



31 October 2012
EMA/PRAC/635842/2012
Patient Health Protection

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the Meeting 1-3 October 2012

Explanatory notes

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

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

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

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

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as reports of adverse events from healthcare professionals or patients (so called spontaneous reports), clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

After evaluation of a safety signal the conclusion could be that the medicine caused the adverse reaction, that a causal relationship with the adverse event was considered unlikely, or that no clear answer could be given and the signal therefore is to be further investigated. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the product information (the summary of product characteristics and the package leaflet).

For completeness the information on signals is complemented, when available, by information on worldwide population exposure.

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

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



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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC Minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC Minutes)

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

Product-related pharmacovigilance inspections

(Item 8 of the PRAC Minutes)

These are inspections carried out by regulatory agencies to ensure that marketing authorisation holders have systems in place that enable them to comply with their obligations to closely follow the safety of a medicine after authorisation.

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

Chair: June Raine – Vice-Chair: Almath Spooner

1. Introduction

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

The Chairperson opened the meeting and welcomed all participants to the October 2012 meeting of the PRAC.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of Committee members for the upcoming discussions (see ANNEX II); in accordance with the Agency's Policy and Procedure 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. No new or additional conflicts were declared.

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

1.2. Agenda of the meeting of 1-3 October 2012

The agenda was adopted with the addition of the following topics upon request from the Members and from the EMA: 10.2.1. ondansetron and risk of QT prolongation and Torsade de Pointes; 11.1.1. Establishment of PRAC review teams; 11.1.2. Role of PRAC Co-Rapporteur; 11.9.1.1. Q&A on practical implementation of Urgent Union Procedures. Changes to the descriptive title of some signals were also proposed to better reflect the underlying data.

1.3. Minutes of the previous meeting of the [PRAC 3-5 September 2012](#)

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

Post-meeting note: the minutes were published on 5 October 2012 on the EMA website www.ema.europa.eu.

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

2.1. Newly triggered procedures

None

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

3.1. Newly triggered Procedures

3.1.1. Codeine (NAPs)

- Risk of fatal or life-threatening drug toxicity in CYP2D6 ultra-rapid metabolisers - Article 31 of Directive 2001/83/EC as amended for codeine-containing medicines

Regulatory details:

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

For further **background** see Codeine under 4.3.2.

Discussion

The Committee noted a notification letter dated 3 October 2012 from the Medicines and Healthcare products Regulatory Agency (MHRA - UK) triggering an official referral procedure under Article 31 of Directive (EC) No 2001/83/EC.

The Committee appointed Dolores Montero (ES) as PRAC Rapporteur and Julie Williams (UK) as PRAC co-Rapporteur.

The Committee adopted a [List of Questions and Timetable](#) for the procedure (published on the EMA website) as follows:

- Start of procedure: October (1-3) 2012 PRAC meeting;
- List of Questions: 3 October 2012;
- Submission of responses: 3 December 2012;
- Restart of the procedure: 10 December 2012;
- Rapporteur and Co-rapporteur assessment reports circulated to PRAC and to CMDh: 14 January 2012;
- Comments: 22 January 2013;
- PRAC Recommendation or PRAC List of Outstanding Issues (LoOI): February 2013 PRAC.

Post-meeting note: the PRAC adopted an extended scope and timetable of the procedures at their 29 - 31 October 2012 meeting (see www.ema.europa.eu – [Codeine-containing medicines](#)).

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

None

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Aripiprazole – ABILIFY (CAP)

- Signal of hypothyroidism

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pego (PT)

Background

Aripiprazole is an antipsychotic used in the treatment of bipolar disorder and schizophrenia.

Abilify, a centrally authorised medicine containing aripiprazole, is estimated to have been used by more than 10 million patients worldwide, in the period from 2002 to 2011.

During routine signal detection activities, a signal of hypothyroidism was identified by the Dutch national pharmacovigilance centre and the Medicines Evaluation Board (MEB), based on 2 cases reported in the Netherlands and those contained in EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the analysis of the cases of hypothyroidism reported. Given the physiologic effect of dopamine on thyrotropin (TSH), the PRAC discussed the biological plausibility of the reaction and the possibility of investigating the association of aripiprazole with hypothalamus and pituitary gland disorders (as High Level Group Term (HLGT)) as well as thyroid gland disorders (HLGT), and agreed that the signal warranted further review.

Recommendation(s)

- The MAH for Abilify (aripiprazole) should submit within 30 days a cumulative review of the signal of hypothyroidism including available data on hypothalamus and pituitary gland disorders (HLGT), as well as thyroid gland disorders (HLGT) following exposure to aripiprazole.
- This review will be assessed in the framework of the PSUR procedure to start on 11 October 2012 leading to PRAC recommendation at the February 2013 PRAC meeting.

