4 December 2013
EMA/PRAC/729184/2013
Pharmacovigilance Risk Assessment Committee (PRAC)

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Minutes of the meeting on 4-7 November 2013

Chair: June Raine – Vice-Chair: Almath Spooner

Explanatory notes

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

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

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

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

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

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

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

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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.

Table of contents

1. Introduction

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

The Chairperson opened the meeting, welcoming all participants to the 4-7 November 2013 meeting of the PRAC.

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

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

The PRAC welcomed Verlinde Veerle as the new alternate for BE.

1.2. Adoption of agenda of the meeting on 4-7 November 2013

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

1.3. Adoption of minutes of the previous PRAC meeting on 7-10 October 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 7-10 October 2013 EMA/PRAC/708968/2013 were published on the EMA website on 15 November 2013.

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

None

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

3.1. Newly triggered Procedures

None

3.2. Ongoing Procedures

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

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

Regulatory details:

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

Background

A referral procedure under Article 31 is ongoing for medicines containing agents acting on the renin-angiotensin system (see PRAC minutes 13-16 May 2013). The (Co)Rapporteurs for each substance prepared preliminary assessment reports according to agreed timelines. Moreover an overall assessment report was prepared by the lead PRAC Rapporteur.

Summary of recommendation(s)/conclusions

The PRAC discussed the main conclusion of the assessment and agreed on a proposal for updating the product information as part of a list of outstanding issues to be addressed by the MAHs. Moreover the PRAC agreed that further expert advice was needed on the interpretation of the findings and supported the organisation of a scientific advisory group (SAG) meeting. The PRAC agreed on the expertise required and agreed a list of questions to be addressed by the SAG in the framework of the current proc[1]edure. Members were invited to propose candidates from the Member States. EMA clarified that the current provisions in terms of the handling of conflicts of interest will be applied.

The PRAC also considered that there would be value in posing some questions to the investigators of the 'Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy' (VA NEPHRON-D) study. The PRAC therefore addressed a letter to the the Veterans Affairs Pittsburgh Healthcare System and Department of Medicine. A revised timetable for the procedure was agreed EMA/PRAC/290691/2013 rev1.

3.3. Procedures for finalisation

3.3.1. **Acipimox** (NAP)

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

Regulatory details:

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

[1] *V Strassmann took over the Rapporteurship for the concerned products for DE instead of M Huber

Background

A referral procedure under Article 31 of Directive 2001/83/EC for acipimox-containing medicines (see minutes of the PRAC 7-10 September 2013 meeting) is to be finalised. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the available data from the HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) study and from studies with acipimox and evidence from the literature, as well as spontaneous reports and advice from the ad-hoc expert group. The PRAC considered that acipimox continues to have a role in reducing triglyceride levels in patients with hypertriglyceridaemia (Fredrickson type IV hyperlipoproteinaemia) and with hypercholesterolaemia and hypertriglyceridaemia (Fredrickson type IIb hyperlipoproteinaemia) but only as a second- or third-line agent in patients who have not responded adequately to other treatments such as a statin or fibrate treatment. Therefore the PRAC agreed that the product information for acipimox-containing medicinal products should be updated.

Summary of recommendation(s) / conclusions

The PRAC adopted, by majority vote, a recommendation to amend the marketing authorisations for acipimox-containing medicines. This recommendation is to be considered by CMDh – see "PRAC recommends using acipimox only as additional or alternative treatment to lower high triglyceride levels" EMA/618574/2013.

Thirty members/alternates, out of the 31 eligible to vote who were present in the room, voted in favour of the variation together with Iceland and Norway, while one member had divergent views[2] (see Appendix to PRAC assessment report on medicinal products containing acipimox[3]).

3.3.2. **Diacerein** (NAP)

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

Regulatory details:

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for diacerein-containing medicines (see PRAC minutes of the PRAC 8-11 July 2013 meeting for background) is to be finalised. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the evidence on the known risks of severe diarrhoea and hepatotoxicity with diacerein in the context of its therapeutic effects in the clinical management of osteoarthritis. It considered that the available data from pre-clinical studies, clinical trials, post-marketing spontaneous case reports and the published literature showed that the use of diacerein-containing products is associated with frequent cases of severe diarrhoea and cases of potentially serious hepatotoxicity. Furthermore, the available data showed only limited clinical efficacy. The PRAC also considered that

[2] Isabelle Robine (FR)
[3] See www.ema.europa.eu Home>Find medicine>Human medicines>Referrals - Publication pending at XX Month 2013

the available data did not provide any reassurance that measures to reduce the risk of severe diarrhoea and hepatic reactions would be effective and concluded that the risk of severe reactions associated with the use of diacerein-containing medicinal products outweighed its limited clinical benefits in the approved indications.

Summary of recommendation(s)/conclusions

The PRAC adopted, by majority, a recommendation to suspend the marketing authorisations for diacerein-containing medicines to be considered by CMDh – see "PRAC recommends suspension of diacerein-containing medicines" EMA/679264/2013. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

Twenty-five members/alternates, out of the 32 eligible to vote who were present in the room, voted in favour of the suspension together with Iceland and Norway, while seven members/alternates had divergent views[4].

Post-meeting note: after the meeting, the EMA was notified by the MAHs of their intention to request a re-examination of the PRAC recommendation. Follow up discussion on this request will take place at the December 2013 PRAC meeting.

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

None

4. Signals assessment and prioritisation[5]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Adalimumab - HUMIRA (CAP)

- Signal of possible missed dose due to malfunction of the pre-filled pen device

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 exposure for Humira, a centrally authorised medicine containing adalimumab, is estimated to have been up to 35,000 patient-years worldwide, in the period from 2012 to 2013.
A signal of malfunction of the pre-filled pen device potentially leading to inappropriate dose delivery was identified by the UK medicines agency (MHRA), based on 11 cases reported in the United

[4] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded.
[5] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required.

Kingdom. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the cases of malfunctioning reported, and agreed that further information on the signal should be gathered in a timely fashion, with a full analysis of all the cases and their follow-up as well as further analysis of the root cause. Members highlighted that it was also necessary to understand whether the cases reported were linked to a previously marketed version of the device, since a new device was approved in late 2012. The PRAC noted that patients may self-inject the medicine only after training in injection technique, if their physician determines that is appropriate, and with medical follow-up as necessary. However, the PRAC agreed that the review should also consider whether any risk due to malfunctioning of the device could be minimised with improved product information.

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should submit to the EMA, within 60 days, a cumulative analysis of malfunction reports.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. **Bupropion** (NAP)

- Signal of pancytopenia

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background

Bupropion is an antidepressant used in the treatment of various conditions.

Until 2010 the cumulative exposure for Zyban, a nationally authorised medicine containing bupropion, has been estimated to have been more than 92 million patients worldwide.
During routine signal detection activities, a signal of pancytopenia was identified by the Netherlands, based on 14 cases retrieved from EudraVigilance. The Netherlands as lead MS for signal detection activities for bupropion confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available information on the cases of pancytopenia reported and commented that, although the absolute number of cases was small in the context of the large population exposure, drug-induced pancytopenia is generally a condition with a very low background incidence[6].

It was emphasised how some cases were confounded by medical history of lymphoma or other malignancies or by use of other medications known to induce blood dyscrasias. However, overall the PRAC agreed that the information available on the cases merited further investigation.

