome (PRES) also with a view to proposing an update of the product information as necessary.

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

- In the next PSUR, the MAH should provide a detailed review of cases of oedema, discuss the mechanism of action and make a proposal for updating the product information and RMP if necessary. In addition, the MAH is requested to provide a cumulative safety review of thyroid malignancy and provide details on other concomitant or prior medications with immune-modulating effect. Finally, the MAH should submit an updated RMP with the next PSUR to address the risk of hypotension, multiple sclerosis relapse and skin cancer.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 28 February 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.18. Hepatitis A and hepatitis B (rDNA) (HAB) vaccine – AMBIRIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Ambirix, a centrally authorised hepatitis A and hepatitis B vaccine, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.19. Hepatitis A and hepatitis B (rDNA) (HAB) vaccine – TWINRIX ADULT (CAP), TWINRIX PAEDIATRIC (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Twinrix Adult and Twinrix Paediatric, centrally authorised hepatitis A and hepatitis B vaccines, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.20. Human fibrinogen thrombin – EVICEL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Evicel, a centrally authorised product containing human fibrinogen thrombin, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.21. Iloprost – VENTAVIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Ventavis, a centrally authorised product containing iloprost, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.22. Indinavir – CRIXIVAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Crixivan, a centrally authorised product containing indinavir, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.23. Ipilimumab – YERVOY (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Yervoy, a centrally authorised product containing ipilimumab, remains favourable in the approved indication(s)

and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 28 February 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

Irbesartan is a selective angiotensin-II receptor antagonist and is indicated for the treatment of essential hypertension in adults and for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aprovel, Irbesartan Zentiva and Kareva, centrally authorised medicines containing irbesartan, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Aprovel, Irbesartan Zentiva and Kareva (irbesartan) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- The MAH(s) should submit to EMA within 60 days a variation to include pancreatitis as an adverse reaction in the product information. The MAH(s) should present a proposal based on a comprehensive analysis of all of the serious cases of pancreatitis reported to date considering several parameters including the number of cases, the patients' age and sex, daily dose and therapeutic indication.
- In the next PSUR, the MAH(s) should closely monitor cases of interstitial lung disease and should provide detailed safety data on hypertensive type 2 diabetic patients with renal disease and interactions with drugs metabolised by CYP 2C8. In addition, the MAH(s) should provide cumulative reviews of alopecia, rhabdomyolysis, and paresthesia/hypoesthesia. Finally the MAH(s) should consider the need for additional pharmacovigilance activities regarding the risk of skin cancers.

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

6.1.25. Lacosamide – VIMPAT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Vimpat, a centrally authorised product containing lacosamide, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.26. Leflunomide – ARAVA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Arava, a centrally authorised product containing leflunomide, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Background

Lopinavir and ritonavir are indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children above the age of 2 years.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Kaletra, a centrally authorised medicine containing lopinavir/ritonavir, as well as the benefit-risk balance of Aluvia, a medicine evaluated by the CHMP in accordance with Article 58 of Regulation (EC) No 726/2004 and issued a recommendation on their respective marketing authorisation(s) and scientific opinion.

Summary of recommendation(s) and conclusions

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

- The current terms of the marketing authorisation(s) and scientific opinion should be maintained.
- The MAH/Scientific Opinion Holder should submit to EMA within 60 days detailed reporting rates of adverse reactions and fatal outcomes.

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

6.1.28. Measles, mumps, rubella and varicella vaccine – PROQUAD (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Proquad, a centrally authorised measles, mumps, rubella and varicella vaccine, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.29. Memantine – AXURA (CAP), EBIXA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Axura and Ebixa, centrally authorised products containing memantine, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.30. Micafungin – MYCAMINE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Micafungin is an antifungal agent used for the treatment of invasive candidiasis and the treatment of oesophageal candidiasis in adult patients as well as for the prophylaxis of Candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Mycamine (micafungin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- The MAH should submit to EMA within 60 days a re-analysis of all cases of thrombocytopenia to assess the possible contribution of the low platelet counts to the bleeding events reported, especially gastrointestinal haemorrhage.
- In the next PSUR, the MAH should further analyse cases of lack of efficacy in the context of possible off-label use as first-line treatment option. The MAH should also closely monitor cases of acute respiratory distress syndrome (ARDS), respiratory distress, respiratory failure and eosinophilic pneumonia.

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

6.1.31. Midazolam – BUCCOLAM (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Buccolam, a centrally authorised product containing midazolam (oromucosal solution), remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The frequency of submission of PSURs should be changed from 6 monthly to yearly. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal should be updated accordingly for the substance for midazolam (oromucosal solution).

