6 February 2014
EMA/PRAC/96908/2014 *corr[1]
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 6-9 January 2014

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 these 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)

[1] Correction of a reference to Annex number in section 7.4.

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

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

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

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

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

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

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

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

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1. Introduction

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

The Chairperson opened the meeting, welcoming all participants to the 6-9 January 2014 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 related 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 noted that that Regulation (EU) No 1235/2010, Regulation (EU) No 1027/2012, Directive 2010/84/EU and Directive 2012/26/EU had been transposed into Norwegian law.

1.2. Adoption of agenda of the meeting on 6-9 January 2014

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

1.3. Adoption of the minutes of the previous PRAC meeting on 2-5 December 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 held on 2-5 December 2013 EMA/PRAC/807963/2013 were published on the EMA website on 17 January 2014.

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-Rapporteurs: 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 agents acting on the renin-angiotensin system - (see PRAC Minutes November 2013).

Summary of recommendation(s)/conclusions

EMA secretariat informed the PRAC of the confirmed date of the cardiovascular scientific advisory group (SAG) - to be convened on 11 February 2014 – and of some practicalities related to the attendance of MAHs at the meeting. The PRAC agreed on an amended list of questions for the SAG as well as a revised timetable to take into account this date (EMA/PRAC/290691/2013 rev2 published on the EMA website).

3.2.2. **Domperidone** (NAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)
PRAC Co-Rapporteur: Jean-Michel Dogné (BE)

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for domperidone-containing medicines (see PRAC minutes 2-5 December 2013). A request for extension of the previously agreed timetable for providing a response to the agreed list of questions was requested by one of the MAH involved.

Summary of recommendation(s)/conclusions

Taking into account the MAH's justification for an extension to the timetable, the PRAC considered that it was important to proceed in accordance to the already established timelines and supported the decision to maintain the previously agreed timetable.

3.3. Procedures for finalisation

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

- Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20(8) of Regulation (EC) No 726/2004 based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)
PRAC Co-Rapporteur: Harald Herkner (AT)

Background

A referral procedure under Article 20 of Directive 2001/83/EC for strontium-containing medicines (see PRAC Minutes October 2013) is to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs on the data provided by the MAH. An oral explanation took place at the meeting.

The PRAC agreed that strontium ranelate use was associated with a number of serious risks; namely serious cardiac disorders including myocardial infarction, venous thromboembolic events (VTE), serious skin reactions (including DRESS syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis), disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders., Frequencies for the cardiac and thromboembolic events have been calculated based on the data from controlled clinical studies. In these studies, a statistically significant increase of serious cardiac disorders of 4 events per 1,000 patient treatment years (PY) was observed for the strontium ranelate group compared to placebo. The number of additional thromboembolic events associated with strontium ranelate treatment was also 4 per 1000 PY.

The PRAC considered that there were serious concerns about whether the contraindications and warnings implemented to mitigate cardiac and thromboembolic risks could be achievable in clinical practice, considering that strontium ranelate is intended for long-term treatment of a population of elderly patients whose cardiovascular status may deteriorate over time.

The PRAC concluded that when the identified serious risks, for which there are doubts that they can be adequately mitigated in view of the long-term treatment, are considered in the context of the modest benefit shown in terms of fracture prevention, the benefit-risk balance of strontium ranelate is negative.

Summary of recommendation(s)/conclusions

The PRAC adopted, by majority, a recommendation for the suspension of the marketing authorisations for Protelos and Osseor, to be considered by the CHMP. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

Twenty members/alternates, out of the 35 eligible to vote who were present in the room, voted in favour of the suspension together with Iceland and Norway, while fifteen members/alternates had divergent views[2].

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

None

[2] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded. CHMP opinion planned at the March 2014 meeting.

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Abatacept - **ORENCIA** (CAP)

- Signal of angioedema

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Background

Abatacept is an immunosuppressant (fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to a modified Fc portion of human immunoglobulin G1 (IgG1) used in the treatment of rheumatoid arthritis and polyarticular juvenile idiopathic arthritis in selected patients.

The exposure for Orencia, a centrally authorised medicine containing abatacept, is estimated to have been more than 200,000 patient-years worldwide, in the period from first authorisation in 2007 to 2013.

During routine signal detection activities, a signal of angioedema was identified by the EMA, based on 8 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of angioedema reported and noted that the product information for Orencia (abatacept) includes immune-mediated adverse reactions ranging from hypersensitivity, allergic reactions, to anaphylactic and anaphylactoid reactions (with potentially fatal outcome) as well as infusion related reactions including dyspnoea, wheezing and urticaria. In many of the reported cases of angioedema, a possible alternative aetiology could be identified. However, cases with positive rechallenge and a plausible biological mechanism suggested the possibility of a causal relationship. Therefore the PRAC agreed that the signal should be further investigated, especially regarding to the role of complement activation as well as any other possible biological mechanism.

Summary of recommendation(s)

- The MAH for Orencia (abatacept) should submit to the EMA a cumulative review of the signal of angioedema and related terms within the next PSUR (DLP 23/12/2013).

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

- Signal of vasculitis

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

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

Background

Duloxetine is an antidepressant used in the treatment of major depressive disorder as well as in the treatment of diabetic peripheral neuropathic pain, generalised anxiety disorder and in women for the treatment of moderate to severe stress urinary incontinence (SUI).

The exposure for centrally authorised medicine containing duloxetine is estimated to have been approximately 53 million patient-years worldwide, in the period from first authorisation in 2004 until 31 July 2012.

During routine signal detection activities, a signal of vasculitis was identified by the EMA, based on 19 cases including cutaneous vasculitis and leukocytoclastic vasculitis retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of vasculitis and concluded that in some of them a temporal relationship between the start of the treatment and the development of the reaction was apparent. In some of the cases vasculitis was confirmed by biopsies. However, some cases were confounded by concomitant medications known to be associated with vasculitis.

The PRAC agreed that in consideration of wide exposure for duloxetine the reports were few in absolute terms. Nonetheless it was judged appropriate to collect more detailed information on cutaneous small vessel vasculitis and to confirm the product information is still adequate.

Summary of recommendation(s)

- The MAHs for duloxetine-containing products should submit to the EMA, a cumulative review of the signal of cutaneous small vessel vasculitis within the next PSUR (DLP: 03/08/2014).

4.1.3. Fluticasone furorate - AVAMYS (CAP)

- Signal of oral and upper respiratory fungal infection

Regulatory details:
PRAC Rapporteur: Adam Przybylkowski (PL)

Background

Fluticasone furoate is a corticosteroid and Avamys is a centrally authorised nasal spray formulation of fluticasone furoate indicated for the treatment of the symptoms of allergic rhinitis in adults and adolescents (12 years and over) and children (6-11 years).
The exposure for Avamys is estimated to have been more than 2.9 million patient years worldwide, in the period from first authorisation in 2008 to 2011.

During routine signal detection activities, a signal of fungal infection disorders was identified by the EMA, based on 11 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of candidiasis and oesophageal candidiasis reported and considered that - based on a compatible temporal association and taking into account the plausibility of the biological mechanism underlying the reaction – a possible causal role of fluticasone furoate in the development of the adverse reaction could not be excluded.

Therefore the PRAC agreed that the signal of oral and upper respiratory fungal infections associated with the use of fluticasone furoate nasal spray should be further reviewed.

The relevance of this risk to other corticosteroid nasal spray formulations authorised in Europe will need to be further considered once a review is concluded.

Summary of recommendation(s)

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

4.1.4. Leuprorelin (NAP) suspension for injection

- Signal of medication errors - wrong technique in drug usage process

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Leuprorelin is a gonadotrophin-releasing hormone analogue used in the treatment of prostate cancer. The exposure for Eligard a nationally authorised medicine containing leuprorelin suspension for injection is estimated to have been more than 45 million patient-days worldwide, according from data available for the year 2008.