4.1.2. Aripiprazole – ABILIFY (CAP)

- Signal of serotonin syndrome

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pego (PT)

Background

Aripiprazole is an antipsychotic used in the treatment of bipolar disorder and schizophrenia.

Abilify, a centrally authorised medicine containing aripiprazole, is estimated to have been used by more than 10 million patients worldwide, in the period from 2002 to 2011.

During routine signal detection activities, a signal of serotonin syndrome was identified by the EMA based on 18 case reports retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the analysis of the cases of serotonin syndrome reported and noted that the current product information for products containing aripiprazole includes reports of neuroleptic malignant syndrome which, as the members highlighted, shares some clinical features with serotonin syndrome. Therefore, the PRAC emphasised that a further review should take into account validated differential diagnostic criteria in assessing the strength of the evidence.

Additionally, especially in consideration of the nature of the reaction, the PRAC agreed that the signal warranted further investigation.

Recommendation(s)

- The MAH for Abilify (aripiprazole) should submit within 30 days a cumulative review of all reported cases of serotonin syndrome; classification of these cases should be in accordance to validated criteria.
- This review will be assessed in the framework of the PSUR assessment procedure to start on 11 October 2012 leading to a PRAC recommendation at the February 2013 PRAC meeting.

4.1.3. Erlotinib - TARCEVA (CAP)

- Signal of pancreatitis

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Discussion

Erlotinib is an antineoplastic agent used in the treatment of non-small-cell lung carcinoma and pancreatic neoplasms.

Tarceva, a centrally authorised medicine containing erlotinib, is estimated to have been used by more than 130,000 patients worldwide, in the period from 2008 to 2009.

During routine signal detection activities, a signal of pancreatitis was identified by the UK Medicines and Healthcare products Regulatory Agency (MHRA) based on a single case reported in the UK and on others retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Background

The PRAC discussed the information arising from the analysis of the cases of pancreatitis reported and, given that some of the cases were unconfounded (i.e. only erlotinib had been given before pancreatitis developed and no underlying disease was reported), agreed that the signal warranted further investigation. However, the PRAC acknowledged the relevance of having an appropriate and consistent case definition of pancreatitis to be used when further assessing the data.

Recommendation(s)

- The MAH for Tarceva (erlotinib) should submit a cumulative review of all reported cases of pancreatitis within the next PSUR with data lock point on 17 November 2012.
- This review will be assessed in the framework of the next PSUR assessment procedure; the timing of the PRAC recommendation following this review and the accompanying PSUR will be in accordance with the published EMA [PSUR timetable](#).

4.1.4. Erlotinib - TARCEVA (CAP)

- Signal of palmar-plantar erythrodysesthesia syndrome (PPES)

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Erlotinib is an antineoplastic agent used in the treatment of non-small-cell lung carcinoma and pancreatic neoplasms.

Tarceva, a centrally authorised medicine containing erlotinib, is estimated to have been used by more than 130,000 patients worldwide, in the period from 2008 to 2009.

During routine signal detection activities, a signal of palmar-plantar erythrodysesthesia syndrome (PPES) was identified by the UK Medicines and Healthcare products Regulatory Agency (MHRA) based on 3 cases reported in the UK and on others retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the analysis of the cases of PPES reported. The PRAC noted that other medicines of the same therapeutic class (epidermal growth factor receptor (EGFR) inhibitors) contain reports of PPES in their product information. Furthermore, the PRAC recognised that the majority of the cases reported with erlotinib were unconfounded (i.e. only erlotinib had been given before the condition developed) and that in many cases there was a positive re-challenge (the adverse reaction resolved on withdrawal of the medication and returned when it was given again). Therefore the PRAC agreed that, in light of the strength of the signal, an update of the product information should be considered.

Recommendation(s)

- The MAH for Tarceva (erlotinib) should submit a type II variation in order to update the product information to address the signal.

- A 60-day timetable was supported for this variation, which will lead to a further PRAC recommendation.

4.1.5. Erlotinib - TARCEVA (CAP)

- Signal of vasculitis

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Erlotinib is an antineoplastic agent used in the treatment of non-small-cell lung carcinoma and pancreatic neoplasms.

Tarceva, a centrally authorised medicine containing erlotinib, is estimated to have been used by more than 130,000 patients worldwide, in the period from 2008 to 2009.

During routine signal detection activities, a signal of vasculitis was identified by the EMA based on 35 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the cases of vasculitis reported. The PRAC considered that the time-to-onset of the reactions reported, in many cases, showed a consistent pattern. However, members pointed out that vasculitis can also occur as a clinical manifestation of a para-neoplastic syndrome or can be associated with infections. For this reason information such as results of biopsy and titre of anti-neutrophil cytoplasmic antibodies could be important in the differential diagnosis. Therefore PRAC agreed that the signal warranted a further review.