6.1.32. Orlistat – XENICAL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Orlistat is an inhibitor of gastrointestinal lipases and is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m², or overweight patients (BMI > 28 kg/m²) with associated risk factors.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xenical, a centrally authorised medicine containing orlistat, 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 Xenical (orlistat) in the approved indication(s) remains favourable.
- The product information should be updated to better reflect the risk of renal toxicity and provide updated data on renal and hepatic toxicities as undesirable events. In addition, the product information should be updated to include interactions with antidepressants, antipsychotics and lithium. Therefore the current terms of the marketing authorisation should be varied[18].
- In the next PSUR, the MAH should provide a detailed analysis of cases of depression with prior history of psychiatric illness.

Following the conclusion of the Article 20 referral procedure in 2012 (CHMP review of orlistat-containing medicines), PSURs for orlistat-containing products including generics were to be submitted 6 monthly. The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 7 February 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.33. Oseltamivir – TAMIFLU (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Background

Oseltamivir is a neuraminidase inhibitor indicated for the treatment and prevention of influenza under certain conditions.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Tamiflu (oseltamivir) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit annual reviews on pregnancy cases and submit a revised RMP with updated sections on pregnancy monitoring.

The frequency of submission of PSURs should be changed from yearly to 3 yearly. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal should be updated accordingly.

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Pandemic Influenza Vaccine H5N1 Baxter, a centrally authorised pandemic influenza vaccine (whole virion, vero cell derived, inactivated), remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 28 February 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.35. Pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a) – PANDEMRIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Pandemrix, a centrally authorised pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted), remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.36. Panitumumab – VECTIBIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Vectibix, a centrally authorised product containing panitumumab, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 31 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.37. Pazopanib – VOTRIENT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Votrient, a centrally authorised product containing pazopanib, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.38. Retigabine – TROBALT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Trobalt, a centrally authorised product containing retigabine, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

See also 5.2.18.

6.1.39. Rivaroxaban – XARELTO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Rivaroxaban is an antithrombotic agent indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Xarelto (rivaroxaban) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation should be maintained.
- In view of the available data on the use of oral coagulants in patients at risk factor for major bleeding, drug-drug interactions, bleeding in the elderly, post-surgical patients and patients at high surgical mortality risk and the management of serious bleeding, the MAH should submit to EMA a variation within 60 days to include relevant contraindications in the product information (see 6.1.8.).
- In the next PSUR, the MAH should monitor any interactions, especially those listed above, and provide summaries of case reports, with particular emphasis on those with an outcome of bleeding.
- The MAH should provide an update on the implementation of the patient alert card as part of the package leaflet (IIIA) and provide updated data on implementation on the effectiveness of this measure.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 18 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.40. Rosiglitazone, metformin – AVANDAMET (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Avandamet, a centrally authorised product containing rosiglitazone/metformin, remains unfavourable and therefore recommends the maintenance of the suspension of the marketing authorisation with amendments to the product information to be incorporated at time of lifting of the suspension of the marketing authorisation of Avandamet, should the conditions for the lifting of the suspension of the marketing authorisation be fulfilled The PRAC adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.41. Strontium ranelate – OSSEOR (CAP), PROTELOS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Osseor and Protelos, centrally authorised medicines containing strontium ranelate, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy the PRAC agreed, by majority vote, that the risk-benefit balance of Osseor and Protelos (strontium ranelate) remains favourable provided the terms of the marketing authorisations are varied and adopted a recommendation for consideration by the CHMP– see Q&A EMA/220628/2013). Twenty-three members/alternates together with Iceland and Norway, out of 33 eligible to vote, voted in favour of the recommendation, while ten[19] members/alternates had divergent views (see EMEA website Home>Find medicine>Human Medicines - PRAC PSUR assessment report to be published following EC decision).
- The product information should be updated to restrict the indication to severe osteoporosis in postmenopausal women at high risk of fractures and severe osteoporosis in men at increased risk of fracture. The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks. In addition, the product information should be updated to contraindicate the use of strontium ranelate in patients with a current or past history of ischaemic heart disease, peripheral arterial disease or cerebrovascular disease and in patients with uncontrolled hypertension. Other recommended changes to the product information are the addition of text stating that the treatment should only be initiated by a physician with experience in the treatment of osteoporosis, the addition of an updated warning on cardiac ischaemic events and the listing of myocardial infarction as adverse reaction with 'common' frequency. Finally, the PRAC recommended that the conditions of the MA regarding the supply should be changed to 'restricted medical prescription' and that the MAH should conduct post-authorisation measures to assess the effectiveness of the agreed risk minimisation measures.
- Therefore the current terms of the marketing authorisation should be varied[20].