A signal of medication errors describing wrong technique in the drug administration process and potentially leading to the delivery of an insufficient dose was identified by ES based on 11 cases retrieved from the Spanish Pharmacovigilance System Database FEDRA database following a search triggered by a case reported to the Andalusian Regional Centre of Pharmacovigilance. The lead Member State for signal monitoring activities for leuprorelin confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reporting suspected wrong technique in the drug administration and reconstitution process. The vast majority of the cases reported were in the context of patients diagnosed with advanced prostate cancer and treated with Eligard, a nationally authorised product containing leuprolin acetate powder and solvent for subcutaneous injection. After several months of treatment, testosterone levels were increased above 'castration' levels (≤50 ng/dl) and/or prostate specific antigen (PSA) levels were increased. Considering the serious consequences of an incorrect technique in reconstitution or administration in advanced prostate cancer patients, the PRAC agreed that the root cause of this signal should be further investigated and the MAH of Eligard (leuprorelin) should submit a cumulative review of all cases of medication errors and discuss if the instructions about the product reconstitution and administration process need to be improved or simplified. Furthermore, the appropriateness of improvement in the presentation should be considered.

The PRAC appointed Carmela Macchiarulo (IT) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Eligard (leuprorelide acetate) should submit to the EMA, within 60 days, a cumulative review of all cases concerning medication errors, including a root cause analysis and propose risk minimisation measures.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.5. Pazopanib – VOTRIENT (CAP)

- Signal of retinal detachment and retinal tear

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Background

Pazopanib is a multi-target tyrosine kinase inhibitor used in the treatment of renal cell carcinoma and advanced soft tissue sarcoma in selected patients.

The post-authorisation exposure for Votrient a centrally authorised medicine containing pazopanib, is estimated to be 14,675 patient-years, in the period from first authorisation in 2010 to 2013.

During routine signal detection activities, a signal of retinal detachment and retinal tear was identified by the UK, based on 12 cases retrieved from the UK national database. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of suspected retinal detachment reported. A review of the individual case reports submitted to the MHRA revealed that the time to onset suggested a compatible temporal relationship. The PRAC noted that retinal detachment is an 'important potential risk' investigated in the RMP for another substance of the same pharmacological class. Moreover tyrosine-kinase receptor inhibitors bind to vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-α and –β, and stem cell factor receptor (c-KIT). This could provide a plausible biological mechanism underlying the reaction. Given these considerations the PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

- The PRAC agreed that this signal should be evaluated within the PSUR assessment procedure (DLP 18/10/2013).

4.2. New signals detected from other sources

4.2.1. Tenofovir disoproxil fumarate – VIREAD (CAP); Diclofenac (NAP)

- Signal of acute kidney injury caused by co-administration of tenofovir disoproxil fumarate and diclofenac - publication from Bickel et al, HIV Medicine 2013

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor, used in the treatment of HIV infection and chronic hepatitis B. TDF is part of a number of fixed combinations of centrally authorised medicines. The exposure for Viread, a centrally authorised medicine containing tenofovir, is estimated to have been more than 2 million patient-years worldwide, in the period from first authorisation in 2002 to 2013.

France brought a signal of acute kidney injury caused by co-administration of tenofovir disoproxil fumarate and diclofenac for initial analysis and prioritisation by the PRAC triggered by a recent publication by *Bickel et al*[4].

Discussion

The PRAC noted the retrospective analysis of data for all patients from the Frankfurt HIV Cohort who had diclofenac prescriptions between January 2008 and June 2012 as reported by *Bickel et al*. Among the 89 patients with diclofenac use, 61 patients (68.5 %) were treated with TDF and 28 patients (31.5 %) were treated with TDF-sparing combination antiretroviral therapy. A total of 13 patients treated with tenofovir experienced acute renal injury shortly after starting diclofenac although all had stable renal function. Even though the authors acknowledge some limitations in their study, mostly linked to the retrospective design, the analysis suggested that diclofenac may exacerbate TDF-associated nephrotoxicity through a drug-drug interaction. In addition to the inhibition of the efflux transporter, the reduced glomerular filtration induced by diclofenac but also by other nonsteroidal anti-inflammatory drugs (NSAIDs) may also contribute to increasing the nephrotoxicity of tenofovir.

The PRAC emphasised that tenofovir had already been associated with acute and chronic renal failure. Its renal toxicity seemed to be caused by proximal tubular injury that may lead to different manifestations such as Fanconi syndrome, hypophosphatemia, and normoglycaemic glycosuria attributable to impaired reabsorption of glomerular filtrate. Nevertheless, although prescribers are expected to be aware of the nephrotoxicity of NSAIDs and of the higher risk of renal toxicity in case of co-administration with TDF, a specific warning against the concomitant use of TDF and NSAIDs in the EU product information of concerned products was supported by this new evidence. The PRAc agreed that this could raise further awareness of prescribers to the potentially deleterious effects of co-administration.

Summary of recommendation(s)

- The MAH for the centrally authorised[5] tenofovir-containing medicines should be requested to submit to the EMA by 3 February 2014, a review of cases of renal injury reported in association with the concomitant use of tenofovir and NSAIDs, and of the available literature data, including a proposal for an update of the product information.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[4] Bickel M et al. Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac coadministration, HIV Medicine (2013), 14, 633-638

[5] 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.

4.3. Signals follow-up and prioritisation

4.3.1. Dexmedetomidine – DEXDOR (CAP)

- Signal of infantile apnoeic attack

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

For background information, see PRAC Minutes September 2013. The MAH responded to the request for information on the signal of infantile apnoeic attack and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the responses received and noted that the initial review provided by the MAH had not provided further supporting data to strengthen the original signal.

The PRAC noted, however, that the data submitted highlighted cases of apnoeic attack in other age groups than neonates, although full details of these cases had not been provided.

The PRAC also noted that other respiratory disorders have been observed with dexmedetomidine in patients of all ages. Therefore, PRAC recommended that further exploration is performed on the mechanism of action underlying respiratory related reactions, including apnoea, and whether this is influenced by age.

Summary of recommendation(s)

- The MAH for Dexdor (dexmetedomidine) should be requested to submit to the EMA within 60 days a further review to assess a possible causal association between dexmedetomidine and apnoea in all paediatric and adult patients.

4.3.2. Orlistat – ALLI (CAP), XENICAL (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Input from the Pharmacokinetic Working Party (PKWP) was sought following discussion of this signal at the October 2013 PRAC meeting. For background information, see PRAC Minutes 7-10 October 2013.

Discussion

The PRAC noted the input received from the PKWP, which highlighted the lack of robust data to demonstrate a clear pharmacokinetic interaction. The PRAC discussed the evidence and noted the lack of pharmacokinetic studies but considered that the available case reports described in the literature did provide some evidence to support the potential for orlistat containing medicines to reduce the efficacy of antiretroviral treatment.

In light of this, given the critical importance of adequate therapeutic management of HIV, and the subsequent risk of emergence of viral resistance, the PRAC recommended that a general warning should be introduced in the product information of orlistat containing products advising against the concomitant use of orlistat with HAART without careful consideration of the possible impact on their effectiveness.

Summary of recommendation(s)

- The MAHs for the reference centrally authorised[6] orlistat containing product should be requested to submit to the EMA within 60 days a variation to update the product information to address the signal[7].

For the full PRAC recommendations see EMA/PRAC/25732/2014 published on the EMA website on 28/01/2014.

4.3.3. **Tapentadol** (NAP)

- Signal of suicidal ideation and behaviour

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Background

For background information, see PRAC minutes of 7-10 October 2013.
The MAH replied to the request for information on the signal of suicidal ideation and behaviours and the responses were assessed by the Rapporteur.

Discussion

The PRAC noted that during the clinical development programme of tapentadol some adverse events associated with suicidality were reported. However these were equally distributed over all treatment groups including active comparators and placebo and therefore did not suggest a causal relationship between the therapeutic use of tapentadol and a risk of risk of suicidality. A review of individual case safety reports did not provide evidence in support of a causal association between tapentadol therapy and Review provide any convincing evidence to support a causal the onset of suicidality. The majority of the reports included information that provided plausible alternative explanations or confounding factors such as pre-existing psychiatric disorders, medications which have a known potential to induce psychiatric events, social circumstances or inadequate analgesia.