Moreover, the PRAC noted that a signal of leukocytoclastic vasculitis and vasculitis had been discussed in the past. At that time the MAH had been proposed the use of a guided questionnaire and to request confirmation of vasculitis, when reported, by biopsy. This information should be taken into account in the review of the signal.

Recommendation(s)

- The MAH for Tarceva (erlotinib) should submit a cumulative review of all reported cases of vasculitis within the next PSUR with data lock point on 17 November 2012.
- This review will be assessed in the framework of the next PSUR assessment procedure; the timing of the PRAC recommendation on this review and the accompanying PSUR will be in accordance with the published EMA [PSUR timetable](#).

4.1.6. Human papillomavirus vaccine [types 6,11, 16, 18] – GARDASIL, SILGARD (CAPs)

- Signal of severe dyspnoea in a patient with poorly controlled asthma

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Background

Human papillomavirus vaccine [types 6, 11, 16, 18] is used in women for the prevention of premalignant genital lesions and cervical cancer, as well as genital warts causally related to HPV types 6, 11, 16 or 18.

Gardasil, a centrally authorised vaccine, is estimated to have been given to more than 7 million girls in Europe and 35 million worldwide, in the period from 2006 to 2012.

A signal of severe dyspnoea was triggered by the Swedish Medicines Agency (MPA) following the report of a fatal case after vaccination with Gardasil in a patient with poorly controlled asthma.

Discussion

Based on the available information on the case, the PRAC noted that there was currently insufficient evidence to suggest a causal association with the vaccination. However, to provide context for the case evaluation and as part of the continuous monitoring of the vaccine, the PRAC agreed to further investigate the signal.

Recommendations(s):

- The MAH for Gardasil should be requested to respond to an agreed list of questions within 30 days.
- A 30-day timetable for assessment of the MAH's responses to the list of questions was supported.

4.1.7. Seasonal influenza vaccines - (NAPs)

- Signal of extensive limb swelling (ELS)

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

Seasonal influenza vaccines are used in the prophylaxis of influenza, especially in those patients who are at an increased risk of associated complications.

More than 25 million doses of seasonal, nationally authorised vaccines such as Influxac, Batrevac and Vacciflu have been distributed worldwide, in the period from May 2011 and April 2012. Vaxigrip, another nationally authorised vaccine, is estimated to have been given to more than 48 million adults and more than 3.5 million children in 2011.

During routine signal detection activities, a signal was identified by the Dutch Medicines Agency (MEB) based on 10 reports of extensive limb swelling (ELS), received by the Netherlands Pharmacovigilance Centre (Lareb) following vaccination with Vaxigrip or Influxac. NL confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the cases of ELS reported.

The PRAC discussed the biological plausibility of the reaction, and a type III hypersensitivity reaction was suggested as a possible mechanism. The PRAC agreed that the signal might not only apply to

Influvac and Vaxigrip, but could also be relevant for other seasonal influenza vaccines. Some members commented that whilst ELS of the limb in which the vaccine was administered is normally transient and often resolves without *sequelae*, there was a potential for misclassification of ELS with cellulitis, which could lead to an unnecessary prescription of antibiotics.

An update of the product information could help minimise this risk, and the PRAC was informed that other nationally authorised vaccines in the EU might already contain some information on ELS. Based on this information the PRAC considered that the signal warranted further review.

The Committee appointed Menno van der Elst (NL) as PRAC Rapporteur.

Recommendation(s)

- The PRAC Rapporteur should collect information on ELS currently reflected in the product information of seasonal influenza vaccines authorised in the EU, through a non-urgent information (NUI) request to Member States. Discussion of the results of this NUI request is preliminarily scheduled for the 26-29 November 2012 PRAC meeting, which will lead to a further PRAC recommendation.

4.1.8. Ipilimumab - YERVOY (CAP)

- Signal of anaphylactic reaction

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Ipilimumab is a monoclonal antibody used in the treatment of melanoma.

Yervoy, a centrally authorised medicine containing ipilimumab, is estimated to have been used by more than 3,000 patients worldwide in the post-marketing setting from the issue of the marketing authorisation in July 2011 to December 2011.

During routine signal detection activities, a signal of anaphylactic reaction was identified by the EMA based on 4 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the analysis of the cases of anaphylactic reaction reported. The PRAC noted that the product information of ipilimumab-containing medicines includes hypersensitivity reactions, however, anaphylactic reaction is not mentioned. The PRAC commented that several monoclonal antibodies, such as ipilimumab, are known to be associated with anaphylactic reactions and cytokine release syndrome. The two conditions share some clinical features but differences in the underlying pathophysiological mechanism mean that they require different clinical management. Since more information was needed on these aspects, the PRAC agreed that the signal warranted further investigation.