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

[6] Kaufman DW, Kelly JP, Jurgelon JM, Anderson T, Issaragrisil S, Wiholm BE, Young NS, Leaverton P, Levy M, Shapiro S.Eur Drugs in the aetiology of agranulocytosis and aplastic anaemia. J Haematol Suppl. 1996;60:23-30.

Summary of recommendation(s)

- The MAHs for the innovator products for bupropion should submit to the Rapporteur, within 60 days, a cumulative review of the cases of pancytopenia.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

- Signal of angioedema

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Background

Glycopyrronium bromide is muscarinic receptor antagonist (anticholinergic) used as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The exposure for centrally authorised medicines containing glycopyrronium bromide is estimated to have been more than 15,000 patient-years worldwide, in the period from first authorisation in 2012 to 2013 .
During routine signal detection activities, a signal of angioedema was identified by the EMA, based on 14 cases, retrieved from EudraVigilance, of angioedema and related terms. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the cases of angioedema reported and agreed that they displayed a common pattern, typical of hypersensitivity reactions. Furthermore, in these cases, a occurred with a plausible temporal association between angioedema and treatment with glycopyrronium bromide was apparent. The patients recovered or improved following drug discontinuation, or in some instances, following corticosteroid/antihistamine treatment. In light of the information reviewed, and of the seriousness and potentially life-threatening nature of the reaction, the PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

- The MAH for the above mentioned glycopyrronium bromide-containing medicines should submit to the EMA a cumulative review of the cases of angioedema within the next PSUR (DLP 28 September 2013).

4.1.4. **Goserelin** (NAP)

- Signal of flushing and hyperhidrosis with prolonged duration

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

Background

Goserelin is a synthetic analogue of naturally occurring luteinizing-hormone-releasing hormone (LHRH) used in the treatment of prostate cancer, breast cancer and endometriosis.

During routine signal detection activities, a signal of flushing and hyperhidrosis of prolonged duration was identified by UK, based on 61 cases of flushing, hot flush, hyperhidrosis (increased sweating) and night sweats reported in the UK. The UK as reference member state (RMS) for a nationally authorised product containing goserelin confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the cases of flushing and hyperhidrosis reported and noted that, although these reactions are well recognised in the product information, in some of the cases reported the reactions seemed to be of a more prolonged nature than would normally be expected based on the way the medicine is metabolised.

The PRAC noted that the MAH had replied to a previous request for information by the UK. In this reply, the MAH had concluded that, for those cases where the duration of the adverse reaction extended beyond the expected duration of the medicine's pharmacological effect, there was either minimal information available or the cases could be explained by the patient's age or comorbidities or by the concomitant treatment. Whilst the limited number of cases and potential confounding was acknowledged, the PRAC considered that before a decision could be reached on whether any further updates to the product information would be necessary, further information should be sought

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

Summary of recommendation(s)

- The MAH for Zoladex (goserelin) should submit to the Rapporteur, within 60 days, further detailed information as requested by the PRAC.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.5. Leflunomide - ARAVA (CAP)

- Signal of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background

Leflunomide is an immunosuppressant used in the treatment of active rheumatoid arthritis as a 'disease-modifying antirheumatic drug' (DMARD) and also used in active psoriatic arthritis.

The exposure for Arava, a centrally authorised medicine containing leflunomide, is estimated to have been more than 2 million patient-years worldwide, in the period from first authorisation in 2005 to 2012.

During routine signal detection activities, a signal of drug reaction with eosinophilia and systemic symptoms (DRESS) was identified by the EMA, based on 14 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the reported cases of suspected DRESS reported and acknowledged that some of them, including the cases described in the literature, had a consistent temporal association with leflunomide treatment.

The PRAC noted the classification criteria for the reaction as proposed by the RegiSCAR consortium and a recent publication by Kardaun et al[7] on DRESS. The PRAC concurred that, as reported in the literature, cases of DRESS might not have been reported as such since its symptoms mimic those of several other pathologies and they can appear a long time after initial drug exposure.

The PRAC noted that effects on the skin by leflunomide had been seen in animal studies, and in clinical trials too, with 33% of the adverse events reported concerningthe skin and subcutaneous tissue. Consistently with these findings, serious skin and subcutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have been reported since the launch of Arava (leflunomide). This is why in 1999 the former Committee for Proprietary Medicinal Products (CPMP) issued a public statement on these serious skin and subcutaneous reactions with leflunomide. Based on the information reviewed the PRAC agreed that a causal association between leflunomide and DRESS could not be ruled out and that the product information should be updated regarding the cases of DRESS and possible risk minimisation measures.

Summary of recommendation(s)

- The MAH for Arava (leflunomide) should submit to the EMA, within 60 days, a variation to update the product information with regard to DRESS.
- The MAHs of generic products containing leflunomide should update their product information in line with that of the reference product.

For the full PRAC recommendation see EMA/PRAC/693228/2013 published on the EMA website.

4.1.6. Teriparatide - **FORSTEO** (CAP)

- Signal of anaphylactic shock

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Teriparatide is a fragment of endogenous human parathyroid hormone used in the treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture and in the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

The exposure for Forsteo, a centrally authorised medicine containing teriparatide, is estimated to have been more than 1 million patients worldwide, in the period since first authorisation in 2003 to 2013. During routine signal detection activities, a signal of anaphylactic shock was identified by the EMA,

[7] Kardaun, S.H., Sekula, P., Valeyrie-Allanore, L., Liss, Y., Chu, C.Y., Creamer, D., Sidoroff, A., Naldi, L., Mockenhaupt, M., Roujeau, J.C. and the RegiSCAR study group (2013), Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. British Journal of Dermatology, 169: 1071–1080. doi: 10.1111/bjd.12501

based on 10 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the cases of anaphylactic shock reported and noted that, as well as the 10 above mentioned cases, 13 cases of anaphylactic/anaphylactoid reaction were also identified in EudraVigilance. Allergic events happening soon after injection (acute dyspnoea, oro/facial oedema, generalised urticaria, chest pain, oedema (mainly peripheral)) were reported with teriparatide and were already included in the product information; however, anaphylaxis is not currently described. Based on these considerations and on the fact that a strong temporal association was suggested in a number of cases the PRAC agreed that the product information of teriparatide should be updated to add anaphylaxis as a potential adverse event.

Summary of recommendation(s)

- The MAH for Forsteo (teriparatide) should submit to the EMA, within 60 days, a variation to amend the product information regarding anaphylaxis. Additionally, the MAH should include anaphylaxis in the RMP as an identified risk within 90 days.

For the full PRAC recommendation see EMA/PRAC/693228/2013 published on the EMA website.

4.2. New signals detected from other sources

4.2.1. **Paracetamol** (NAP)

- Signal of drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP)

Regulatory details:
PRAC Rapporteur: Veerle Verlinden (BE)

Background

Paracetamol is an analgesic and antipyretic agent and one of the most widely used non-prescription medicines for the control of pain and fever.

A signal of serious skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) was identified by the Belgian Medicines Agency following an FDA Drug Safety Communication 'FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen' which triggered a review of the issue by BE and a further search in EudraVigilance. BE confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the cases reported in the light of the extensive worldwide exposure for paracetamol, as well as possible biases that might have occurred in reporting, and the strength of the evidence available in published data. A more detailed and comprehensive analysis of all the cases was deemed necessary to draw any firm conclusion on causality and PRAC recommended gathering data from registries of severe cutaneous reactions.

The PRAC appointed Veerle Verlinden (BE) as Rapporteur for the signal.