[19] Jean-Michel Dogné (BE); Carmela Macchiarulo (IT); Miguel-Angel Macia (ES); Isabelle Robine (FR); Julia Pallos (HU); Almath Spooner (IE); Jolanta Gulbinovic (LT); Qun-Ying Yue (SE); Hervé Le Louet, Jane Ahlqvist Rastad (Independent scientific experts nominated by the European Commission)

[20] Update of SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8 and Annex II.The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

- The MAH should inform healthcare professionals of these changes via a Direct Healthcare Professional Communication (DHPC).
- The medical products should be subject to additional monitoring.
- In view of the newly identified risk of serious cardiac disorders including myocardial infarction, the benefit/risk balance of medicinal products containing strontium ranelate should be further evaluated.
- The MAH should also submit an updated RMP to reflect these changes.

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

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Tegafur, gimeracil and oteracil are used in combination in oral fluoropyrimidine anti-cancer therapy indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Teysuno (tegafur/gimeracil/oteracil) in the approved indication(s) remains favourable.
- The product information should be updated to change the frequency of corneal disorders from 'rare/very rare' to 'common' and to include a description of the reported cases of corneal disorders. Therefore the current terms of the marketing authorisation should be varied[21].
- In the next PSUR, the MAH should continue to closely monitor corneal disorders and evaluate if these events occur more frequently with prolonged administration. The MAH should also continue to closely monitor serious cases of dehydration.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 14 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.43. Telaprevir – INCIVO (CAP)

- Evaluation of a PSUR procedure

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Incivo, a centrally authorised product containing telaprevir, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 19 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.44. Telavancin – VIBATIV (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Vibativ, a centrally authorised product containing telavancin, remains unchanged in the approved indication(s), however the marketing authorisation(s) for Vibativ remain suspended until the conditions defined by the CHMP for lifting the current GMP related suspension are fulfilled. The PRAC adopted a recommendation to maintain the suspension of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 11 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.45. Telbivudine – SEBIVO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Sebivo, a centrally authorised product containing telbivudine, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.46. Telmisartan, amlodipine – ONDUARP (CAP), TWYNSTA (CAP)

- Evaluation of a PSUR procedure

***Regulatory details*:**

PRAC Rapporteur: Martin Huber (DE)

Background

Telmisartan and amlodipine are used in combination in antihypertensive medicine and are indicated for the treatment of essential hypertension in adults under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Onduarp and Twynsta, centrally authorised medicines containing telmisartan and amlodipine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Onduarp and Twynsta (telmisartan/amlodipine) in the approved indication(s) remains favourable.
- The product information should be updated to include information relating to the interaction of telmisartan with aliskiren and with digoxin. Therefore the current terms of the marketing authorisation should be varied[22].
- In the next PSUR, the MAH should monitor the unlisted cases of joint swelling and include a cumulative review of these cases. In addition, the MAH should continue to closely monitor cardiovascular events leading to a fatal outcome and should specify any concomitant diseases.

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

6.1.47. Teriparatide – FORSTEO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Forsteo, a centrally authorised product containing teriparatide, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

[22] Update of SmPC sections 4.2, 4.3, 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

6.1.48. Trabectedin – YONDELIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Yondelis, a centrally authorised product containing trabectedin, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.49. Trastuzumab – HERCEPTIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Herceptin, a centrally authorised product containing trastuzumab, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

The next PSUR should be submitted to the EMA within 70 days of the data lock point set at 24 March 2013. Subsequent PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6.1.50. Vandetanib – CAPRELSA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Based on the assessment of the PSUR, the PRAC concluded that the benefit-risk balance of Caprelsa, a centrally authorised product containing vandetanib, remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. This procedure was finalised at the PRAC level without further plenary discussion as per agreed criteria.

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

6.1.51. Vinflunine – JAVLOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

Background

Vinflunine is a vinca alkaloid indicated as monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Javlor (vinflunine) in the approved indication(s) remains favourable.
- The product information should be updated to include syndrome of inappropriate antidiuretic hormone secretion (SIADH) with a frequency 'uncommon' and phlebitis with a frequency 'common' as undesirable effects. Therefore the current terms of the marketing authorisation should be varied[23].

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

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of post-authorisation safety studies

7.1.1. Aclidinium Bromide – BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

For background see PRAC minutes 26-29 November 2012. The MAH provided an amended protocol as per previous request of the PRAC.

[23] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Endorsement/refusal of the protocol

Having considered the updated protocol for Eklira/Bretaris Genuair (aclinidium bromide), in accordance with Article 107n of Directive 2001/83/EC, the PRAC considered that some clarification was still required concerning the study design and that an amended protocol should be submitted.

- Therefore, the PRAC recommended that the MAH should submit a revised PASS protocol within 30 days to reflect the additions recommended by the PRAC with regard to the study objectives and design. A standard 30-day assessment timetable will apply.

7.1.2. Aclidinium Bromide – BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

For background see PRAC minutes 29-31 October 2012. The MAH provided an amended protocol as per previous request of the PRAC.

Summary of advice

- The updated study protocol for the drug utilisation study was considered acceptable.