However, considering that apart from being a strong μ-opioid receptor agonist, tapentadol acts as a prominent norepinephrine reuptake inhibitor and has minimal effects on serotonin levels it cannot be excluded that tapentadol is associated with a similar risk for suicidal ideation and behaviour as observed for some antidepressants. Therefore this should be further investigated and considered in the risk management plan. Moreover, the PRAC agreed that further review of the safety concern "overdose" with tapentadol was needed.

[6] 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
[7] Section 4.4 and 4.5 of the SmPC and PIL

Summary of recommendation(s)

- The MAHs for the reference, nationally authorised[8] tapentadol containing medicine should be requested to submit to the NCAs of the MSs within 60 days a variation to update the RMP to further investigate of the safety concern "suicidal ideation and behaviour" as well as the safety concern "overdose" in the context of suicidality.

For the full PRAC recommendations see EMA/PRAC/25732/2014 published on the EMA website on 28/01/2014.

4.3.4. **Triamcinolone acetonide** (NAP)

- Signal of postmenopausal haemorrhage with parenteral use

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

For background information, see PRAC Minutes September 2013. The MAH replied to the request for information on the signal of postmenopausal haemorrhage with parenteral use and the responses were assessed by the Rapporteur.

Discussion

The PRAC noted that the post-marketing case reports of postmenopausal haemorrhage had been identified in association with the parenteral use of triamcinolone acetonide and that the pattern of reports differed to that on non-parenteral forms. Given the estimated patient exposure, the reporting rate for triamcinolone associated postmenopausal bleeding was considered potentially low but could not be exactly determined due to lack of detailed exposure data including information on the route of administration.

Furthermore, the PRAC noted that the post-marketing cases included a number of cases with positive dechallenge and positive rechallenge suggesting a causal relationship with the treatment. The cases with a potentially strong causal relationship included patients at least five years post menopause who experienced vaginal bleeding at an onset between three and eighteen days following administration of triamcinolone.

Evidence from the published literature suggested an increased risk of abnormal vaginal bleeding following treatment with triamcinolone. This includes a recently published paired observational retrospective cohort study using data from the Kaiser Permanente Northern California system that provided further evidence to support a causal association with triamcinolone and the risk of abnormal vaginal bleeding in both premenopausal and postmenopausal women (*Suh-Burgmann et al* Am J Obstet Gynecol 2013; 209:206.e1-6). Furthermore, published studies would indicate that systemic exposure to triamcinolone can result in an alteration of normal sex hormone physiology which may provide a potential biological explanation for the observed changes in menstrual bleeding patterns.

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

Given these findings the PRAC agreed that the product information of parenteral triamcinolone containing medicine for parenteral use should be updated. The PRAC agreed that the update to product information for parenteral triamcinolone products should not be such as to deter the appropriate investigation of postmenopausal bleeding.

Summary of recommendation(s)

- The MAHs for the nationally authorised triamcinolone containing medicine for parenteral use (intraarticular/intramuscular use)[9] should be requested to submit to the EMA within 60 days a variation to update the product information to include information regarding the risk vaginal haemorrhage[10].

For the full PRAC recommendations see EMA/PRAC/25732/2014 published on the EMA website on 28/01/2014.

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. Etarfolatide

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

5.1.3. Folic acid

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

5.1.4. Hepatitis B, surface antigen vaccine

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

5.1.5. Ketorolac trometamol, phenylephrine

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

[9] 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

[10] Sections 4.4, 4.8 of the SmPC and PIL

5.1.6. Naloxegol

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

5.1.7. Ramucirumab

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

5.1.8. Siltuximab –

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

5.1.9. Vintafolide

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

5.2. Medicines already authorised

RMP in the context of a PSUR procedure

See Cabazitaxel (JEVTANA); Galsulfase (NAGLAZYME); Paliperidone (INVEGA, XEPLION); Pegaptanib (MACUGEN); Pertuzumab (PERJETA); Roflumilast (DAXAS, DALIRESP, LIBERTEK); Ticagrelor (BRLILIQUE).

RMP in the context of a variation

5.2.1. Darbepoetin alfa – ARANESP (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Background

Darbepoetin alfa is an analogue of recombinant human erythropoietin (rHuEPO). Erythropoietins (epoetin alfa, beta, zeta, theta, darbepoetin alfa) are used in the treatment of anaemia in patients with cancer and other conditions.

The CHMP is evaluating a type II variation procedure for Aranesp, a centrally authorised product containing darbepoetin alfa, to include some amendments to the RMP following an update of the SmPC in relation to new data supporting a new dosing schedule for darbepoetin alfa for the correction phase in patients with chronic renal failure not on dialysis (adults only) based on results of a recently concluded clinical study. The safety of the higher weekly dose necessary for correcting and maintaining haemoglobin levels with a once monthly (QM) dosing regimen was added as missing information in the EU RMP. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The updated RMP version 4 for Aranesp (darbepoetin alfa) in the context of the variation under evaluation by the CHMP was considered acceptable.
- The PRAC noted that a meta-analysis using individual patient data, previously requested by the EMA as a post-authorisation measure to evaluate all cardiovascular risks based on haemoglobin

concentrations, was also added to the EU RMP as an additional pharmacovigilance activity to further inform on this safety concern.

5.2.2. Ranibizumab – LUCENTIS (CAP)

- Evaluation of an RMP in the context of a variation

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

Background

Lucentis is a centrally authorised product containing ranibizumab a monoclonal antibody used in the treatment of neovascular (wet) age-related macular degeneration (AMD); visual impairment due to diabetic macular oedema (DME); visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO); visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).

The CHMP is evaluating a type II variation procedure for Lucentis, in order to remove the recommendation to use topical antibiotics before treatment. Consequential changes to Annex II and the RMP are proposed to remove the related risk minimisation measures. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 12.2 for Lucentis (ranibizumab) in the context of the variation under evaluation by the CHMP was considered acceptable. Some minor points should be taken into account in the next update of the RMP.

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

See Abacavir (ZIAGEN) 8.1.1. ; Lapatinib (TYVERB) **Error! Reference source not found.**; Mecasermin (INCRELEX) ; Tocofersolan (VEDROP) **Error! Reference source not found.**

RMP in the context of a stand-alone RMP procedure

See ANNEX I 14

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[11]

6.1.1. 5-aminolevulinic acid – AMELUZ (CAP), NAP

- Evaluation of a PSUSA[12] procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

[11] 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
[12] PSUR single assessment, referring to CAP, NAP

Background

5-aminolevulinic acid is an antineoplastic agent indicated for the treatment of actinic keratosis on the face and scalp.

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of 5-aminolevulinic acid-containing products 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 5-aminolevulinic acid-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) for Ameluz (5-aminolevulinic acid) should be maintained. Nevertheless, the product information for nationally authorised medicinal products containing 5-aminolevulinic acid should be updated to add known photodermatoses and diseases precipitated or aggravated by exposure to sunlight such as lupus erythematosus or pemphigus erythematosus as a contraindication. In addition, the product information should be updated to reflect that the success and assessment of treatment may be impaired if the treated area is affected by the presence of skin diseases or tattoos, and to warn about the potential enhancement of phototoxic reactions to photodynamic therapy when 5-aminolevulinic acid is used concomitantly with medicinal products with known phototoxic or photoallergic potential. Therefore the current terms of the marketing authorisation should be varied[13].
- In the next PSUR, MAHs should closely monitor cases of post-treatment hypertension (APH), safety of repeated treatment for incompletely cleared lesions, and infections (particularly nasopharynigitis).
- MAHs with an RMP in place for their medicinal product should submit an updated RMP in the framework of an upcoming procedure, to reflect several changes, in particular, application site reaction should be added as an important identified risk, severe application site reaction in combination with photosensitizing medication or in patients with photodermatoses as a potential important risk; and safety in paediatric or adolescent patients, treatment of immunosuppressed patients, safety in patients with skin type I as missing information.