Summary of recommendation(s)

- The Rapporteur should perform a further assessment of the available data within 60 days including a literature review, an assessment of available epidemiological studies and of the data from registries of severe cutaneous reactions (i.e. RegiSCAR).
- Further PRAC recommendations will be provided once the review is concluded.

4.2.2. Calcium channel blockers (CAP, NAP):
Aliskiren, amlodipine - RASILAMLO (CAP)
Amlodipine, valsartan - **COPALIA,** (CAP), **DAFIRO** (CAP), **EXFORGE** (CAP), **IMPRIDA** (CAP)
Amlopdine, valsartan, hydrochlorothiazide - **COPALIA HCT** (CAP), **DAFIRO HCT** (CAP), **EXFORGE HCT** (CAP);
Telmisartan, amlodipine - ONDUARP (CAP), **TWYNSTA** (CAP)

- Signal of calcium-channel blockers and breast cancer risk

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

Background

Calcium channel blockers (CCBs) are a widely used class of medicines for the treatment of hypertension, angina pectoris and cardiac rhythm disorders.

A signal of breast cancer, triggered by a publication in Journal of the American Medical Association[8] reporting that current use of calcium-channel blockers for 10 or more years was associated with higher risks of ductal breast cancer (odds ratio [OR], 2.4; 95% CI, 1.2-4.9) (P= .04 for trend) and lobular breast cancer (OR, 2.6; 95% CI, 1.3-5.3) (P= .01 for trend) was identified by Sweden for initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed a preliminary review of the study by Daling et al. and discussed its main strengths and limitations including possible sources of biases - such as reporting, selection and information bias - and how they were addressed in the publication. Overall the PRAC considered that the evidence constituted a weak signal. However, the PRAC agreed that, to confirm or refute the reported relationship, the possibility of using prospectively gathered data by conducting a registry study on CCBs, other antihypertensive drugs and breast cancer may be of interest. Such a study could be performed using existing registries including long term exposure data within Europe and should preferably contain information on long-term use of CCBs.

The PRAC noted that the Swedish National Board for Health and Welfare (Socialstyrelsen) had initiated a case-control study on CCBs and breast cancer by using data in existing Swedish registries. No increased crude risk of breast cancer with up to 4.5 years of use of CCBs was observed in this prospective analysis based on preliminary results. Final study results are awaited during the first quarter of 2014.

The PRAC also noted that a series of observational studies are being conducted within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Work Package 2 and Working Group 1. The PRAC agreed that it would be important to

[8] Daling JR, Tang MT, Haugen KL, Porter PL, Malone KE. Use of Antihypertensive Medications and Breast Cancer Risk Among Women Aged 55 to 74 Years. JAMA Intern Med. 2013 Aug 5. doi: 10.1001/jamainternmed.2013.9071

consider the protocol and results of these studies and propose any additional analysis as appropriate. Therefore the EMA secretariat will facilitate the interaction with PROTECT.

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

Summary of recommendation(s)

- The PRAC noted the possible submission of the results from the case control study undertaken by the Swedish National Board for Health and Welfare within 4-6 months. The PRAC Rapporteur and the Swedish Medical Product Agency will take forward this request.
- The PRAC will consider the protocol and results of the studies being carried out within the framework PROTECT and propose any additional analysis as appropriate. EMA secretariat will support such interaction and the PRAC Rapporteur will assess the results of these studies within a 60 day timetable once available.

4.3. Signals follow-up and prioritisation

4.3.1. **Bevacizumab - AVASTIN** (CAP)

- Signal of anaphylactic shock

Status*: for discussion*

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

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

The MAH submitted a response to the request for submission of a variation and further information on the signal of anaphylactic shock with bevacizumab which was assessed by the Rapporteur.

Discussion

The PRAC noted that the MAH had submitted a detailed analysis of clinical trial data from their integrated clinical study database which did not identify an imbalance in the incidence of anaphylactic reactions between patients who received bevacizumab and patients included in the comparator chemotherapy control arm. Moreover, the analysis of data from the MAH safety database and EudraVigilance demonstrated that anaphylactic reactions had been reported in many cases with potential confounding or risk factors. Therefore, it was considered that the information on anaphylactic reactions was covered appropriately in the current product information, and the submission of a variation was no longer necessary.

Regarding the request for information on the development of an assay aiming at diagnosing anaphylaxis due to IgE hypersensitivity, and possible recommendations for prophylactic medication, given the low incidence rate of hypersensitivity and anaphylaxis with bevacizumab shown in the analyses and the uncertain benefit of premedication, the PRAC agreed that there was no need for new or additional recommendations in the product information for prophylactic treatment and that the development of a bevacizumab-specific IgE antibody assay was not warranted.

Summary of recommendation(s)

- Overall, the evidence provided by the MAH from randomised clinical trials, epidemiological studies, the MAH's safety databases and EudraVigilance indicated that the risk of anaphylactic reactions with bevacizumab is in line with the current product information and no new safety concerns have been identified; therefore no further regulatory action is recommended at this point in time.
- However, the MAH should continue to monitor any hypersensitivity reactions that might be reported with bevacizumab.

For the full PRAC recommendation see EMA/PRAC/693228/2013 published on the EMA website.

4.3.2. **Simvastatin** (NAP)

- Signal of risk of myopathy and rhabdomyolysis associated with high doses – follow-up to previous PhVWP review

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

In 2012 the PhVWP reviewed the risk of myopathy and rhabdomyolysis associated with high doses of statins - in particular simvastatin - following an initial signal triggered by the publication of the 'Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine' (SEARCH) trial[9]. The innovator MAH was requested to further investigate the data associated with high-dose simvastatin therapy. The UK as RMS for a nationally authorised simvastatin product prepared an assessment of the responses received by the MAH for analysis by the PRAC, complemented by drug utilisation data for primary and secondary cardiovascular event prevention, between 2007-2011, generated from the Clinical Practice Research Datalink (CPRD).

Discussion

The PRAC discussed the conclusions of the UK assessment and agreed that in terms of safety 80 mg simvastatin had a similar safety profile to that of lower simvastatin doses, except for the incidence of myopathy. A higher rate of myopathy-related adverse reactions with 80mg simvastatin than with other statins seemed apparent. On the other hand, whilst acknowledging the importance of muscle side effects, the PRAC emphasised the need for alternative high-dose statin regimens in cases where liver function abnormalities limit the use of long term treatment with other statins. The PRAC concluded that the data generally supported what was already known about dose-dependent risk of myopathy and rhabdomyolysis, which is already reflected in the product information for all statins.

The PRAC noted that utilisation data in the UK showed that the use of 80 mg simvastatin is low but considered that it would be informative to gather further information on the overall pattern of statin use especially at high doses in the EU. It was therefore agreed to collect further relevant data on statins usage across the EU since simvastatin 80 mg is not available in all MSs, and other statins (e.g. atorvastatin or rosuvastatin) may be more widely prescribed. According to the CPRD analysis, simvastatin use in primary prevention was less than 25% of its total use, the UK use of 80 mg

[9] Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. Lancet. 2010 Nov 13;376(9753):1658-69. doi: 10.1016/S0140-6736(10)60310-8. Epub 2010 Nov 8.

simvastatin was less than 3% in total, and new use of 80 mg simvastatin as a starting dose constituted about 0.1-0.2% of new simvastatin use per year.

Additionally, the PRAC discussed the potential importance of genetic polymorphisms (such as variants of the *SLCO1B1* gene) in the metabolism of statins, which may help identify patients predisposed to myopathy/rhabdomyolysis with statins use.