7.1.3. Catridecacog – NOVOTHIRTEEN (CAP)

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

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Novothirteen is a centrally authorised medicine containing catridecacog, an antihaemorrhagic agent indicated for long-term prophylactic treatment of bleeding in selected patients.

As part of the RMP for Novothirteen (catridecacog), the MAH for was required to conduct a PASS (as part of the RMP but outside the scope of Article 107n-q of Directive 2001/83/EC) in order to gather further information on the safety profile and effectiveness of recombinant factor XIII in routine clinical practice, notably regarding FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of efficacy. The PRAC provides advice to CHMP on protocols submitted by the MAH and assessed by the Rapporteur.

Summary of advice

- The study protocol for the PASS NN1841-3868: treatment of congenital FXIII deficiency, a prospective multi-centre observational study version (7) was considered acceptable.

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

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

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

Glycopyrronium bromide is a long-acting antimuscarinic agent (LAMA). Centrally authorised products containing glycopyrronium bromide are indicated for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

At the time of the centralised marketing authorisation of the glycopyrronium bromide-containing medicines, the CHMP requested that the MAH perform a PASS to assess the risk of cardiac and cerebrovascular events and of mortality in patients using Seebri Breezehaler (glycopyrronium bromide) compared to patients using LAMA or long acting β2 agonists (LABAs).

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 Seebri Breezehaler (glycopyrronium bromide) and associated names 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.

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

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

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

Glycopyrronium bromide is a, long-acting antimuscarinic agent (LAMA). Centrally authorised products containing glycopyrronium bromide are indicated for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

At the time of the centralised marketing authorisation of the glycopyrronium bromide-containing medicines, the CHMP requested that the MAH perform a drug utilisation study (as part of the RMP but outside the scope of Article 107n-q of Directive 2001/83/EC) to describe the characteristics of patients initiating treatment with glycopyrronium bromide and to determine the prevalence of off-label use and of other conditions described in the special warnings and precautions section of the product information. A protocol for such study (multinational, multi-database drug utilization study of inhaled NVA237 in Europe) was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for the drug utilisation study could be acceptable provided an updated protocol is submitted to address some points raised by the PRAC within 60 days.

7.1.6. Nomegestrol, estradiol – ZOELY (CAP)

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

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

In February 2013 the PRAC advised, in the framework of the assessment of the latest PSUR, that the PASS titled CELINA which will allow the risk of venous thromboembolism (VTE) and arterial thromboembolism (ATE) to be better characterised (see PRAC minutes 4-7 February 2013) should start as soon as possible. A study protocol had been assessed by the Rapporteur who raised some objections concerning the methodology and recruitment of patients. However the responses from the MAH were not considered satisfactory. The assessment of the latest protocol (updated version of 2 January 2013) was presented to the PRAC for further advice to the CHMP.

Summary of advice

The PRAC considered that as regards sample size and the definition of the primary analysis the Committee's concerns had been addressed. However, the PRAC concluded that the study did not satisfactorily address some outstanding methodological issues to achieve its aim of demonstrating non-inferiority of nomegestrol acetate-estradiol (NOMAC-E2) in comparison to levonorgestrel-containing combined oral contraceptives at the level of a hazard ratio of 1.5.

In particular, measures to limit the length of the recruitment period so that results can be obtained within an appropriate timeframe were still lacking.

The PRAC considered that a study with results delivered in 2015 was essential for the further characterisation of the venous- and arterial thrombotic risk of the product. The PRAC therefore advised that the CHMP impose an obligation for post-authorisation safety study for Zoely/IOA in accordance with Article 10a of the Regulation (EC) No 726/2004.

The PRAC advice was finalised in writing on 18 April 2013.

7.2. Results of post-authorisation safety studies

None

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

8.1.1. Agalsidase alfa – REPLAGAL (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Agalsidase alfa is human α-galactosidase A indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease.

Replagal, a centrally authorised product containing agalsidase alfa, was authorised under exceptional circumstances in 2001. The benefit-risk balance 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 Replagal could be finalised. Results of a specific obligation evaluating long-term safety in children are expected for submission to EMA in July 2013.

8.1.2. Antithrombin alfa – ATRYN (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Antithrombin alfa is an inhibitor of blood coagulation indicated for the prophylaxis of venous thromboembolism in surgery in adult patients with congenital antithrombin deficiency.

ATryn, a centrally authorised product containing antithrombin alfa, was authorised under exceptional circumstances in 2006. The benefit-risk balance 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 ATryn could only be finalised if satisfactory clarification is given on some pending issues.

8.1.3. Brinzolamide, timolol – AZARGA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Line Michan (DK)

Background

Brinzolamide and timolol in combination are used to decrease intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.

Azarga, a centrally authorised medicine containing brinzolamide/timolol, was authorised in 2008.