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

6.1.2. Fidaxomicin – DIFICLIR (CAP)

- Evaluation of a PSUR procedure

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

Background

Fidaxomicin is an antibiotic indicated in adults for the treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD).

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dificlir, a centrally authorised medicine containing fidaxomicin, 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 Dificlir (fidaxomicin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on possible hypersensitivity reactions to fidaxomixin in patients with a previous history of macrolide allergy. Therefore the current terms of the marketing authorisation should be varied[14].
- In the next PSUR, the MAH should provide a comprehensive review of cases of lack of or poor efficacy and of cases of reduced renal function/blood creatinine increase. The MAH should also provide a final study protocol of the planned PASS that will investigate the safety profile of fidaxomicin in patients with reduced renal function. In addition, the MAH should provide a review of fidaxomicin-treated patients with pseudomembranous colitis, life-threatening or fulminant disseminated intravascular coagulation (CDI) and a review of patients with mild to moderate CDI who deteriorate during fidaxomicin treatment. The MAH should closely monitor several undesirable effects, including cases of hypersensitivity and gastrointestinal adverse events.

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

6.1.3. Human hepatitis B immunoglobulin – ZUTECTRA (CAP), NAP

- Evaluation of a PSUSA procedure

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

Background

Human hepatitis B immunoglobulin is indicated for the prevention of hepatitis B virus (HBV) re-infection in HBV-DNA negative patients ≥ 6 months after liver transplantation for hepatitis B induced liver failure.

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of human hepatitis B immunoglobulin-containing products 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 human hepatitis B immunoglobulin-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.

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

- In the next PSUR, MAHs for nationally approved products should provide additional data as detailed in the PRAC assessment report.

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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.4. Human normal immunoglobulin – **FLEBOGAMMA DIF** (CAP), **HIZENTRA** (CAP), **KIOVIG** (CAP), **PRIVIGEN** (CAP), NAP

- Evaluation of a PSUSA procedure

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

Background

Human normal immunoglobulin is indicated for the replacement therapy in primary immunodeficiency syndromes with impaired antibody production, hypogammaglobulinaemia under certain conditions and congenital acquired immunodeficiency syndrome (AIDS) and recurrent bacterial infections. Human normal immunoglobulin is also indicated for immunomodulation in primary immune thrombocytopenia (ITP), Guillain Barré syndrome, Kawasaki disease and multifocal motor neuropathy (MMN).

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of human normal immunoglobulin-containing products 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 human normal immunoglobulin-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, MAHs are requested to provide additional information as detailed in the PRAC assessment report.

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. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – **GARDASIL** (CAP), **SILGARD** (CAP)

- Evaluation of a PSUR procedure

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

Background

Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) is indicated for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) types as well for the prevention of genital warts (condyloma acuminata) causally related to specific HPV types.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Gardasil and Silgard, centrally authorised human papillomavirus vaccines, 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 Gardasil and Silgard (human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- Nevertheless, the MAHs should submit to EMA within 60 days a detailed analysis of all cases of leukoencephalomyelitis/acute disseminated encephalomyelitis (ADEM) and transverse myelitis including information on time to onset in relation to number of doses given, and a causality assessment according to the revised WHO classification[15]. The review should also include an observed *vs* expected analysis performed on all cases as well as a literature review and discussion on the biological plausibility for an association between quadrivalent human papillomavirus vaccines and ADEM and transverse myelitis respectively. In addition, MAHs should propose further measures to characterise potential risks of ADEM and transverse myelitis and update the product information as appropriate. Moreover, the MAHs should submit to EMA within 60 days a detailed review of cases of postural orthostatic tachycardia syndrome (POTS), including diagnosed cases and cases of POTS-related symptoms and should develop a questionnaire to ensure a more systematic method of data collection for suspect cases.
- In the next PSUR, MAHs should report any information on congenital anomalies and should keep vaccination site reactions under close monitoring.

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

The PRAC agreed to request the MAH for Cervarix (human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)) to submit to EMA the same data relating to cases of ADEM and transverse myelitis within the next PSUR (DLP: 17/11/2013).

6.1.6. Nitric oxide – **INOMAX** (CAP), NAP

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Nitric oxide is indicated in conjunction with ventilatory support and other appropriate active substances for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation; and is also indicated as part of the treatment of peri- and post-operative pulmonary hypertension in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

[15] http://www.who.int/vaccine_safety/publications/aevi_manual.pdf

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of nitric oxide-containing products 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 nitric oxide-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- MAHs should review any future cases related to the Nitric Oxide Delivery System (NODS) device failures/malfunctions and any other device related issues and should discuss any related issues including device failure/malfunction, misuse or error in the next PSUR.
- In the next PSUR, the MAH for INOmax should discuss the issue of occupational exposure associated with the administration of inhaled NO taking into consideration literature and occupational health guidelines.
- MAHs with an RMP in place for their medicinal product should ensure that NO_2 formation is listed correctly as an important identified risk in order to ensure consistency with the current approved RMP for the innovator medicinal product INOmax.

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[16]

6.2.1. **Sugammadex – BRIDION** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Background

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

Summary of recommendation(s) and conclusions

Based on the conclusion of the PRAC rapporteur, the PRAC considered that no changes to the product information are warranted at the time in the light of the current knowledge. In the next PSUR, the MAH should continue to closely monitor all hypersensitivity-related events and include a cumulative review.

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

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[17]

7.1.1. Defibrotide – DEFITELIO (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Defitelio is a centrally authorised medicine containing defibrotide indicated for the treatment of severe hepatic veno-occlusive disease (VOD), also known as sinusoidal obstructive syndrome (SOS) in haematopoietic stem-cell transplantation therapy (HSCT). Defitelio is a medicine with an orphan designation authorised under exceptional circumstances.

A draft protocol for a patient registry study to investigate the long term safety, health outcomes and patterns of utilisation of defibrotide during normal use was assessed by the Rapporteur and presented for review by the PRAC.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.0 - in accordance with Article 107n of Directive 2001/83/EC, considered that the study is non-interventional and the PASS protocol can be endorsed with minor changes. In particular the PRAC stressed that despite challenges posed by recruitment, a comparator arm was necessary since historical controls were used in the clinical development. The limitations associated with the control group (challenges in the selection of an appropriate control group with the risk of selection bias and potential for selective prescribing) would be far outweighed by the value of the data that will be obtained.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 15 days to the EMA. A 30 day-assessment timetable will be applied.

7.1.2. Imatinib – GLIVEC (CAP)

- Evaluation of an imposed PASS protocol

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

Background

Glivec is a centrally authorised medicine containing imatinib indicated for the treatment of bcr-abl positive chronic myelogenous leukaemia, gastrointestinal stromal tumours (GIST), myelodysplastic-myeloproliferative diseases, dermatofibrosarcoma, precursor cell lymphoblastic leukaemia-lymphoma and hypereosinophilic syndrome.

The protocol for a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ acute lymphoblastic leukaemia (ALL) patients, treated with chemotherapy

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

with imatinib plus or minus hematopoietic stem cell treatment was assessed by the Rapporteur and presented for review by the PRAC. In November 2013 some amendments to the protocol were requested to clarify the rationale and background, clarify data on exposure that will be recorded, and to provide a data validation plan. An updated version was submitted by the MAH.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 00 - in accordance with Article 107n of Directive 2001/83/EC -, considered that the study is non-interventional and the PASS protocol can be endorsed.