Summary of recommendation(s)

- The PRAC Rapporteur should circulate a Non Urgent Information request (NUI) to obtain information on the availability and usage of high-dose statins in the EU as well as the wordings on the risk of myopathy and rhabdomyolysis that exist in the currently approved product information.
- Exploration of the whether drug utilization analyses similar to that performed for simvastatin can be performed for other statins and extended to other Member States as available in the medical research/drug utilization data bases.
- The MAH for simvastatin should provide further data on the bio-markers recently identified for statins and myopathy to the PRAC Rapporteur within 60 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.3. **Lenograstim** (NAP)

- Signal of (systemic) capillary leak syndrome (CLS)

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

For background information see, PRAC minutes of 10-13 May 2013.
The MAH replied to the request for information on the signal, and the responses were assessed by the Rapporteur.

The cumulative exposure to lenograstim is estimated to have been approximately 1.4 million patients and 77,000 healthy donors in the period between 1991 and 2012.

Discussion

The PRAC noted that over one hundred cases were identified with the recommended search criteria, including nine cases of capillary leak syndrome (CLS). A temporal association had been observed in most cases, with a positive dechallenge in six cases and/or a positive rechallenge in one case. Additionally, cases had been reported for other substances of the same therapeutic class (a similar reviews had already been performed for filgrastim and pegfilgrastim, see PRAC minutes 4-7 March 2013). Based on this evidence and on the potential seriousness of the reaction, the PRAC confirmed that the product information of lenograstim products should be updated with respect to CLS , that healthcare professionals should be informed of these changes as well as of the similarity of these adverse effects with the other medicines of the same therapeutic class.

Summary of recommendation(s)

- The MAHs for the reference[10] lenograstim medicines should submit to the NCA of the MSs within 30 days a variation to update the product information to include "capillary leak syndrome"[11] as an undesirable effect, including a proposal for a DHPC letter and a communication plan. An RMP should be submitted within 90 days.

For the full PRAC recommendation see EMA/PRAC/693228/2013 published on the EMA website.

4.3.4. Levetiracetam – KEPPRA (CAP)

- Signal of hyponatraemia and inappropriate antidiuretic hormone secretion (SIADH)

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

Background

For background information, see PRAC minutes of 8-11 July 2013.
The MAH replied to the further request for information on the signal and the responses were assessed by the Rapporteur. While a causal relationship between levetiracetam and SIADH was not confirmed, more information was needed on hyponatraemia.

Discussion

The PRAC discussed the conclusions of the assessment of the further data and the review of spontaneous post-marketing cases of hyponatraemia which had identified two cases reporting a positive rechallenge. Despite some confounding factors and/or missing information in these two cases, dechallenge and rechallenge results strengthened the signal of levetiracetam-induced hyponatraemia. Analyses of the available data did not suggest that drug-drug interactions between levetiracetam and other antiepileptic drugs would have a role in promoting hyponatraemia. Therefore, the PRAC agreed that the product information should be updated to reflect these findings.

Summary of recommendation(s)

- The MAH of Keppra [12] should submit to the EMA within 60 days a variation to update the product information to include "hyponatraemia"[13] as an undesirable effect.
- The MAHs of generic products should then submit to the EMA or to the national competent authorities of the MSs, as applicable, a variation to align their product information to that of the originator.

For the full PRAC recommendation see EMA/PRAC/693228/2013 published on the EMA website.

[10] 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
[11] Section 4.4 and 4.8 of the Summary of Product Characteristics
[12] 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
[13] Section 4.8 of the Summary of Product Characteristics

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.

Please refer to the CHMP pages for upcoming information (http://www.ema.europa.eu/ Home>About Us>Committees>CHMP Meetings).

5.1.1. Albiglutide

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

5.1.2. Laquinimod

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

5.1.3. Riociguat

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

5.1.4. Sofosbuvir

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

5.1.5. Trametinib

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

5.1.6. Umeclidinium bromide, vilanterol

- 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. Cidofovir – VISTIDE (CAP)

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

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Background

Cidofovir is an antiviral used in the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction - only when other agents are considered unsuitable.

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

Summary of advice

- The updated RMPs version 4 for Vistide (cidofovir) could be acceptable provided that an updated risk management plan and satisfactory responses to the questions raised by the PRAC are submitted. The RMP should be updated in relation to HIV-related cytomegalovirus (CMV) retinitis in the light of the current epidemiologic review with data from 2011. The MAH should provide an updated analysis of the epidemiologic data specifically within the EU, by collecting such data from competent authorities (ECDC, WHO, and any other national or supranational source).

RMP in the context of a variation

5.2.2. Bortezomib – VELCADE (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

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

The CHMP is evaluating an extension of the therapeutic indication for Velcade, a centrally authorised product containing bortezomib, to add the treatment - in combination with pegylated liposom doxorubicin or dexamethasone - of patients with relapsed and/or progressive multiple myeloma. Some clarifications were requested by the PRAC on the RMP accompanying this variation at the September 2013 meeting. Responses were submitted by the MAH and assessed by the Rapporteur.

Summary of advice

- The RMP version 26 for Velcade (bortezomib) in the context of the variation under evaluation by the CHMP was considered acceptable.
- The educational material should include a graph describing the induction transplant regimes and contain some key elements. The key elements include: instructions for prescribing and administration (including the cycles' length and number of cycles) to minimise the risk of medication and dispensing errors; a reminder that patients receiving Velcade in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide.

5.2.3. Insulin lispro – HUMALOG (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Humalog is a centrally authorised insulin. Previous advice provided by the PRAC in July 2013 was discussed in the framework of a variation under evaluation by the CHMP.

The MAH submitted replies to the questions raised by the PRAC which were assessed by the Rapporteur.

Summary of advice

- The RMP version 1 for Humalog (insulin lispro) in the context of the variation under evaluation by the CHMP was considered acceptable provided an updated risk management plan and satisfactory responses to the requested supplementary information are provided to the PRAC.
- The PRAC concluded that in light of the planned change to purification process it was important that there was effective management of switching of patients from products manufactured using the old purification process to products using the new purification process. It was agreed that a DHPC may not be the most appropriate vehicle given that the further data provided by the MAH had suggested that any potentially associated risk of hypersensitivity or anaphylactic reactions was unlikely to be as a great as initially thought. Nevertheless the PRAC considered that the MAH should be asked to consider other means by which communications could be disseminated in order to raise awareness and also facilitate traceability and reporting of any suspected ADRs.
- The proposed post-marketing surveillance study was considered appropriate to monitor any change in the risk of immunogenicity. However the MAH should provide further details.

5.2.4. **Ponatinib – ICLUSIG** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

Background

Ponatinib is a tyrosine kinase inhibitor used in the treatment of adult patients with:

- chronic-phase, accelerated-phase or blast-phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation;
- Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.

The CHMP is evaluating a type II variation procedure for Iclusig, a centrally authorised product containing ponatinib, to reflect new safety data on vascular occlusive events and other adverse reactions suggesting they occur with greater frequency than was initially observed at the time of granting the European Union (EU) marketing authorisation in July 2013. The PRAC is responsible for providing advice to the CHMP on this variation and its RMP. Furthermore, the PRAC was informed of the recently issued FDA Drug Safety Communication 'FDA asks manufacturer of the leukemia drug Iclusig (ponatinib) to suspend marketing and sales'.