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

Summary of advice

Based on the review of the available pharmacovigilance data for Azarga (brinzolamide/timolol), and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could be finalised, pending some clarification relating to the risk of metabolic acidosis and the potential need to label it as an undesirable effect in the product information. Further PRAC advice will be provided as applicable.

8.1.4. Histamine dihydrochloride – CEPLENE (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Background

Histamine dihydrochloride is an immunotherapy used to induce immune-mediated destruction of residual myeloid leukaemic cells and is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2).

Ceplene, a centrally authorised medicine containing histamine dihydrochloride, was authorised in 2008.

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

Summary of advice

Based on the review of the available pharmacovigilance data for Ceplene (histamine dihydrochloride), and the CHMP Rapporteur's assessment report, the PRAC considered that this first five year renewal procedure could not be yet finalised. Clarification was still required with regard to the processing and assessment of biomarker and minimal residual disease (MRD) data collection, which may affect the benefit-risk balance and the risk management system currently in place. Consequently, the PRAC considered that the MAH should be requested to submit an updated RMP within this procedure. Further PRAC advice will be provided as applicable.

8.1.5. Sugammadex – BRIDION (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Background

Sugammadex is a modified gamma cyclodextrin used to reverse neuromuscular blockade induced by rocuronium or vecuronium under certain conditions.

Bridion, a centrally authorised medicine containing sugammadex, was authorised in 2008.

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

Summary of advice

Based on the review of the available pharmacovigilance data for Bridion (sugammadex), and the CHMP Rapporteur's assessment report, the PRAC concluded that no relevant safety concerns had arisen from the assessment of this first five renewal procedure. The RMP should be updated in line with the current PRAC advice to include bronchospasm and pulmonary obstructive events, at the time of the next regulatory procedure to be submitted to the EMA.

8.1.6. Tafamidis – VYNDAQEL (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

Background

Tafamidis is a specific stabiliser of transthyretin indicated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.

Vyndaqel, a centrally authorised product containing tafamidis, was authorised under exceptional circumstances in 2011. 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 this first annual re-assessment procedure for Vyndaqel could only be finalised if satisfactory clarification is given on some pending issues. These include further details relating to a registry safety database.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. On-going or concluded pharmacovigilance inspection

None

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

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

10.1.1. Pazopanib – VOTRIENT (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

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

Pazopanib is with a risk of drug-induced hepatotoxicity. Analysis of serum liver test results is therefore necessary before initiation of treatment with Votrient, a centrally authorised medicine containing pazopanib. This should be repeated at least once every 4 weeks for at least the first 4 months of the treatment, and as clinically indicated. Periodic monitoring should then continue after this time period.

Data from a recently concluded phase III study of pazopanib versus sunitinib (VEG108844) in advanced RCC in conjunction with data from the pivotal advanced RCC trial (VEG105192) have suggested the need for earlier and more frequent serum liver function tests during the first 9 weeks of pazopanib therapy.

The CHMP is currently considering whether a different scheme would be more appropriate and whether, based on the present data, more intensive liver monitoring would be justified. A list of outstanding issues to be addressed by the MAH was presented for advice by the PRAC as well as a proposal for a DHPC.

Summary of advice

The PRAC agreed that more intensive liver monitoring is needed based on the present data and therefore supports the proposed amendment of the product information for Votrient (pazopanib).

The PRAC suggested that it might be useful to assess the feasibility of implementing the proposed intensive monitoring schedule and whether or not it is compatible with routine consultations.

The PRAC expressed concerns over whether a DHPC is a sufficient risk minimisation tool given the observed existing compliance issues with current recommendations on liver monitoring. The MAH should be requested to discuss the clinical relevance of the observed increased liver enzymes and

consequently to propose additional measures that will improve the relatively poor compliance. Once responses are received, further comments will be consolidated in the proposed DHPC.

10.1.2. Tolvaptan – SAMSCA (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

For background see PRAC minutes 4-7 February 2013.

A signal of hepatotoxicity in clinical trials in a non-approved indication was discussed at the February PRAC meeting. As a result of the discussion PRAC felt that whilst there was insufficient evidence at that time to draw any firm conclusions about the hepatotoxic potential of tolvaptan when used in accordance with its authorised EU indications and posology, an increase in risk could not be excluded and further information was urgently required.

As requested, the MAH submitted a cumulative review of the signal in the framework of a 30 day type II variation to update product information and a proposal for a DHPC and communication plan, which were assessed by the Rapporteur. The PRAC was requested to provide advice to the CHMP on this variation.

Summary of advice

The PRAC reviewed the information provided by the MAH and the assessment of the Rapporteur. The PRAC considered that the variation to the marketing authorisation could be acceptable subject to proposed wording changes and additions in the product information. The MAH should provide further clarification on the cases of hepatotoxicity described, before finalisation of the procedure at CHMP level.