Recommendation(s)

- The MAH for Yervoy (ipilimumab) should submit a cumulative review of all reported cases of anaphylactic reaction within the next PSUR with data lock point on 24 September 2012. As part

of this review the MAH should also include information on clinical differences between cytokine release syndrome and anaphylactic reactions.

- This review will be assessed in the framework of the next PSUR assessment procedure; the timing of the PRAC recommendation on this review and the accompanying PSUR will be in accordance with the published EMA [PSUR timetable](#).

4.1.9. Mirtazapine (NAPs)

- Signal of pancreatitis

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Mirtazapine is an antidepressant used in the treatment of major depression.

The patient exposure for nationally authorised medicines containing mirtazapine has been estimated to be more than 6 million patient-years worldwide in the period from 2007 to 2010.

During routine signal detection activities, a signal of pancreatitis was identified by the Dutch Medicines Agency (MEB) based on 13 cases retrieved from EudraVigilance. The NL confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the analysis of the cases of pancreatitis reported to EudraVigilance, including case reports described in the published literature. The PRAC noted that pancreatitis is included in the product information for the innovator product authorised outside the EU; however, data supporting the inclusion of this information were not known. The PRAC agreed that to address the signal more data on risk factors, on possible differences in the occurrence of the reaction between the sexes, as well as on a possible biological mechanism were needed. Therefore the PRAC agreed that the signal warranted further investigation.

The Committee appointed Sabine Straus (NL) as PRAC Rapporteur

Recommendation(s)

- The MAH for the innovator product containing mirtazapine should submit within 60 days a cumulative review of the signal of pancreatitis including all available data (preclinical, clinical, post-marketing and literature).
- A 60 day-timetable was supported to assess the results of this review, which will lead to a further PRAC recommendation.

4.1.10. Sugammadex - BRIDIION (CAP)

- Signal of respiratory symptoms unrelated to hypersensitivity reaction

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Background

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

Bridion, a centrally authorised medicine containing sugammadex, is estimated to have been used by more than 2.5 million of patients worldwide, in the period from 2008 to 2012.

During routine signal detection activities, a signal of respiratory adverse reactions was identified by the Regional Pharmacovigilance Centre of Madrid (ES) based on 21 cases retrieved from FEDRA (Spanish Pharmacovigilance Database). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the analysis of the cases reported to the FEDRA database in the context of the totality of cases contained in EudraVigilance. The PRAC noted that bronchospasm is listed as an undesirable effect in the product information for sugammadex-containing medicines only for pulmonary patients. Furthermore, bronchospasm in patients with a history of pulmonary complications is a potential adverse drug reaction that has been kept under close review and is included in the risk management plan for Bridion. Nevertheless, in order to consider whether additional pharmacovigilance measures are needed, the PRAC agreed that the signal warranted further investigation.

Recommendation(s)

- The MAH for Bridion (sugammadex) should submit within 60 days a cumulative review of reported cases of respiratory disorders focusing on, but not restricted to, bronchospasm, respiratory obstruction and pulmonary oedema.
- A 60 day-timetable was supported to assess the results of this review, which will lead to a further PRAC recommendation.

4.1.11. Temozolomide - TEMODAL (CAP)

- Signal of hepatic failure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Background

Temozolomide is an antineoplastic agent used in the treatment of glioblastoma.

The patient exposure for Temodal, a centrally authorised medicine containing temozolomide, has been estimated to be more than 19,000 patient-years worldwide in the period from 2008 to 2011.

During routine signal detection activities, a signal of hepatic failure was identified by the EMA based on 23 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the analysis of the cases reported and of the cases described in the literature, and commented that, when documented, the time-to-onset observed for the reaction showed a consistent pattern. Furthermore, some evidence indicated a dose-dependent liver toxicity associated with temozolomide, as discussed in the latest PSURs and as mentioned in the product information for temozolomide-containing medicines. Based on this information the PRAC agreed that the signal warranted further investigation.

Recommendation(s)

- The MAH for Temodal (temozolomide) should submit within 60 days a cumulative review of the signal of hepatic failure and related terms and discuss possible risk minimisation measures.
- A 60 day-assessment timetable was supported to assess the results of this review, which will lead to a further PRAC recommendation.

4.1.12. Trazodone (NAPs)

- Signal of postural hypotension and somnolence at high starting dose

Regulatory details:

PRAC Rapporteur: Jolanta Gulbinovic (LT)

Discussion

Trazodone is an antidepressant used in the treatment of depression including depression accompanied by anxiety.

The patient exposure for nationally authorised medicines containing trazodone has been estimated, based on a 300mg daily dose, to be around 20 million treatment-days in the period from 2008 to 2011.