The PRAC agreed that clarifications and further information were urgently needed and a list of questions was agreed for the MAH who was invited to present its responses in an oral explanation at the meeting.

Summary of advice

Having reviewed the most recently available data the PRAC agreed that patients and healthcare professionals may continue to use Iclusig with increased caution in its authorised use, which is limited

to patients who had no other available treatment options with medicines of this class, and should monitor carefully for evidence of thromboembolism and vascular occlusive events.

The PRAC recommended updates to the product information to include strengthened warnings on cardiovascular risk and guidance on optimising the patient's cardiovascular therapy before starting treatment. In addition to changes in the product information, the PRAC also highlighted the need to carry out an in-depth review benefit-risk profile of the medicine and the PRAC agreed that communication on these outcomes was necessary (see 'PRAC updates on the risks of serious vascular occlusive events associated with cancer medicine Iclusig' EMA/686491/2013).

The RMP version 6 for Iclusig (ponatinib) in the context of the variation under evaluation by the CHMP should be updated.

Ischaemic cardiac events, ischaemic cerebrovascular events and ischaemic peripheral vascular events should be combined into a single important identified risk of 'vascular occlusive events, including cardiac, cerebrovascular and peripheral vascular events'.

Additional data is required to further characterise the risk of vascular occlusive events, including full consideration of the dose-effect relationship and the underlying biological mechanism, and also to monitor the effectiveness of risk minimisation measures agreed as part of this variation. These should be considered as additional pharmacovigilance activities for this important identified risk, and should be reflected in the RMP.

Post meeting note: in line with previous advice of the PRAC the CHMP agreed an opinion for an update of the EU product information for Iclusig at their November 2013 meeting (see EMA/716841/2013).

Furthermore, on 28 November 2013, the EC sent a notification letter triggering a review under Article 20 of Regulation (EC) No 726/2004 for Iclusig.

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

None

RMP in the context of a stand-alone RMP procedure

See paragraph 14.

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[14]

6.1.1. **Abiraterone – ZYTIGA** (CAP)

- Evaluation of a PSUR procedure

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

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

Background

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, and is indicated in combination with prednisone or prednisolone for the treatment of metastatic castration-resistant prostate cancer in adult men under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Zytiga (abiraterone) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add sepsis as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation should be varied[15].
- In the next PSUR, the MAH should provide a cumulative review of myocardial infarction and acute coronary syndrome, and assess any possible causal relationship between abiraterone and myocardial ischaemic events (especially in patients with pre-existing cardiovascular risk factors). The MAH should also closely monitor several adverse drug reactions, in particular, cases of thrombocytopenia and gastrointestinal haemorrhage.

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.

6.1.2. Cidofovir – VISTIDE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Background

Cidofovir is a cytidine analogue indicated for the treatment of cytomegalovirus (CMV) retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction.

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

[15] 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.

The PRAC noted that cidofovir was used off-label for the treatment of serious viral infection where current treatment options are very limited, but did not consider that communication via a DHPC was justified at the present time.

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.

6.1.3. Decitabine – DACOGEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Decitabine is a cytidine deoxynucleoside analogue indicated for the treatment of adult patients aged 65 years and above with newly diagnosed *de novo* or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dacogen, a centrally authorised medicine containing decitabine, 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 Dacogen (decitabine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to reflect the increased risk of infections (viral, bacterial, and fungal) as a warning and as an undesirable effect with a very common frequency. Therefore the current terms of the marketing authorisation should be varied[16].
- In the next PSUR, the MAH should address some comments regarding the format of the PSUR and provide cumulative reviews of cases of caecitis, typhlitis and neutropenic colitis reported spontaneously and collected from clinical trials.

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.

6.1.4. Febuxostat – ADENURIC (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

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

Background

Febuxostat is a non-purine selective inhibitor of xanthine oxidase (NP-SIXO) indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Adenuric, a centrally authorised medicine containing febuxostat, 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 Adenuric (febuxostat) in the approved indication remains favourable.
- Nevertheless, the product information should be updated to refine the existing warning on serious allergic/hypersensitivity reactions by reflecting information on toxic epidermal necrolysis (TEN) and drug reactions with eosinophilia and systemic symptoms (DRESS). In addition, liver injury, TEN and DRESS should be added as undesirable effects with a rare frequency. Therefore the current terms of the marketing authorisation should be varied[17].
- In the next PSUR, the MAH should closely monitor several adverse drug reactions and provide a discussion on lack of reversibility of hepatic enzyme increases and on risk factors in patients treated with febuxostat experiencing rhabdomyolysis and in patients experiencing syncope. In addition, the MAH should discuss the mechanism of hypersensitivity reactions related to febuxostat, including potential cross-sensitivity reactions with allopurinol.

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.

6.1.5. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – **OPTAFLU** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Background

Optaflu is an influenza vaccine (surface antigen, inactivated, prepared in cell cultures) indicated for the prophylaxis of influenza for adults, especially in those who run an increased risk of associated complications.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Optaflu, a centrally authorised influenza vaccine, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Optaflu (influenza vaccine (surface antigen, inactivated, prepared in cell cultures)) in the approved indication(s) remains favourable.

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

- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should closely monitor cases of dyspnoea. Furthermore, additional data is needed to justify an update of the product information regarding immune response. To this end, the MAH should provide a cumulative review, including all case reports substantiating the need to have a specific warning in addition to other relevant information already included in the product information.

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

6.1.6. Regadenoson – RAPISCAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Regadenoson is a selective coronary vasodilator for use as a pharmacological stress agent for radionuclide myocardial perfusion imaging (MPI) in adult patients unable to undergo adequate exercise stress.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rapiscan, a centrally authorised medicine containing regadenoson, 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 Rapiscan (regadenoson) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add several warnings to limit the off-label use of Rapiscan in combination with exercise, to apply caution when Rapiscan is used in patients with a history of seizures or other risk factors for seizures, as well as when Rapiscan is used in patients with a history of atrial fibrillation or flutter since it may cause a worsening or recurrence of atrial fibrillation. In addition, the warning on myocardial ischemia should be refined to emphasise that caution should be applied when Rapiscan is used in patients with a recent myocardial infarction. Also, the recurrence of atrial fibrillation should be reflected as an undesirable effect. Therefore the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should address several issues, in particular the MAH should provide a cumulative review of cases of convulsion/seizures and specify any concomitant treatment with aminophylline in view of a published case series[19] suggesting that administration of aminophylline may prolong regadenoson-induced seizures. The MAH should propose changes to the product information as warranted.

[18] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.
[19] Page RL 2nd, Spurck P, Bainbridge JL et al. Seizures associated with regadenoson: a case series. J Nucl Cadiol 2012;19(2):389-91

- In the next RMP update, seizure and worsening/recurrence of atrial fibrillation should be included as important identified risks and cerebrovascular accident/stroke (CVA) as an important potential risk.

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.

6.1.7. Sunitinib – **SUTENT** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Sunitinib is a multiple receptor tyrosine kinase (RTK) inhibitor indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST), for the treatment of advanced/metastatic renal cell carcinoma (MRCC) and for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sutent, a centrally authorised medicine containing sunitinib, 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 Sutent (sunitinib) 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 provide further data in particular the MAH is requested to closely monitor all the cases related to glucose metabolism disorders and provide a detailed description of the reported cases.

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.