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

None

10.3. Other requests

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

- PRAC consultation on risk of tumour growth progression and thromboembolic events in cancer patients, upon CHMP's request

Regulatory details:

PRAC Rapporteur (overall): Isabelle Robine (FR)
PRAC Co-Rapporteur (overall): Martin Huber (DE)

Background

Erythropoetins (epoetin alfa, beta, zeta, theta, darbepoetin alfa) are used in the treatment of anaemia in patients with cancer and other conditions.

In patients with cancer, treatment with an erythropoiesis-stimulating agent (ESA) could influence the tumour growth either directly or through increased availability of oxygen due to the pharmacodynamic effects of epoetins. This may lead to a shortened time to tumour progression, shortened overall survival, and, in certain cases, increased mortality.

The PhVWP and the CHMP had discussed the issue in the past and a review was concluded in 2007/8 (see public statement Doc. Ref. EMEA/496188/2007 and Doc. Ref. EMEA/CHMP/333963/2008 –corr.*).

More recently, in 2011, following availability of new data (including a Cochrane meta-analysis referring to results from 53 randomised clinical trials reviewed by CHMP/PhVWP[24]), the PhVWP recommended an amendment to the RMPs for epoetins requiring a systematic investigation of the overall survival and the risk of tumour progression associated with the use of epoetins in cancer anaemia indications. The concerned MAHs were required to conduct double-blind placebo controlled studies or carefully designed observational cohort studies.

The EMA had suggested that the safety topic: 'Epoetins: Risk of tumour growth progression and thromboembolic events in cancer patients and cardiovascular and cancer risk in chronic kidney disease' be included in the 5th call of the European Union Seventh Framework Programme for Research and Technological Development. The EpoCan consortium coordinated by Tel Aviv University had been chosen to conduct a study on epoetins and the risk of thromboembolic events and tumour growth progression in cancer patients, and cardiovascular and cancer risk in chronic kidney disease.

In March 2013, the CHMP considered that the risk of tumour growth progression in cancer patients had not been clarified to a satisfactory level and requested a further follow-up.

Therefore PRAC advice was requested by the CHMP on a list of questions to all MAHs involved on the risk of tumour progression and increased mortality in cancer patients treated with erythropoiesis-stimulating agents.

Summary of advice

The PRAC discussed a list of questions for the MAHs. The questions concern a summary of pharmacovigilance measures implemented in the RMP to address the potential risk of tumour progression, including details of implementation dates, status, milestones and due dates and a review of all available relevant data, including published or unpublished data from independent or MAH-sponsored studies, regarding ESAs effects on tumour initiation, growth, progression, invasion and angiogenesis in animal models, and the respective mechanisms of action.

The MAHs should discuss whether any changes in the ESAs prescription patterns for cancer indications were observed after changes to the product information were introduced in 2008. Moreover a review of current recommendations/guidelines of use of ESAs in cancer indication in EU is needed.

The MAHs should submit a reply to the list of questions by May 2013, leading to further PRAC advice in June/July 2013.

[24] Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, Zwahlen M, Clarke MJ, Weingart O, Kluge S, Piper M, Napoli M, Rades D, Steensma D, Djulbegovic B, Fey MF, Ray-Coquard I, Moebus V, Thomas G, Untch M, Schumacher M, Egger M, Erythropoietin or Darbepoetin for patients with cancer--meta-analysis based on individual patient data; Engert ACochrane Database Syst Rev. 2009 Jul 8;(3):CD007303. doi: 10.1002/14651858.CD007303.pub2.

In the framework of the discussion the PRAC heard an update of the EpoCan consortium describing the general objectives of the project as well as the mechanistic models it intends to use in its assessment. The final study report will be available at the end of September 2014.

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Ondansetron (NAP)

- Risk of QT prolongation and Torsade de Pointes

Regulatory details:

Lead member: Julie Williams (UK)

Background

For background see PRAC minutes 29-31 October 2013.

As discussed in October 2012 the MAH submitted, in the framework of an ongoing national type II variation, additional information taking into account some points raised by the PRAC and proposed an updated wording for the product information as well as an updated RMP. The advice of the PRAC was requested on the assessment of the variation provided by the Rapporteur.

Summary of advice

The PRAC noted the additional information provided with regard to the QT study and subsequent modelling. Whilst this was considered generally reassuring, it was noted that the study was conducted in healthy subjects at low risk of QT prolongation compared to the ondansetron patient population. Patients taking ondansetron would generally have concomitant medication, electrolyte disturbances and underlying conditions.

Taking into account, the currently authorised posology in some Member States, the PRAC made a number of recommendations to amend to the posology in adult patients, including the elderly. The MAH should be asked to update the product information accordingly and the revised product information, along with a draft Direct Healthcare Professional Communication and communication plan, should be submitted by the MAH within 15 days to the reference MS (UK).