During routine signal detection activities, a signal of postural hypotension and somnolence associated with a high starting dose was identified by the Irish Medicines Board (IMB), based on new information on a previously identified risk arising from 10 cases reported to the IMB. IE confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the analysis of the cases reported to the IMB and also to EudraVigilance. The PRAC noted that the product information for trazodone-containing medicines carries warnings in relation to hypotension, orthostatic hypotension and syncope, particularly in elderly patients. Nevertheless, while both orthostatic hypotension and somnolence are known effects of trazodone, the signal suggested a new aspect of this known risk, underlying the need to evaluate the clinical *sequelae* of early orthostatic effects in the elderly, with a particular view to strengthening risk minimisation. Therefore the PRAC agreed that the signal warranted further investigation.

The PRAC appointed Jolanta Gulbinovic (LT) as PRAC Rapporteur.

Recommendation(s)

- The MAHs for trazodone-containing medicines should submit within 60 days a review of available data relating to the recognised risk of orthostatic effects, particularly in the elderly, and discuss whether this review would support strengthening of risk minimisation measures.
- A 90 day-assessment timetable was supported to assess this review, which will lead to a further PRAC recommendation.

The EMA will explore options to obtain data on patterns of exposure (e.g. exposure groups and associated therapies) in order to focus on possible risk minimisation strategies.

4.2. *New signals detected from other sources*

None

4.3. *Signals follow-up and prioritisation*

4.3.1. **Anticholinergic drugs for inhaled use: ipratropium, ipratropium / salbutamol, tiotropium bromide (NAPs)**

- Signal of increased incidence of myocardial infarction and stroke in patients with chronic obstructive pulmonary disease (COPD)

Regulatory details:

PRAC Rapporteurs: tiotropium: Sabine Straus (NL); ipratropium: Julia Pallos (HU); ipratropium / salbutamol: Maria Alexandra Pego (PT)

Background

Ipratropium, the combination of ipratropium and salbutamol, and tiotropium bromide are inhaled anticholinergic agents widely used in the treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD) and chronic asthma.

In 2012 the Pharmacovigilance Working Party (PhVWP) was informed of the publication of an article by Wang *et al.*¹ based on data from the Longitudinal Health Insurance Database (LIHD) of the Taiwan National Health Insurance (NHI) programme for ipratropium-containing products. At that time, the PhVWP agreed that the results were also relevant for chemically related substances such as tiotropium. The UK MHRA proposed to address the signal of increased incidence of myocardial infarction and stroke in patients with COPD triggered by the publication and confirmed that initial analysis and prioritisation by the PRAC was needed.

Discussion

PRAC discussed the study by Wang *et al.* On the basis of the information provided in the publication, the PRAC considered that, given the methodological limitations of this study (e.g. confounders such as smoking status were not available) and the apparent lack of any biological plausibility, the interpretation of the results was challenging and no regulatory action is considered necessary at the moment. However the PRAC considered that stroke events with inhaled anticholinergics should be closely monitored.

¹ Wang MT, Tsai CL, Lo YW, Liou JT, Lee WJ, Lai IC.

Risk of stroke associated with inhaled ipratropium bromide in chronic obstructive pulmonary disease: a population-based nested case-control study. *Int J Cardiol.* 2012 Jul 12;158(2):279-84. Epub 2012 Mar 3.

Recommendation(s)

The PRAC agreed to appoint the following Rapporteurs according to the lead Member State reported in the '[List of active substances subject to worksharing for signal management](#)': tiotropium: Sabine Straus (NL); ipratropium: Julia Pallos (HU); ipratropium / salbutamol: Maria Alexandra Pego (PT).

The PRAC agreed the following recommendations:

- No regulatory action is justified on the basis of the information provided in the publication by Wang *et al.* However, stroke events with inhaled anticholinergics should continue to be closely monitored (e.g. in the literature and via signal detection activities).

The EMA will explore options to obtain relevant data from other sources, taking into account confounding factors such as Body Mass Index (BMI) and smoking status.

Post-meeting note: in consideration of the potential overlap with the work being undertaken by the [ASTROLAB](#) (project funded by the European Commission through the Seventh Framework Programme (FP7)) and the present research question, the EMA will make progress contacting the consortium.

4.3.2. Codeine (NAPs)

- Signal of fatal or life-threatening drug toxicity in CYP2D6 ultra-rapid metabolisers

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

A signal of fatal or life-threatening drug toxicity in CYP2D6 ultra-rapid metabolisers with codeine was discussed by the PRAC at its [3-5 September 2012](#) meeting for follow-up at the 1-3 October 2012 meeting.