6.1.8. Telmisartan – **KINZALMONO** (CAP), **MICARDIS** (CAP), **PRITOR** (CAP), **TELMISARTAN TEVA** (CAP), **TELMISARTAN TEVA PHARMA** (CAP), **TOLURA** (CAP), NAPs **Telmisartan, hydrochlorothiazide – KINZALKOMB** (CAP), **MICARDIS PLUS** (CAP), **PRITOR PLUS (**CAP), **TOLUCOMBI** (CAP), NAP

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Telmisartan is an angiotensin II receptor (type AT_1) antagonist used for the treatment of essential hypertension and reduction of cardiovascular morbidity in adults under certain conditions.

Based on the assessment of the PSURs part of the PSUR Single assessment procedure[20], the PRAC reviewed the benefit-risk balance of telmisartan- and telmisartan/hydrochlorothiazide-containing products[21] 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 telmisartan-containing products and telmisartan/hydrochlorothiazide-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- MAHs for generic products should update their product information in line with that of the originator products, thus a variation should be submitted to EMA and/or relevant National Competent Authorities, as per the submissions rules applying to each marketing authorisation as appropriate. Moreover, MAHs for generic products should closely monitor the same safety concerns as those monitored by the originator products as detailed in the PRAC assessment report.
- In the next PSURs, MAHs should closely monitor cases of dizziness, hypoesthesia, paraesthesia, pollakiuria, gynaecomastia, drug ineffective, headache and joint swelling. In addition, MAHs should provide a review of all cases of foetotoxicity and discuss the need for additional risk minimisation measures to avoid off-label use. In addition, cases of myocardial infarction in diabetic patients should be kept under close monitoring until a relationship between telmisartan and increased cardiovascular risk is further evaluated. Finally, MAHs should provide an analysis of post-marketing cases of adverse effects of dual blockade of the renin-angiotensin-aldosterone system (RAAS) as well as to closely monitor cases of rhabdomyolysis.

The next PSUR for the originator-products (Micardis/Kinzalmono/Pritor and Micardis Plus/Kinzalcomb/Pritor Plus) 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.

Considering that data from PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended did not raise any safety concerns, the PRAC agreed that no further PSURs are required for those products. This will be reflected in the EURD list.

6.1.9. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of a PSUR procedure

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

Background

Tocilizumab is an immunosuppressant indicated for the treatment of moderate to severe active rheumatoid arthritis (RA), for the treatment of active systemic juvenile idiopathic arthritis (sJIA), for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) under certain conditions. Tocilizumab has also been shown to reduce the rate of

[20] Abbreviated PSUSA, assessing PSURs for CAPs and NAPs
[21] Including products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended, as requested by Competent Authorities [DIR Article 107b (3b)] and reflected in the EURD list for the current PSUSA procedure

progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of RoActemra, a centrally authorised medicine containing tocilizumab, 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 Roactemra (tocilizumab) 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 present an evaluation of the incidence rate of events relating to worsening of psoriasis from all clinical trials and observational studies per 100 patient years. In addition, the MAH should continue to monitor adverse events of special interest and events with fatal outcome.
- The MAH should also review the categorisation of the important potential risk "neutropenia" for both adult and paediatric patients within the next RMP update.

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.

6.2. Follow-up to PSUR procedures[22]

6.2.1. Pneumococcal polysaccharide conjugate vaccine (adsorbed) – SYNFLORIX (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

Background

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

Summary of advice and conclusions

- Following the review of clinical trial meta-analysis data submitted by the MAH showing a statistically significant increased relative risk of Kawasaki's disease compared to controls, the PRAC considered that an association between Synflorix and Kawasaki's disease could not be ruled out. Therefore, the MAH should submit to the EMA within 60 days a variation to include Kawasaki's disease in the product information (Section 4.8 of the SmPC).
- In the next PSUR, the MAH should continue to closely monitor cases of hypotonic hyporesponsive episode (HEE) and provide detailed reporting rates as well as information on any concomitant treatment.

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

7. Post-authorisation Safety Studies (PASS)

See paragraph 16.

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

8.1.1. Capsaicin – QUTENZA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pêgo (PT)

Background

Capsaicin is a local counter-irritant indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.

Qutenza, a centrally authorised cutaneous patch containing the active substance capsaicin (8%), was authorised in 2009.

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

Summary of advice

Based on the review of the available pharmacovigilance data for Qutenza (capsaicin) and the CHMP Rapporteur's assessment report, the PRAC considered that an additional renewal after five years should be required based on pharmacovigilance grounds, due to ongoing post-marketing studies in particular the STRIDE[23] study, expected to yield important new safety data.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. On-going or concluded pharmacovigilance inspections

None

9.3. Others

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

[23] Safety and effectiveness of repeated administration of Qutenza patches for treatment of pain caused by nerve damage (STRIDE)

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. **Temozolomide – TEMODAL** (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Background

For background information, see PRAC minutes 4-7 March 2013. The MAH for Temodal (temozolomide) had been requested to submit to the EMA a variation to address the signal of hepatic failure and provide further information. The Rapporteurs assessed the variation and the supplementary information received by the MAH and the PRAC provided advice to CHMP.

Summary of advice

The PRAC considered that the information provided in the reply to their request was satisfactory. The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate the risk of liver toxicity associated with temozolomide and the potential for severe liver toxicity which may lead to liver failure with some fatal cases reported; some changes to the text of the DHPC and communication plan were recommended. The PRAC supported that the MAHs holding a licence for temozolomide-containing medicines should co-operate to transmit a joint DHPC to healthcare professionals.

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

None

10.3. Other requests

10.3.1. Delamanid

- PRAC consultation on a re-examination procedure of an initial marketing authorisation

Background

On 25 July 2013, the CHMP adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product delamanid, intended for the treatment of multi-drug resistant tuberculosis - see EMEA/H/C/002552.

The applicant requested a re-examination of the opinion. In accordance with the CHMP request in the re-examination procedure the PRAC provided advice relating to risk management aspects..

Post-meeting note: after considering the grounds for this request, the CHMP re-examined the initial opinion, and adopted a final positive opinion recommending the granting of a conditional marketing authorisation for Deltyba on 21 November 2013 (see EMA Q&A EMA/713953/2013).

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

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

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

12.3.1.1. Consultation on the draft List, version November 2013

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

Post-meeting note: following the PRAC meeting in November 2013, the updated EURD list was adopted by the CHMP at its November 2013 meeting and was published on the EMA website on 29 November 2013 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.3.2. PSURs repository

12.3.2.1. Functional specifications of repository and confirmation of its full functionality

- Timetable PSUR Repository functionalities to be audited

This topic of the proposed functionalities of the PSUR repository was discussed at the organisational matters teleconference on 21 November 2013. The EMA secretariat reminded PRAC that Article 25a of Regulation (EC) 726/2004 states that the Agency, in collaboration with the national competent authorities and the Commission, has to set up and maintain a repository for periodic safety update reports (PSURs) and the corresponding assessment reports. The Agency, in collaboration with the national competent authorities and the Commission and after consultation with the PRAC, has to draw up the functional specifications for the PSUR Repository. The proposed timetable for agreement of PSUR Repository functionalities to be audited was outlined and PRAC recommended careful selection of business requirements to ensure that the repository functionalities will be equivalent to existing functionalities in national repositories. In particular, alert systems on new submissions into the database was considered essential. EMA confirmed that MSs will have opportunities to input at each milestone in the development of the repository.