The PRAC noted that in the absence of appropriate pharmacokinetic modelling data for repeated intravenous doses, it is not possible to conclude whether any changes to the current authorised paediatric posology are necessary. The PRAC agreed that the MAH should provide these data or a suitable justification why this is not possible.

In conclusion, the MAH is asked to submit updated product information to the reference MS (UK) with this variation in order that harmonised wording can be agreed. This should reflect the updated recommendations for repeat dosing following an initial dose of 16 mg in adult patients and proposals for elderly and paediatric patients. The RMP was considered acceptable; however, some outstanding points need to be addressed and the MAH should submit an updated RMP to address these points. Further PRAC advice will be provided upon request of the MSs.

11.2. Renewals of the Marketing Authorisation

None

11.3. Other requests

11.3.1. Dexamphetamine (NAP)

- Risk Management Plan

Regulatory details:

Lead member: Julie Williams (UK)

Background

Dexamphetamine is an amphetamine derivative and dexamphetamine-containing medicines are currently authorised in some EU Member States for the treatment of narcolepsy and/or attention deficit hyperactivity disorders (ADHD).

A marketing authorisation application for a dexamphetamine-containing medicine has been submitted under Article 10a ('well-established use') of Directive 2001/83/EC using the decentralised procedure with the UK as Reference Member State.

In line with the requirements for other medicines used in the treatment of ADHD, use of dexamfetamine for the treatment of children with ADHD must be initiated by a specialist in childhood and adolescent behavioural disorders.

The important risks associated with the use of dexamfetamine are those common to other stimulant medicines used in the treatment of ADHD.

The UK requested the advice of the PRAC on the proposed RMP in the framework of the ongoing application procedure - and on whether the RMP adequately reflects the key important identified and potential risks involved. The proposed RMP for dexamfetamine is considered to be generally in line with RMPs for compounds used in similar indications.

The PRAC agreed that more refinements are needed on the areas of safety concern of the RMP and that a list of outstanding issues should be addressed to the MAH including consideration of the need for a PASS to further analyse the safety of dexamphetamine specifically targeting assessment of cardiovascular events, growth relating to sexual maturation and psychiatric disorders. Therefore follow-up discussion will take place at the May 2013 meeting.

The PRAC appointed Julie Williams as Rapporteur for follow-up on this issue.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Pharmacovigilance audits and inspections

None

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

12.3.1. Union Reference Date List

- Consultation on the draft List, version April 2013

This topic was discussed at the organisational matters teleconference of the PRAC on 24th of April 2013. The EURD list entered into force on 1st April 2013 and PSURs should be submitted in line with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

The EU single assessment of PSURs for substances or combinations of substances contained in both centrally and nationally authorised medicinal products (CAPs and NAPs) also starts in line with the DLPs specified in the list (see relevant EMA News Item). This new procedure has implications for the PSUR submission scheme, as MAHs of NAPs concerned are requested to submit their PSURs to the EMA and the National Competent Authorities of the Member States in which the medicinal products have been authorised, and to the PRAC Rapporteur appointed for the procedure, since the concerned NAPs may not all be authorised in the Rapporteur's country.

The EMA presented a proposal for PRAC Rapporteur appointment process for EU single assessment of PSURs for substances or combination of substances contained in both CAPs and NAPs, based on the PRAC Rapporteur country of the first CAP authorised in the EU. The PRAC endorsed the proposal. An amended EURD list reflecting the Rapporteurship will be discussed at the May 2013 PRAC meeting.

12.4. Signal Management

12.4.1. Signal Management

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

This topic was discussed at the organisational matters teleconference of the PRAC on the 24th of April 2013. EMA reported back on the progress made by the group on a proposal for implementing necessary updates of product information arising from the assessment of signals and best practice for exchanging information with the CMDh in order to facilitate harmonised implementation across the EU.

12.4.2. PRAC recommendation leading to changes to the product information

- Draft proposal on coordination of the implementation for nationally authorised products

This topic was discussed at the organisational matters teleconference of the PRAC on the 24th of April 2013. See also above 12.4.1. The PRAC discussed a preliminary proposal on the necessary updates of product information arising from the assessment of signals and on coordination of the implementation for nationally authorised products. The PRAC will further discuss the issue at the May 2013 in parallel with the CMDh proposal.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. List of Products under Additional Monitoring

- Update on creation and maintenance of the List

EMA presented the list of products under additional monitoring to be published on the EMA website. The list includes all the products under the mandatory scope and will be updated monthly according to regulatory requirements.

Post-meeting note: the list was published on the EMA website on 25 April 2013. Home>Regulatory>Human medicines>Pharmacovigilance>List of medicines under additional monitoring.

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of Risk Minimisation

Risk Management Systems

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

- Progress report of the activity

For background, please see PRAC minutes 4-7 March meeting. This topic was deferred to the June 2013 meeting.