Discussion

The PRAC discussed the outcome of a survey (responses to the request of Non Urgent Information (NUI) to the EU member states) on the authorisation status of codeine-containing products indicated in children in the EU.

The survey indicated that in all member states there was at least one codeine-containing prescription-only medicine that was authorised for use in children (tablets, syrups and suppositories) for the treatment of pain, cough or migraine. The PRAC noted that products had different warnings across EU member states regarding post-operative pain relief in children. The PRAC considered that further review of risk minimisation measures was necessary and that such measures should be consistently applied across all codeine-containing products indicated in children in the EU.

Given the potentially very wide use of codeine in children for post-operative pain within Europe, the potentially serious consequences of opiate toxicity, particularly when used in certain clinical settings in a susceptible population, and the lack of consistent risk minimisation measures across Europe, the PRAC agreed that a full evaluation of this issue was warranted.

Recommendation(s)

- A formal review should be conducted in order to further evaluate the risk of toxicity in children who are CYP2D6 ultra-rapid metabolisers and to ensure that appropriate risk minimisation

measures are in place to help optimise the safe use of codeine when it is used for post-operative pain relief in children.

- An Article 31 of Directive (EC) No 2001/83/EC (as amended) EU referral procedure for safety reasons was considered the most appropriate tool to evaluate the benefit-risk balance of codeine-containing medicines.

See also under **3.1.1.**

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

- Signal of arterial thrombotic events

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Background

In 2012 the Pharmacovigilance Working Party (PhVWP) was informed of the publication by Lidegaard *et al.*² on thrombotic stroke and myocardial infarction with hormonal contraception. As PRAC Rapporteur for Evra, a centrally authorised product containing norelgestromin and ethinylestradiol, the NL reviewed the signal of arterial thrombotic events triggered by the publication and confirmed it needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the review of the results of the study, which provided further information on the risk of arterial thrombotic events with oral contraceptives.

Given that the study did have some limitations that hampered the interpretation of the results and that arterial thrombotic events are already a recognised very rare risk with oral contraceptives, further PRAC discussions on whether there is a need to update the current labelling should be supported by data on the existing warnings contained in the product information of hormonal contraceptive products currently authorised in the EU.

The Committee appointed Menno van der Elst (NL) as Rapporteur.

Recommendations(s)

- The PRAC Rapporteur should collect information on the existing warnings regarding the risk of arterial thrombotic events contained in the product information of hormonal contraceptive products currently authorised in the EU (including novel delivery systems) through a NUI request to the EU member states.
- Discussion on the results of this NUI request, which will lead to a further PRAC recommendation, is preliminarily scheduled for the 26-29 November 2012 PRAC meeting. Individual PRAC Rapporteurs for follow-up procedures will be appointed as appropriate.

² Lidegaard O, Lokkegaard E, Jensen A, Skovland CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012;366:2257-2266

5. Risk Management Plans (RMPs)

5.1. Medicines in the pre-authorisation phase

None

5.2. Medicines already authorised

5.2.1. Golimumab – SIMPONI (CAP)

- Evaluation of the updated RMP in the context of a type II variation, extension of indication

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)
PRAC Co-Rapporteur: Isabelle Robine (FR)

Background

Golimumab is a monoclonal antibody used in the treatment of ankylosing spondylitis, rheumatoid arthritis and psoriatic arthritis.

The CHMP is evaluating a new therapeutic indication in the area of ulcerative colitis for Simponi, a centrally authorised product containing golimumab. The PRAC has to provide advice to the CHMP on the necessary updates to the RMP to support this indication.

Advice

The PRAC agreed the following advice to the CHMP:

- The RMP for Simponi (golimumab), in the context of the extension of the indication under evaluation, was considered acceptable, provided that satisfactory responses to an agreed list of questions are submitted by the MAH. A further PRAC advice to CHMP will be provided as applicable.

5.2.2. Mannitol – BRONCHITOL (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Isabelle Robine (FR)

Background

Mannitol is a hyperosmolar agent used in the treatment of cystic fibrosis.

The PRAC has to provide advice to the CHMP on the necessary updates to the RMP in light of the results arising from the conclusion of the open label phase (OLP) and open-label extension phase (OLEP) of two placebo-controlled phase III studies: 'Long Term Administration Of Inhaled Dry Powder Mannitol In Cystic Fibrosis – A Safety And Efficacy Study' and 'Long Term Administration of Inhaled Mannitol in Cystic Fibrosis (DPM-CF-301 and DPM-CF-302)', of which the double blind phase (DBP) was complete at time of authorisation.

The updates related to the increased exposure to inhaled mannitol in studies described in the safety specification and the number of events reported in the OLP and OLEP of these studies, particularly for the important identified and potential risks in the RMP.