12.4. Signal Management

12.4.1. Signal Management

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

The EMA secretariat reminded the Committee of the legal background and current activities concerning the publication of the 'stand-alone' PRAC recommendations for signals analysed by the PRAC which started as of September 2013. The EMA will be publishing retrospectively all PRAC recommendations agreed from September 2012 until July 2013, further to what is currently reported in the published minutes, to facilitate access to this information. MAHs are reminded to regularly check for updated publications on the EMA website: Home>Regulatory>Human medicines>Pharmacovigilance>Signal management>PRAC recommendations.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Additional Monitoring

12.5.1.1. List of Products under Additional Monitoring

- Consultation on the draft List, version November 2013

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 27 November 2013 (see: Home>Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.6. EudraVigilance Database

12.6.1. Activities related to the confirmation of full functionality

- EudraVigilance (EV) functionalities to be audited

This topic was discussed at the organisational matters teleconference on 21 November 2013. The EMA secretariat reminded the Committee that in accordance with Article 24 of Regulation (EC) 726/2004 the Agency, in collaboration with the Member States and the Commission, has to draw up functional specifications for the EudraVigilance database, together with a timeframe for their implementation.

The EMA Management Board will confirm and announce when full functionality of EudraVigilance (EV) has been achieved and the system meets defined functional specifications. Confirmation will be based on an independent audit that takes into account the recommendations of the PRAC.

Therefore the EMA secretariat presented a timetable for agreeing the EV functionalities to be audited as well as the methodology to define EV functionalities to be audited and a draft list of current functionalities to be considered. Members provided preliminary comments; a progress report including contributions of all parties involved (Project Teams for the implementation of the new pharmacovigilance legislation, European Risk Management Strategy Facilitation Groups (ERMS-FG, and the), Telematics Management Board) will be provided at the December 2013 PRAC meeting.

12.6.2. Changes to EudraVigilance Database and functional specifications

None

12.7. Risk Management Plans and Effectiveness of risk Minimisations

12.7.1. Risk Management Systems

- Process for RMP review

This topic was discussed at the organisational matters teleconference on 21 November 2013. A paper listing some options for optimisation of the process for consideration by the PRAC was proposed by the EMA secretariat.

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. Committees

None

12.12.2. Blood Products Working Party

12.12.2.1. Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration: consultation on the ongoing revision

The EMA secretariat presented a revision of the above mentioned guideline. The PRAC agreed with the proposed changes. PRAC would welcome at a suitable point an update on thrombogenic activity testing for immunoglobulins and on the work carried out in order to revise current requirements. The EMA secretariat will follow-up on this and plan an update at a subsequent PRAC meeting. Comments in writing on the guideline are awaited until 25 November 2013.

12.12.2.2. Guideline on core SmPC for plasma-derived fibrin sealant / haemostatic products: consultation on the ongoing revision

The PRAC supported the changes and considered the update a useful addition which became necessary following the conclusion of the Article 31 of Directive 2001/83/EC referral on fibrinogen-containing solutions authorised as sealants for administration by spray application.

12.13. Interaction within the EU regulatory

None

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

None

13. Any other business

13.1.1. Awareness session on the new pharmacovigilance training resource

The EMA secretariat presented an outline of the new pharmacovigilance legislation training resource prepared by the Training Content Group. The Pharmacovigilance Training Catalogue is available for use by the NCA from the Eudraportal and contains training material from previously organised training sessions. Publication to a wider audience is being considered.

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

- Letters received following the conclusion of the referral under Article 107i and 31 of Directive 2001/83/EC
- Complementary analyses of the CRISTAL study submitted following conclusion of the referral under Article 107i of Directive 2001/83/EC

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

The EMA secretariat informed the PRAC of letters addressed to the EMA Executive Director regarding the October 2013 PRAC's recommendation on hydroxyethyl starch. An 'Open Letter to the Executive Director of the EMA concerning the licensing of hydroxyethyl starch solutions for fluid resuscitation', signed by clinicians and researchers in this field, was also received. The PRAC noted the letters and the EMA secretariat clarified that responses to these letters will be forwarded to the PRAC for their information.

The PRAC was also informed that on 31 October 2013 a complementary analyses of the CRISTAL study was submitted to the EMA by the principal investigator following the request formalised at the September 2013 PRAC meeting. Since the referral procedure for hydroxyethyl starch had already concluded (on 10 October 2013 by PRAC and on 23 October 2013 by CMDh), it was agreed that the EMA secretariat would provide a request to the PRAC, which outlined the timetable and approach for these data to be considered through a written procedure.

Post-meeting note: following a written request from the EMA Executive Director, the PRAC concluded via written procedure, on 21 November 2013, that the complementary analyses provided by the investigator of the CRISTAL study do not change the final conclusion of PRAC in the Art. 107i referral on hydroxyethyl starch.

Post-note: EMA sent a reply to the letters received on 22 November 2013.

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

14. ANNEX I Risk Management Plans

14.1. Medicines in the pre-authorisation phase

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

14.1.1. Ataluren

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

14.1.2. Brimonidine tartare, brinzolamide

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

14.1.3. Cholic acid

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

14.1.4. Colecalciferol, strontium ranelate

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

14.1.5. Dapagliflozin, metformin

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

14.1.6. Dolutegravir

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

14.1.7. Etarfolatide

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

14.1.8. Folic acid

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

14.1.9. Follitropin alfa

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

14.1.10. Nalfurafine

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

14.1.11. Perflubutane

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

14.1.12. Vintafolide

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

14.1.13. Zoledronic acid

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

The rapporteur assessment report for this procedure was agreed via written procedure on 14 November 2013.

14.2. Medicines already authorised

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

RMP in the context of a PSUR procedure

See also related PSUR under 6 or 15 as applicable.

14.2.1. Abiraterone – ZYTIGA (CAP)

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

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

14.2.2. Ceftaroline fosamil – ZINFORO (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.3. Dapagliflozin – FORXIGA (CAP)

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

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

14.2.4. Febuxostat – ADENURIC (CAP)

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

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

14.2.5. Fenofibrate, pravastatin – PRAVAFENIX (CAP)

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

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

14.2.6. Fesoterodine – **TOVIAZ** (CAP)

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

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

14.2.7. Histamine dihydrochloride – **CEPLENE** (CAP)

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

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

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

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

14.2.9. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – **OPTAFLU** (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.10. Insulin glargine – **LANTUS** (CAP), **OPTISULIN** (CAP)

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

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

14.2.11. Ivabradine – **CORLENTOR** (CAP), **PROCORALAN** (CAP)

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

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

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

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

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

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

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.14. Orlistat – **XENICAL** (CAP)

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

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

14.2.15. Pasireotide – **SIGNIFOR** (CAP)

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

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

14.2.16. Regadenoson – **RAPISCAN** (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.17. Sunitinib – **SUTENT** (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

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

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

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

RMP in the context of a variation

14.2.19. Abiraterone – **ZYTIGA** (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.20. Bazedoxifene – CONBRIZA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.21. Bevacizumab – AVASTIN (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.22. Ceftaroline fosamil – ZINFORO (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

The rapporteur assessment report for this procedure was agreed via written procedure on 19 November 2013.