7.1.3. Lenalidomide – REVLIMID (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

For background, see PRAC minutes 4-7 November 2013. A revised protocol was submitted by the MAH following PRAC objection. The original proposed study was divided in two parts: a prospective disease registry and a retrospective drug utilisation study (DUS) to describe the pattern of use of lenalidomide in routine clinical practice in the treatment of patients with myelodysplastic syndromes (MDS) in the countries concerned. A synopsis for this drug utilisation study was proposed which was assessed by the Rapporteur and presented for review by the PRAC, together with the revised PASS (prospective MDS disease registry) protocol.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft PASS protocol Amendment 1 (Version 2.0), - in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol, as the PRAC considered that some issue remain to be addressed.

In particular, the PRAC recommended that the protocol should include a discussion on proposed lost to follow-up rate (5 %), updating accordingly the number of patients to be enrolled (if applicable) and discuss measures to be implemented if the observed lost to follow-up rate is higher than the expected one.

The MAH should submit a revised PASS protocol within 30 days to the EMA and a 30 day-assessment timetable will be applied.

Regarding the DUS synopsis, the PRAC commented on the design and data sources. Taking into account that, in the meantime, the MAH has already submitted a draft protocol, further discussion is expected on this study at the February 2014 PRAC meeting.

7.1.4. Levonorgestrel (NAP)

- Evaluation of an imposed PASS protocol

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

Background

Jaydess is a nationally authorised intrauterine contraceptive system (LCS12) containing levonorgestrel. As part of the post approval commitments to the marketing authorisation, a study was requested to further investigate whether there are differences in unintended pregnancy rates with LSC12 compared to the levonorgestrel-releasing intrauterine system Mirena or copper intrauterine devices (IUD). The MAH submitted a protocol for a study (EURAS-LCS12 European Active Surveillance Study of LCS-12) that was assessed by SE and presented for PRAC review.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1 dated 15 February 2013 - in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the PRAC considered that the design did not fulfil the study objectives.

The PRAC therefore recommended a number of points to be addressed regarding the design of the study and data collection. The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 day-assessment timetable will be applied.

The PRAC appointed Ulla Wändel Liminga (SE) as PRAC Rapporteur for any follow-up of the procedure.

7.1.5. **Nomegestrol, estradiol – IOA** (CAP), **ZOELY** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

For background, see PRAC Minutes April 2013.

As requested, the MAH submitted a revised protocol of the PASS study which was assessed by the Rapporteur and presented for review by the PRAC.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version ZEG2013_08 dated 11 October 2013 in accordance with Article 107n of Directive 2001/83/EC, considers that the study is non-interventional and the PASS protocol can be endorsed subject to the following amendments. In addition to recruitment of study participants via gynaecologists, the study is also to recruit study participants via general practitioners. The PRAC agreed that the study focus of the PASS should be the primary endpoint venous thromboembolism, and thus there should not be further delay to start the study in relation to additional secondary endpoints.

The PRAC therefore recommended that a final protocol version, taking into account these amendments is submitted to the EMA by 6 February 2014.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[18]

7.2.1. Bivalirudin – ANGIOX (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Background

Angiox is a centrally authorised medicine containing bivalirudin, a thrombin inhibitor indicated in combination as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. Angiox is also indicated for the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention.

As part of the RMP for Angiox, the MAH submitted a protocol for a study, Eurovision 2, to assess current drug utilisation patterns of Angiox in the EU when used for PCI, following implementation of new risk minimisation measures.

The study objectives are in particular to assess the frequency of bolus-only dosing without subsequent infusion and to assess the frequency of dose adjustment in renally impaired patients. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC considered that a small number of issues in the study design remain to be addressed although the majority have been addressed following previous comments of the Rapporteur. A revised PASS protocol should be resubmitted within 30 days and will follow a 60 day-PRAC review procedure.

7.3. Results of PASS imposed in the marketing authorisation(s)[19]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[20]

See ANNEX I - 16

7.5. 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[21]

7.5.1. Epoetin beta – NEORECORMON (CAP)

- Evaluation of interim PASS results

[18] 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
[19] In accordance with Article 107p-q of Directive 2001/83/EC
[20] 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
[21] In line with the revised variations regulation for any submission before 4 August 2013

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Background

Neorecormon is an analogue of recombinant human erythropoietin (rHuEPO). Erythropoietins (epoetin alfa, beta, zeta, theta, darbepoetin alfa) are used in the treatment of anaemia in patients with chronic renal failure, cancer and other conditions.

As part of the RMP for Neorecormon, the MAH submitted a report on safety data investigating retinopathy to address the potential for a risk of retinopathy of prematurity (ROP), in preterm infants receiving epoetins and the potential for a risk of retinopathy in diabetic patients receiving epoetins, which was assessed by the Rapporteur. The PRAC will provide advice to the CHMP based on these results.

Summary of advice

The PRAC agreed that the current evidence does not allow excluding a possible increase in the risk of retinopathy of prematurity with early treatment initiation of epoetins in preterm infants. Furthermore the use of epoetins in prematurity, in regard to this possible increased risk, is a matter of concern. As an outcome of this assessment, the MAH is requested to update the product information and to revise the posology and administration section in relation to early treatment initiation in preterm infants.

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

8.1.1. Abacavir – ZIAGEN (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Background

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) indicated in antiretroviral combination therapy for the treatment of human immunodeficiency virus (HIV) infection.

Ziagen, a centrally authorised medicine containing abacavir, was authorised in 1999.

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

Summary of advice

Based on the review of the available pharmacovigilance data, the risk management system for Ziagen (abacavir), and the CHMP Rapporteur's assessment report, the PRAC considered that the marketing authorisation(s) of Ziagen (abacavir) could be renewed for unlimited validity provided that section 4.6 of the SmPC on 'fertility, pregnancy and lactation' is updated taking into account clinical experience gained over time on exposed pregnancies, that product information Annex II key elements of the educational material on hypersensitivity reactions is revised according to the SmPC and that the RMP is updated in line with these changes.

9. Product related pharmacovigilance inspections

None

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

None

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

11.1. Safety related variations of the marketing authorisation

11.1.1. **Cyproterone, ethinylestradiol** (NAP)

- PRAC consultation on a variation worksharing procedure, on Member State's request

Regulatory details:
Lead member: Menno van der Elst (NL)

Background

Following the conclusion of the referral procedure under Article 107i of Directive 2001/83/EC for cyproterone 2mg / ethinylestradiol 35 mcg-containing products (PRAC Minutes May 2013), MAH(s) were requested, as part of the conditions to the marketing authorisations, to submit core elements (including outlines for a DUS, PASS and educational materials) of an RMP in EU format, as well as educational materials for prescribers and patients highlighting the risks and warnings of thromboembolism within 90 days of the EC decision issued on 25 July 2013.

The brandleader MAH submitted an EU RMP version 1.0 for all its cyproterone, ethinylestradiol (2 mg/0.035mg)-containing products authorised in the EU, which was assessed by the MEB (Dutch Medicines Agency) acting as reference authority via a worksharing variation. This includes protocol synopses for a PASS to measure physicians' knowledge of the identified risks of venous thromboembolism (VTE) and arterial thromboembolism (ATE), and for a DUS to characterise prescribing behaviour, especially in relation to the potential risk of 'off-label use'. Both studies are regarded as studies that measure the effectiveness of risk minimisation measures (RMM).

Once endorsed, this RMP will be used as a model for all other cyproterone, ethinylestradiol (2 mg/0.035 mg)-containing products (generics). NL sought advice from the PRAC.

Summary of advice

The PRAC agreed with the MEB assessment of the educational materials, including the use of a prescriber checklist and patient information card and also endorsed the MEB request to increase the sample size of the drug utilisation study (DUS) and a proposal to amend the design of the PASS from a survey to a database study.

The PRAC welcomed the progress on collaboration between MAHs regarding the development of joint study protocols.