Advice

The PRAC agreed the following advice to the CHMP:

- The RMP for Bronchitol (inhaled mannitol), as updated, was considered acceptable. The next routine update of the RMP should take into account some points proposed by the PRAC, leading, as applicable, to a further PRAC advice to CHMP.

5.2.3. Saxagliptin – ONGLYZA (CAP) , Saxagliptin / metformin - KOMBOGLYZE (CAP)

- Evaluation of the updated RMP in the context of a Type II variation, extension of indication

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

PRAC Co-Rapporteur: *to be nominated*

Background

Saxagliptin is an antidiabetic agent. Onglyza, a centrally authorised product containing saxagliptin, is indicated as an add-on to existing monotherapies with other agents in the treatment of type 2 diabetes. Komboglyze is a centrally authorised medicine containing saxagliptin in combination with metformin.

The CHMP is evaluating a new therapeutic indication to include triple oral therapy (metformin + sulfonylurea + saxagliptin) in the treatment of type 2 diabetes for Onglyza as well as Komboglyze. The PRAC has to provide advice to the CHMP on the necessary updates to the RMP to support such indication.

Advice

The PRAC agreed the following advice to the CHMP:

- The RMP for Onglyza (saxagliptin) and Komboglyze (saxagliptin / metformin), in the context of the extension of indication under evaluation, was considered acceptable provided that an updated version of the RMP and satisfactory responses to an agreed list of questions are submitted.

6. Assessment of Periodic Safety Update Reports (PSURs)

None

7. Post-authorisation Safety Studies (PASS)

7.1. Post-authorisation safety studies protocols

7.1.1. Ivacaftor – KALYDECO (CAP)

- Evaluation of PASS protocol: observational study to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis (CF)

Regulatory details:

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

Background

Ivacaftor is a selective modulator of the cystic fibrosis transmembrane conductance regulator (CFTR) used in the treatment of cystic fibrosis.

A PASS protocol for Kalydeco, a centrally authorised medicine containing ivacaftor, was presented for review by the PRAC in the context of the evaluation of the long-term safety of ivacaftor in patients with cystic fibrosis (title 'An Observational Study to Evaluate the Long-Term Safety of ivacaftor in Patients with Cystic Fibrosis (CF)').

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.2 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Kalydeco (ivacaftor) as the Committee considered that the design of the study did not fulfil the study objectives.

The PRAC therefore recommended that:

- the MAH should submit a revised PASS protocol within 60 days. A standard 60 day-assessment timetable will be applied.

The MAH was encouraged to contact EMA within two weeks in order to receive clarification on any issues in advance and facilitate the resubmission of an adequate protocol.

7.2. Results of post-authorisation safety studies

None

8. Product related pharmacovigilance inspections**8.1. List of planned pharmacovigilance inspections**

None

8.2. On-going or concluded pharmacovigilance inspections

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

9. Other Safety issues for discussion requested by the CHMP or the EMA**9.1. Safety related variations of the marketing authorisation (MA)**

None

9.2. Renewals of the Marketing Authorisation

9.2.1. Febuxostat – ADENURIC (CAP)

- Renewal of the Marketing Authorisation after first 5 years

Regulatory details:

PRAC Rapporteur: Harald Herkner (AT)
PRAC Co-Rapporteur: Qun-Ying Yue (SE)

Background

Febuxostat is an inhibitor of uric acid production used in the treatment of gout.

Adenuric, a centrally authorised product containing febuxostat, was authorised in 2008. Since the period of validity of the first marketing authorisation expires after 5 years, a renewal of the marketing authorisation was submitted by the MAH for opinion by the CHMP. The PRAC has to provide advice to the CHMP on this renewal with regard to safety aspects.

Advice

Based on the review of the Risk Management System for Adenuric (febuxostat) in the treatment of gout and the CHMP Rapporteur assessment report, the PRAC provided some comments on the RMP and did not raise reservations to an indefinite renewal of the marketing authorisation, as regards the safety of the medicinal product.

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

None

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

10.1. Renewals of the MAs

None

10.2. Safety-related variations of the marketing authorisation

10.2.1. Ondansetron (NAPs)

- Risk of QT prolongation and Torsade de Pointes

Background

Ondansetron is a 5HT-3 receptor antagonist used in the treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting.

In 2012, the results of a thorough QT (TQT) study for ondansetron were discussed by the PhVWP, in the context of a national type II variation for Zofran (ondansetron). Based on the data, which demonstrated a dose-dependent prolongation of the QTc interval, an urgent safety restriction (USR) procedure was initiated to restrict the maximum single intravenous dose of Zofran (ondansetron) for

the management of chemotherapy-induced nausea and vomiting in adults from 32mg to 16 mg (infused over at least 15 minutes).