14.2.23. Dasatinib – SPRYCEL (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.24. Icatibant – FIRAZYR (CAP)

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

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

14.2.25. Iloprost – VENTAVIS (CAP)

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

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

14.2.26. Imatinib – IMATINIB ACTAVIS (CAP)

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

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

14.2.27. Indacaterol – **HIROBRIZ BREEZHALER** (CAP), **ONBREZ BREEZHALER** (CAP), **OSLIF BREEZHALER** (CAP)

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

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

14.2.28. Measles, mumps, rubella and varicella vaccine (live) – **PROQUAD** (CAP)

- Evaluation of an RMP in the context of a variation

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

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

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.30. Prasugrel – **EFIENT** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.31. Rituximab – **MABTHERA** (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.32. Tocilizumab – **ROACTEMRA** (CAP)

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

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

14.2.33. Ulipristal – **ESMYA** (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.34. Ulipristal acetate – **ELLAONE** (CAP)

- Evaluation of an RMP in the context of a variation

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

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

Not applicable

RMP in the context of a stand-alone RMP procedure

14.2.35. Telmisartan – **MICARDIS** (CAP), **KINZALMONO** (CAP), **PRITOR** (CAP)

- Evaluation of a stand-alone RMP

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

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

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

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

15.1. Evaluation of PSUR procedures[24]

15.1.1. Alipogene tiparvovec – **GLYBERA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

15.1.2. Bortezomib – **VELCADE** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

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

15.1.3. Catumaxomab – REMOVAB (CAP)

- Evaluation of a PSUR procedure

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

15.1.4. Ceftaroline fosamil – ZINFORO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

15.1.5. Cytarabine – DEPOCYTE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

15.1.6. Dapagliflozin – FORXIGA (CAP)

- Evaluation of a PSUR procedure

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

15.1.7. Fenofibrate, pravastatin – PRAVAFENIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

15.1.8. Fesoterodine – TOVIAZ (CAP)

- Evaluation of a PSUR procedure

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

15.1.9. Golimumab – SIMPONI (CAP)

- Evaluation of a PSUR procedure

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

15.1.10. Granisetron – SANCUSO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Jolanta Gulbinovic (LT)

15.1.11. Histamine dihydrochloride – CEPLENE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

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

- Evaluation of a PSUR procedure

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

15.1.13. Ivabradine – CORLENTOR (CAP), PROCORALAN (CAP)

- Evaluation of a PSUR procedure

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

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

- Evaluation of a PSUR procedure

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

15.1.15. Mannitol – BRONCHITOL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

15.1.17. Ocriplasmin – JETREA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

15.1.18. Ofatumumab – ARZERRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

15.1.19. Orlistat – XENICAL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Evelyne Falip (FR)

15.1.20. Pasireotide – SIGNIFOR (CAP)

- Evaluation of a PSUR procedure

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

15.1.21. Pazopanib – VOTRIENT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

15.1.22. Retapamulin – ALTARGO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

15.1.23. Tadalafil – ADCIRCA (CAP), CIALIS (CAP)

- Evaluation of a PSUR procedure

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

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

15.2. Follow-up to PSUR procedures[25]

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

- Evaluation of a follow-up to a PSUR procedure

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

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

Since all comments received on the assessment of these studies were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below without further plenary discussion.

16.1. Protocols of PASS imposed in the marketing authorisation(s)[26]

16.1.1. Imatinib – **GLIVEC** (CAP)

- Evaluation of an imposed PASS protocol

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

16.1.2. Lomitapide – **LOJUXTA** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[27]

16.2.1. Adalimumab – **HUMIRA** (CAP)

- Evaluation of a PASS protocol

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

16.2.2. Certolizumab pegol – **CIMZIA** (CAP)

- Evaluation of a PASS protocol

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

[25] Follow up as per the conclusions of the previous PSUR procedure, assessed outside next PSUR procedure.
[26] In accordance with Article 107n of Directive 2001/83/EC
[27] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

16.2.3. Dapagliflozin – FORXIGA (CAP)

- Evaluation of a PASS protocol

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

16.2.4. Emtricitabine, rilpivirine, tenofovir disproxil – EVIPLERA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

16.2.5. Human normal immunoglobulin – PRIVIGEN (CAP)

- Evaluation of a PASS protocol

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

16.2.6. Loxapine – ADASUVE (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

16.2.7. Mifamurtide – MEPACT (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

16.2.8. Nalmefene – SELINCRO (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

16.2.9. Nalmefene – SELINCRO (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

16.2.10. Romiplostim – NPLATE (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

16.3. Results of PASS imposed in the marketing authorisation(s)[28]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[29]

None

16.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS submitted before the entry into force of the revised variations regulation[30]

16.5.1. **Adalimumab – HUMIRA** (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

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

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

17.1.1. **Amifampridine – FIRDAPSE** (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

17.1.2. **Bosutinib – BOSULIF** (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

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

17.1.3. **Canakinumab – ILARIS** (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

17.1.4. **Ofatumumab – ARZERRA** (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

17.1.5. **Rivastigmine – NIMVASTID** (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Evelyne Falip (FR)

17.1.6. **Ulipristal acetate – ELLAONE** (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 4-7 November meeting.

PRAC member PRAC alternate	*Country*	*Outcome restriction following evaluation of e-DoI for the meeting*	*Topics on the current Committee Agenda for which restriction applies* *Product / substance*
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	Telmisartan and agents acting on the renin-angiotensin system, paracetamol, riociguat, iloprost
Veerle Verlinden	Belgium	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Eva Jirsová	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Evelyne Falip	France	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
George Aislaitner	Greece	Full involvement	
Julia Pallos	Hungary	Full involvement	
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Ruchika Sharma	Ireland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Nicolae Fotin	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
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	
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Cannot act as Rapporteur and no part in final discussions for:	Bortezomib
Lennart Waldenlind		Full involvement	

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

Additional European experts participating at the meeting for specific Agenda items	Country	
Per Sindahl	Denmark	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Arnaud Batz	France	
Pierre Demolis	France	
Alexandre Moreau	France	
Vera Luetgendorf	Germany	
Peter Mol	The Netherlands	
Guiseppe Rosano	Italy	
Lies van Vlijmen	The Netherlands	
Gloria Martín-Serrano	Spain	
Pilar Rayon	Spain	
Charlotte Backman	Sweden	
Bertil Jonsson	Sweden	
Sigrid Klaar	Sweden	
Bengt Ljungberg	Sweden	
Ulf Olsson	Sweden	
Tomas Salmonson	Sweden	
Jan Sjöberg	Sweden	
Bjorn Zethelius	Sweden	
Alison Banner-Simpson	United Kingdom	
Benoy Daniel	United Kingdom	
Claire Doe	United Kingdom	
Judith Hilton	United Kingdom	
Max Lagnado	United Kingdom	
Janet Nooney	United Kingdom	
Raquel Rogers	United Kingdom	
Rafe Suvarna	United Kingdom	
Karen Slevin	United Kingdom	

Observer from the European Commission
Helen Lee – DG Health and Consumers
European Medicines Agency
Peter Arlett - Head of Sector for Pharmacovigilance and Risk Management
Maria Boulos – Scientific Administrator, Regulatory Affairs
Christelle Bouygues – Scientific Administrator, Regulatory Affairs
Roberto De Lisa - Scientific Administrator, PRAC Secretariat
Corinne De Vries – Head of Service, Risk Management Review
Georgy Genov – Section Head, Signal Detection and Data Analysis
Sheila Kennedy – Section Head, Scientific Committee Support
Kasia Kmiecik – Assistant, PRAC Secretariat
Geraldine Portier - Scientific Administrator, PRAC Secretariat
Tanya Sepehr – Assistant, PRAC Secretariat
Tania Teixeira – Head of Service, Referral Procedures

ANNEX III – List of abbreviations

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

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