11.2. Other requests

11.2.1. **Cefepime** (NAP)

- PRAC consultation on a PSUR worksharing procedure, on Member State's request

Regulatory details:
Lead member: Margarida Guimarães (PT)

Background

In in 2011 the PhVWP, upon request of the lead MS in the context of a PSUR worksharing procedure, discussed the issue of the use of cefepime in elderly patients with renal impairment. The PhVWP concluded that in the light of the knowledge at the time, there was not a sufficient body of evidence supporting a higher risk of all-cause mortality for cefepime vs. other antibiotics. The PhVWP considered that additional data from the MAH were required, in particular relating to the elderly population, and ADR stratification according to the risk of chronic renal failure. In addition, the MAH should further investigate efficacy/clinical failure as well as pharmakinetic and pharmacodynamic data in the compromised population.

Following assessment of the requested data, including the meta-analysis of all-cause mortality of cefepime compared to other antibiotics and related analysis as well as the FDA requested study on the risk of all-cause mortality among hospitalised patients treated with cefepime, ceftazidime, other cephalosporins or parenteral antibiotics in the USA, PT sought advice from the PRAC.

Summary of advice

In the light of the currently available data, the PRAC did not consider there is sufficient evidence supporting the existence of a higher risk of all-cause mortality for cefepime *vs.* other antibiotics although it could not be excluded. The PRAC considered it was premature to reinforce the product information to health professionals on the risk of using monotherapy cefepime in febrile neutropenic patients.

The PRAC considered it appropriate to consult the Infectious Disease Working Party (IDWP) to obtain their input on the use of monotherapy cefepime in febrile neutropenic patients and adopted a list of questions to be transmitted to IDWP.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. Outcome from the Informal PRAC meeting

- Action plan following the CHMP and PRAC informal meetings in Lithuania, October 2013

At the organisational matters teleconference held on 22 January 2014, the EMA secretariat presented to PRAC for endorsement a consolidated document with input from the MSs summarising the actions taken from the PRAC and CHMP informal meetings dated October 2013. The next steps include developing further these topics with the PRAC and EMA sponsors identified in line with the proposed timelines. Follow-up discussion is planned at PRAC in March 2014.

12.2. Pharmacovigilance audits and inspections

12.2.1. Pharmacovigilance Inspections

12.2.1.1. Union Procedure on Follow-up to Pharmacovigilance Inspections

- Union procedure on the management of pharmacovigilance inspection findings with potential significant impact on the benefit-risk profile of the concerned medicinal products

The topic was deferred to the February 2014 PRAC meeting.

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

12.3.1. Periodic Safety Update Reports

12.3.1.1. PSUR single assessment of substances contained in both centrally and nationally authorised products (PSUSA)

The EMA Secretariat presented to PRAC proposed criteria for the handling of the PSUR submissions when part of the PSUR single assessment (PSUSA)[22] procedures, based on the experience gained, and made some proposals for improvement. The PRAC acknowledged the difficulties to manage submissions, as well as late submissions of PSURs for CAPs and/or NAPs as defined in the EURD list and stressed the need to make the PSUR common repository available as soon as possible and consider possible measures for compliance related issues. The EMA is currently reviewing its procedural guidance to NCAs and stakeholders to ensure the best handling of such procedures and increase the knowledge amongst stakeholders by contacting the relevant industry trade associations as applicable. Follow-up is provisionally planned for the March/April 2014 meeting.

The EMA Secretariat also gave a presentation to PRAC on the handling of comments or requests for an updated or new RMP within PSUSA procedures. As a transitional measure, the current European Medicines Agency post-authorisation procedural advice for users of the centralised procedure, Rev 38, February 2014 recommends that MAHs do not submit to EMA an RMP with their individual PSUR part of a PSUSA procedure. During PSUSA assessment, the Rapporteur/PRAC may identify the need for an updated RMP/new RMP. Standard wording will be reflected in the next revision of the PSUR AR template and for inclusion in a future revision of the EMA procedural guidance.

12.3.1.2. Revised PSUR Assessment Report template[23]

The PRAC endorsed the new PSUR Assessment Report template which includes an optional section on RMP to be included when an updated RMP has been submitted alongside the PSUR. This combined PSUR/RMP AR template has been developed to bring it in line with the revised variations regulations, to simplify and clarify some sections of the template. This template replaces the previous version and should be used for any starting or ongoing PSUR and PSUSA procedures due for PRAC recommendation.

This template will be also published on the following EMA webpage: Templates for Assessors.

12.3.2. Union Reference Date (EURD) List

- Consultation on the draft List, version January 2014

[22] Referring to procedures with CAP, NAP
[23] Including RMP section (as applicable) in line with the revised variations regulation

The EMA Secretariat presented to PRAC a draft revised EURD list version January 2014 reflecting the PRAC comments impacting DLP and PSUR submission frequencies of the substances / combinations. The PRAC discussed the upcoming PSUR single assessment (PSUSA)[24] procedures with allocated PRAC Rapporteur MS and Rapporteurs' name in accordance with the principles previously endorsed by the PRAC (see PRAC Minutes April 2013). The PRAC endorsed the updated EURD list, version January 2014.

Post-meeting note: following the PRAC meeting in January 2014, the updated EURD list was adopted by the CHMP at its January 2014 meeting and was published on the EMA website on 31/01/2014 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.4. Signal Management

12.4.1. Signal Management

- Feedback from Signal Management Review Technical (SMART) Working Group
- Consultation on flow charts and definitions for signal Management (SMART WS2)

PRAC was given feed-back from the December 2013 SMART Working Group meeting highlighting the 'Strengthening Collaborations for Operating Pharmacovigilance in Europe' (SCOPE) project, a joint action funded by the EC to facilitate and improve implementation and compliance with the (new) pharmacovigilance legislation which includes several work packages, amongst which, WP4 on ADR collection (HR: lead MS) and WP5 on signal management (NL: lead MS) which are considered of particular relevance for SMART. HR and NL PRAC members agreed to provide regular updates to SMART and provide feedback from SMART to the SCOPE WP teams in order to facilitate efficient progress and prevent duplication of work. In addition SMART discussed additional monitoring, tracking of signals and aspects of the timetables for signals assessment.

The EMA Secretariat also consulted PRAC in writing on draft versions of definitions and flow charts for signal management in the EU. PRAC Delegates were invited to send any comments until 24 January 2014.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. List of Product under Additional Monitoring

- Consultation on the draft List, version January 2014

The PRAC was informed of the products newly added to the additional monitoring list and the updated list. Post-meeting note: The updated additional monitoring list was published on 29/01/2014 on the EMA website (see: Home>Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.6. EudraVigilance Database

12.6.1. Pharmacovigilance legislation implementation planning

- IT-related requirements for adverse reaction reports collection and analysis

[24] Referring to procedures with CAP, NAP

At the organisational matters teleconference held on 22 January 2014, the EMA secretariat presented to PRAC an update on the progress in planning the IT implementation of the pharmacovigilance legislation, providing high level business process requirements. The requirements have been separated into two separate categories as ADR management (ADR) and signal management (SM) for the EudraVigilance deliverables. The detailed processes aim to ensure that every activity carried out by the EMA is traceable to a reference in the applicable GVP modules or to the requirements outlined in the document detailing the EudraVigilance functionalities to the audited (currently being drafted). The PRAC was invited to provide comments by 31 January 2014. To facilitate the review, EMA informed the PRAC of a webinar organised on 24 January 2014. EMA will provide in due course a high-level plan including the milestones of when PRAC will be further consulted on the project deliverables.

12.7. Risk Management Plans and Effectiveness of risk Minimisations

12.7.1. Risk Management Systems

12.7.1.1. Progressive multifocal leukoencephalopathy (PML): possibilities for monitoring and labelling

- Development of an evidence-based strategy

The EMA Secretariat provided an update on the activities of the PML consortium, a joint effort between several MAHs. A project to develop an evidence-based regulatory is also on-going and currently finalising PML case validation. A PML labelling strategy is under preparation and will be presented to the plenary at a later stage.

12.7.2. Tools, Educational Materials and Effectiveness Measurement for Risk Minimisation

12.7.2.1. Publication of RMP summaries – process implementation

The preparation and publication of RMP summaries are described in Article 26 of Regulation (EU) 726/2004 and Article 106 of Directive 2001/83/EC requiring MSs and EMA to make public by means of a web-portal RMP summaries for medicinal products authorised in the EU.