12.7.2. Timetables for RMP assessment

- Proposed revised timetables for RMP assessment in pre-authorisation phase

The PRAC endorsed a slightly revised timetable for the assessment of the RMPs of medicines in the pre-authorisation phase (2nd and 3rd phase). Some members expressed doubts on the effectiveness of this revision in facilitating the information flow and exchange of information between the two Committees. The PRAC recommended that this should be taken into consideration in the review of the process for the assessment of the RMPs. The EMA will propose an implementation plan by May 2013.

12.7.3. Templates for RMP assessment

- Proposed revised templates for RMP assessment

Following implementation of comments provided on the RMP templates at the PRAC April 2013 meeting the Committee adopted the revised templates to be published on the EMA website.

12.8. Post-authorisation Safety Studies

None

12.9. Community Procedures

None

12.10. Risk communication and Transparency

None

12.11. Continuous pharmacovigilance

None

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Pharmacogenomics Working Party

- Draft guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products

An outline of the draft guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products prepared by the Pharmacogenomic Working Party in co-operation with PRAC, was presented. The guideline is now ready for publication on the EMA website for comments, pending adoption at the CHMP in June 2013. The PRAC praised the scientific contribution from Qun-Ying Yue (SE), leading the editorial board, and of Jean-Michel Dogné (BE) in achieving excellent progress. Further discussion will be planned in 1Q 2014 following the public consultation.

12.13. Interaction within the EU regulatory network

None

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

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

- Proposal for an EMA funded study on the use of metformin in renal impaired patients and the risk of lactic acidosis

EMA proposed an invitation to tender for an ENCePP study looking at the use of metformin in renal-impaired patients in the context of current regulatory guidance and clinical practice. This would be in line with previous similar EMA funded drug safety studies (see EMA/2012/08/CN). EMA had circulated draft technical specifications and supportive comments were received. The EMA also proposed to circulate the study deliverables (protocol and preliminary and final study reports) to the lead Member State for the active substance (FR) for their input into the assessment of these deliverables. The PRAC agreed with the proposal to conduct a study and as a result, the EMA will finalise the procurement process and launch the invitation to tender.

13. Any other business

None

ANNEX I – List of abbreviations

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

www.ema.europa.eu

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

ANNEX II – List of participants: including any restrictions with respect to involvement of members / alternates / experts following evaluation of Declared interests for the 8-11 April 2013 meeting

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance
Bettina Schade	Austria	Full involvement	
Jean-Michel Dogne	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	cyproterone, ethinylestradiol, fluoroquinolones, vardenafil, iloprost, rivaroxaban
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Jana Mlada	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Terhi Lehtinen	Finland	Cannot act as Rapporteur or Peer-reviewer for:	Fluticasone furoate, vilanterol
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
George Aislaitner	Greece	Full involvement	
Julia Pallos	Hungary	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjorg Buajordet	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimaraes	Portugal	Full involvement	
Daniela Pomponiu	Romania	Full involvement	
Anna Marekova	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Julia Dunne	United Kingdom	Full involvement	
June Munro Raine	United Kingdom	Full involvement	

PRAC member PRAC alternate	*Country*	*Outcome restriction following evaluation of e-DoI for the meeting*	*Topics on the current Committee Agenda for which restriction applies* *Product / substance*
Julie Williams	United kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting:**	**Topics on the current Committee Agenda for which restriction applies** ***Product / substance***
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise (Marieke) De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer-reviewer for:	pandemic influenza vaccine, dabrafenib, fluticasone furoate, vilanterol, retigabine, belimumab, eltrombopag, hepatitis a and hepatitis b vaccine, pazopanib
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Full involvement	
Lennart Waldenlind		Full involvement	

Additional European experts participating at the meeting for specific Agenda items	Country	
Cedric Gigot	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Bruno De Schuiteneer	Belgium	
Veerle Verlinden	Belgium	
Arnaud Batz	France	
Benjamin Burrus	France	
Sara Miranda	France	
Bich-Hang Pham	France	
Valerie Strassman	Germany	
Anna-Marie Coleman	Ireland	
Anouk Neuteboom	Netherlands	
Lies van Vlijmen	Netherlands	
Gloria Martín-Serrano	Spain	
Johan Aulin	Sweden	
Charlotte Backman	Sweden	
Kristina Dunder	Sweden	
Nils Feltelius	Sweden	
Bengt Ljungberg	Sweden	
Hans Sjögren	Sweden	
Ingemar Persson	Sweden	
Elina Rönnemaa	Sweden	
Lars Stahle	Sweden	
Tomas Salmonson	Sweden	
Claire Davies	United Kingdom	
Kathryn Ord	United Kingdom	
Angelika Siapkara	United Kingdom	
Karen Slevin	United Kingdom	
Jane Woolley	United Kingdom	

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

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

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