The EMA Secretariat presented to PRAC the implementation plan to publish a RMP summary for every CAP newly authorised from December 2013 or updated according to specific criteria (e.g. new indications, new/updated contraindications, new important risks or important changes to known risks). For products already authorised and for which a RMP summary does not currently exist, the same criteria will be used to produce and publish a RMP summary. EMA will announce the publication of the first RMP summaries on the EMA website. EMA will analyse the experience gained after 1 year of pilot phase operation (1Q2015).

12.8. Post-authorisation Safety Studies (PASS)

12.8.1. Non-imposed PASS required in RMP

- Management of non-imposed PASS

At the organisational matters teleconference held on 22 January 2014, the ES PRAC member, D Montero Corominas, gave a presentation on the management of category 3 PASS (non-imposed PASS required in the RMP) discussing the possibility to modify the procedural timetable for the review of the protocols, allowing more adequate time for review by PRAC members. EMA Secretariat will further review these proposals and plan follow-up discussion in due time.

12.9. Community Procedures

12.9.1. Practical implementation of urgent union procedures and Article 31 pharmacovigilance referral procedures

- Questions and answers documents on practical implementation

At the organisational matters teleconference held on 22 January 2014, the EMA Secretariat presented the Questions & answers on practical implementation of Urgent Union Procedure (Article 107i of Directive 2001/83/EC) (EMA/720443/2012 – Rev.1) and Questions & answers on practical implementation of pharmacovigilance referral procedure (Article 31 of Directive 2001/83/EC) (EMA/33617/2014) recently published on the EMA.

12.9.2. Union referral procedures: dossier submission requirements for centrally authorised products (CAPs) and nationally authorised products (NAPs)

- Refinement of the dossier submission requirements for referral procedures

At the organisational matters teleconference held on 22 January 2014, the EMA Secretariat presented a document entitled 'dossier requirements for referral procedures submission for CHMP and PRAC' delegates. PRAC delegates were invited to provide comments by 24 January 2014. This document will be linked to the Questions and Answers (see under 12.9.1.)

12.10. Risk communication and Transparency

None

12.11. Continuous pharmacovigilance

None

12.11.1. Marketing cessation / withdrawal notification

- Cases of batch-specific recalls

At the organisational matters teleconference held on 22 January 2014, the EMA secretariat was requested to clarify the status of batch-specific recalls and the potential implications in the context of the marketing cessation/withdrawal notification process. Indeed, MAHs have to notify competent authorities of any temporary or permanent cessation of marketing of a medicinal product, of suspension of marketing, of withdrawal of a product from the market or of request for the withdrawal of a MA or non-application for the renewal of a MA. The matter is under further consideration and follow-up discussion is planned in May 2014. Current guidance can be found on the EMA website at: Marketing and cessation notification: questions and answers.

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Paediatric Committee (PDCO)

- Concept paper on revision of the guideline on conduct of pharmacovigilance for medicines used by the paediatric population

The EMA Secretariat presented to PRAC a draft concept paper on the revision of the guideline on conduct of pharmacovigilance for medicines used by the paediatric population. The concept paper was drafted by D Mentzer (PDCO), with input from the UK and Latvian PRAC members. PRAC delegates were invited to provide comments by 16 January 2014. A revised version of the concept paper will be presented to PRAC and PDCO for agreement after implementation of the comments. Timelines aim at presenting a draft revised guideline to the CHMP in July 2014.

12.12.2. Blood Products Working Party (BPWP)

- Intravenous immunoglobulins and haemolysis – Draft strategy

The EMA Secretariat informed the PRAC of the organisation of a workshop on 28-29 January 2014 by the FDA on 'strategies to address haemolytic complications of immune globulin infusions' where the EU experience on epidemiology and risk factors for immunoglobulin-related haemolysis will be presented.

12.12.3. Healthcare Professionals Working Party (HCPWP)

- HCPWP draft work plan 2014

The PRAC endorsed the work plan as proposed, and emphasised the importance of involving healthcare professionals' representatives in strategic discussions on risk communication and DHPCs.

12.12.4. Patients' and Consumers' Working Party (PCWP)

- PCWP draft work plan 2014

The PRAC endorsed the work plan as proposed.

12.12.5. Vaccine Working Party (VWP)

- Explanatory note on the withdrawal of the 'Note for Guidance on Harmonisation of Requirements for Influenza Vaccines' (CPMP/BWP/214/96) and of the Core SmPC/PIL for inactivated seasonal influenza vaccines (CMDh/128/2003/Rev5 and CMDh/129/2008/Rev3)

The EMA secretariat presented to PRAC the revised explanatory note on the withdrawal of the 'note for guidance on harmonisation of requirements for influenza vaccines'. PRAC agreed to the explanatory note, provided modifications highlighted in the course of the discussion were introduced. Specifically PRAC recommended that MAHs put in place robust plans from 2014-2015 influenza season for ensuring adequate risk management and enhanced collection of safety data for the concerned products. PRAC also recommended a small group of PRAC delegates/experts should prepare a new guidance document providing principles on the requirements for MAHs' enhanced safety surveillance with the aim to append it to the GVP module on vaccines. A draft version document will be presented to the PRAC in February/March 2014 so that MAHs are informed of the new requirements by end of March 2014.

12.13. Interaction within the EU regulatory network

12.13.1. Pharmacovigilance Audit Facilitation Group (PAFG)

- Standardisation for preparing, performing and reporting pharmacovigilance audits to European Commission

Following previous discussion (see PRAC Minutes May 2013), the HU PRAC member J Pallos presented a progress report to PRAC on the activities of the PAFG, in particular on risk rating for internal audits currently under development, following the principle of a risk based approach. As per the proposal, PRAC discussed frequencies for audit of pharmacovigilance processes defined in GVP modules based on three broad categorisations, with consideration of likelihood and impact of a failure within the process. PRAC delegates were invited to provide comments in writing by 23 January 2014. Further discussion is planned in March 2014.

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

12.14.1. Innovative Medicines Initiative (IMI): Accelerated development of vaccine benefit-risk collaboration in Europe (ADVANCE) project

The EMA Secretariat provided PRAC with an update on the IMI project of Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE). EMA described the partners involved in the project and presented an outline of the workplan. In December 2013, the European Centre of Prevention and Control (ECDC) invited all NCAs to express interests in being part of one or more review panels by 15 January 2014.

13. Any other business

13.1.1. EMA move in 2014 to new building

The EMA Secretariat provided an outline of the EMA move to Churchill Place in Canary Wharf, London, planned during summer 2014.

ANNEX I

14. List of other advice and recommendations adopted at the meetingANNEX 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(s).

14.1.1. Lurasidone

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

14.1.2. Olaparib

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

14.1.3. Riociguat

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

14.1.4. Simeprevir

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

14.1.5. Umeclidinium bromide

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

14.1.6. Umeclidinium bromide, vilanterol

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

14.1.7. Zoledronic acid

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

14.2. Medicines already authorised

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

RMP in the context of a PSUR procedure

Not applicable

RMP in the context of a variation

14.2.1. Cabazitaxel – JEVTANA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

14.2.2. Capecitabine – XELODA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.3. Catridecacog – NOVOTHIRTEEN (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)
Adopted via written procedure on 17/01/2014

14.2.4. Dabigatran – PRADAXA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.5. Dabigatran – PRADAXA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.6. Dabrafenib – TAFINLAR (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.7. Emtricitabine, efavirenz, tenofovir – ATRIPLA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.8. Eslicarbazepine – ZEBINIX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

14.2.9. Filgrastim – GRASTOFIL (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

14.2.10. Insulin degludec – TRESIBA (CAP)

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

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

14.2.11. Ivacaftor – KALYDECO (CAP)

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

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

14.2.12. Ivacaftor – KALYDECO (CAP)

- Evaluation of an RMP in the context of a variation

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

14.2.13. Ivacaftor – KALYDECO (CAP)

- Evaluation of an RMP in the context of a variation

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

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

- Evaluation of an RMP in the context of a variation

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

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

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

14.2.16. Ofatumumab – ARZERRA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.17. Omalizumab – XOLAIR (CAP)

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

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

14.2.18. Posaconazole – NOXAFIL (CAP)

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

Regulatory details:
PRAC Rapporteur: Julia Dunne (UK)

14.2.19. Rituximab – MABTHERA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

14.2.20. Sorafenib – NEXAVAR (CAP)

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

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

14.2.21. Ustekinumab – STELARA (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

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

14.2.22. Eptotermin alfa – OSIGRAFT (CAP)

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

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

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 remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. 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).

Evaluation of PSUR procedures[25]

15.1.1. Aflibercept – EYLEA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

15.1.2. Ambrisentan – VOLIBRIS (CAP)

- Evaluation of a PSUR procedure

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

15.1.3. Belatacept – NULOJIX (CAP)

- Evaluation of a PSUR procedure

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

[25] 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

15.1.4. Bromelain enriched proteolytic enzymes preparation from ananas comosus – NEXOBRID (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

15.1.5. C1 inhibitor, human – CINRYZE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

15.1.6. Cabazitaxel – JEVTANA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

15.1.7. Caffeine – PEYONA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Harald Herkner (AT)

15.1.8. Canakinumab – ILARIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

15.1.9. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type b conjugate vaccine (adsorbed) – HEXACIMA (CAP), HEXAXIM (Art 58), HEXYON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

15.1.10. Ferumoxytol – RIENSO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

15.1.11. Galsulfase – NAGLAZYME (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julia Dunne (UK)

15.1.12. Icatibant – **FIRAZYR** (CAP)

- Evaluation of a PSUR procedure

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

15.1.13. Influenza vaccine (live attenuated, nasal) – **FLUENZ** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

15.1.14. Liraglutide – **VICTOZA** (CAP)

- Evaluation of a PSUR procedure

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

15.1.15. Nepafenac – **NEVANAC** (CAP)

- Evaluation of a PSUR procedure

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

15.1.16. Omalizumab – **XOLAIR** (CAP)

- Evaluation of a PSUR procedure

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

15.1.17. Paliperidone – **INVEGA** (CAP), **XEPLION** (CAP)

- Evaluation of a PSUR procedure

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

15.1.18. Pegaptanib – **MACUGEN** (CAP)

- Evaluation of a PSUR procedure

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

15.1.19. Pertuzumab – **PERJETA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

15.1.20. Ranibizumab – LUCENTIS (CAP)

- Evaluation of a PSUR procedure

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

15.1.21. Roflumilast – DALIRESP (CAP), DAXAS (CAP), LIBERTEK (CAP)

- Evaluation of a PSUR procedure

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

15.1.22. Sildenafil – REVATIO (CAP)

- Evaluation of a PSUR procedure

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

15.1.23. Ticagrelor – BRILIQUE (CAP)

- Evaluation of a PSUR procedure

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

15.1.24. Tobramycin – TOBI PODHALER (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

15.2. Follow-up to PSUR procedures[26]

15.2.1. Aclidinium bromide – BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

15.2.2. Anidulafungin – ECALTA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

15.2.3. Caspofungin – CANCIDAS (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

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

15.2.4. Infliximab – REMICADE (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

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

Since all comments received on the assessment of these measures were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below.

Protocols of PASS imposed in the marketing authorisation(s)[27]

16.1.1. Tigecycline – TYGACIL (CAP)

- Evaluation of an imposed PASS protocol

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

16.1.2. Deferasirox – EXJADE (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Outcome finalised via written procedure on 15 January 2014.

Protocols of PASS non-imposed in the marketing authorisation(s)[28]

16.2.1. Eltrombopag – REVOLADE (CAP)

- Evaluation of a PASS protocol

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

16.2.2. Eltrombopag – REVOLADE (CAP)

- Evaluation of a PASS protocol

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

[27] In accordance with Article 107n of Directive 2001/83/EC
[28] 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. Eltrombopag – REVOLADE (CAP)

- Evaluation of a PASS protocol

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

16.2.4. Eltrombopag – REVOLADE (CAP)

- Evaluation of a PASS protocol

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

16.2.5. Eltrombopag – REVOLADE (CAP)

- Evaluation of a PASS protocol

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

16.2.6. Golimumab – SIMPONI (CAP)

- Evaluation of a PASS protocol

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

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

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

16.2.8. Voriconazole – VFEND (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

16.3. Results of PASS imposed in the marketing authorisation(s)[29]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[30]

16.4.1. Lomitapide – LOJUXTA (CAP)

- Evaluation of PASS results

[29] In accordance with Article 107p-q of Directive 2001/83/EC
[30] 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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

16.4.2. Maraviroc – CELSENTRI (CAP)

- Evaluation of PASS results

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

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[31]

16.5.1. Epoetin theta – BIOPOIN (CAP), EPORATIO (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

16.5.2. Infliximab – REMICADE (CAP)

- Evaluation of interim PASS results

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

16.5.3. Mannitol – BRONCHITOL (CAP)

- Evaluation of interim PASS results

Status: *for discussion and agreement of advice to CHMP*

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

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. Clopidogrel – CLOPIDOGREL ACINO (CAP)

- PRAC consultation on a renewal of the marketing authorisation

[31] In line with the revised variations regulation for any submission before 4 August 2013

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

17.1.2. Clopidogrel – CLOPIDOGREL RATIOPHARM GMBH (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

17.1.3. Clopidogrel –CLOPIDOGREL TEVA PHARMA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

17.1.4. Everolimus – AFINITOR (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

17.1.5. Lapatinib – TYVERB (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

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

17.1.6. Mecasermin – INCRELEX (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

17.1.7. Raltegravir – ISENTRESS (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

17.1.8. Repaglinide – REPAGLINIDE TEVA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

17.1.9. Tocofersolan – VEDROP (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

17.1.10. Topotecan – TOPOTECAN ACTAVIS (CAP)

- PRAC consultation on a renewal of the marketing authorisation

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

ANNEX II – List of participants:

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 6-9 January 2014 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:	agents acting on the renin-angiotensin system, riociguat, sorafenib, aflibercept, levonorgestrel, cyproterone, ethinylestradiol, cefepime
Veerle Verlinden	Belgium	Full involvement	
Yuliyan Eftimov	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Eva Jirsovà	Czech Republic	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Valerie Strassman	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	
Jelena Ivanovic	Italy	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Nadine Petitpain	Luxembourg	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der	Netherlands	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*
Elst			
Ingebjørg Buajordet	Norway	Full involvement	
Pernille Harg	Norway	Full involvement	
Kamila Czajkowska	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Nicolae Fotin	Romania	Full involvement	
Roxana Stroe	Romania	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	
Julie Williams	United Kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting:**	**Topics on the current Committee Agenda for which restriction applies** *Product / substance*
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise (Marieke) De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer-reviewer for:	albiglutide, dabrafenib, eltrombopag
Birgitte Keller-Stanislawski		Full involvement	
Hervé Le Louet		Cannot act as Rapporteur or Peer-reviewer for:	lenalidomide
Lennart Waldenlind		Full involvement	

Additional European experts participating at	**Country**

the meeting for specific Agenda items		
Per Sindahl	Denmark	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Kim Bouillon	France	
Florent Perin-Dureau	France	
Jens Rotthauwe	Germany	
Charlotte Backman	Sweden	
Rolf Gedeborg	Sweden	
Elina Rönnemaa	Sweden	
Philip Bryan	United Kingdom	
Elena Elliot-Smith	United Kingdom	
Andrew Thomson	United Kingdom	

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	
Marco Greco		Full involvement	
Kirsten Myhr		Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (2013-05-30) http://www.ema.europa.eu/docs/en_GB/document_library/contacts/avanderzeijden_DI.pdf	

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

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:

www.ema.europa.eu

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