Zofran is a nationally authorised product containing ondansetron, and numerous generic products are also licensed; PRAC advice was requested by UK in order to achieve a harmonised position throughout Europe in relation to a Type II variation that has now been submitted for assessment in all EU member states where the product is marketed.

Advice

- The PRAC agreed to further discuss the type II variation submitted in UK and in the other Member States, to update the product information to reflect the findings of the QT study and its implications for the ondansetron dosing regimen.
- The PRAC agreed some points to be addressed during the assessment of the variation as regards the pharmacokinetic profile of ondansetron (in hepatic impairment, in the paediatric population and in the elderly population).

The need to address additional points as part of the variation assessment will be discussed at the 26-29 November 2012 PRAC meeting, which will lead to PRAC advice.

10.3. Timing and message content in relation to Member States' safety announcements

None

10.4. Other

11. Organisational, regulatory and methodological matters

None

11.1. Mandate and organisation of the PRAC

11.1.1. Establishment of PRAC review teams

See also 11.4.

The PRAC discussed a proposal for the establishment of a signal management review team (SMaRT) which will facilitate the workflow of the signal management process in the EU, including methods to integrate the factors to be taken into account in the analysis and prioritisation of signals which will be reported to the plenary meeting of the PRAC. The PRAC endorsed the mandate and the establishment of the team. Follow-up discussion will be held at the 29-31 October 2012 PRAC meeting.

11.1.2. Role of PRAC Co-Rapporteur

The PRAC noted the EMA proposal for PRAC Co-Rapporteur role.

11.2. Pharmacovigilance audits and inspections

11.2.1. Pharmacovigilance Systems and their Quality Systems

11.2.1.1. Use of the conditions of the Marketing Authorisation in relation to the existence of an adequate pharmacovigilance system

On behalf of the Inspection/Audit Project Team for the implementation of the pharmacovigilance legislation, a representative from the Medicines and Healthcare products Regulatory Agency (MHRA) made a presentation on marketing authorisation conditions.

11.2.2. Pharmacovigilance System Master File

None

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

None

11.3.1. Union Reference Date List (EURD List)

11.3.1.1. Consultation on the draft revised List, version October 2012

The PRAC adopted the EURD list version October 2012 with some minor refinements. The PRAC considered it appropriate to include in the list substances contained in medicinal products suspended from the EU market for less than 3 years with an appropriate PSUR frequency.

The list will be transmitted to CHMP and CMDh for adoption at their October 2012 meetings.

11.4. Signal Management

None – see 11.4. Signal Management

11.5. Adverse Drug Reactions reporting and additional reporting

None

11.5.1.1. Selection of black symbol for products subject to additional monitoring

Background

A preliminary discussion on the black symbol to be recommended for products subject to additional monitoring took place at the PRAC September 2012 meeting.

A representative of BEUC (The European Consumer Organisation) was invited to present the outcome of the discussion that took place on the same topic at the [PCWP and Healthcare Professionals' Working Group \(HCPWG\) joint meeting of 24/25 September 2012](#).

Discussion

The PRAC was informed of the conclusion reached at the joint meeting. The inverted black triangle (▼) is the preferred choice of HCPWG and PCWP.

The HCPWG and PCWP considered that the inverted black triangle should be large and prominent and should possibly be located next to the invented name. Moreover the size of the symbol needs to be proportional to the invented name and a minimum size should be defined. Patients and healthcare professionals emphasised the importance of adding a link to EMA/NCAs website for the user who would like to find further information. Therefore EMA/NCAs websites should provide further information on 'additional monitoring' in lay language.

Furthermore the speaker emphasised that communication is key to the successful implementation of additional monitoring, and that patients', consumers' and healthcare professionals' organisations are willing to play a crucial role in conveying the information to their members as well as Member States who should play an active role in raising awareness about the symbol.

The PRAC supported the views of patients, consumers and healthcare professionals regarding the location of the black symbol next to the invented name, the specifications of the symbol and the need to coordinate a communication strategy on the black symbol across Europe.

The following was considered to play a key role in the communication:

- The EMA/NCAs websites should provide further information on '*additional monitoring*' in lay language.
- Member States are expected to play an active role in raising awareness about the symbol.
- Patients', consumers' and healthcare professionals' organisations could use the 'core' explanatory information prepared by the EMA in their 'awareness campaign'.
- EMA's website should provide specific information material as a point of reference.
- Patients', consumers' and healthcare professionals' organisations will play a crucial role in conveying the information to their members.

The UK and BE reported on their experience of the use of the inverted black triangle. In the UK evidence showed that the symbol promoted reports of suspected adverse drug reactions; the symbol has been used in the context of the yellow card reporting scheme for decades and the symbol is included in the product information for healthcare professionals, national formularies and advertising material. In Belgium the symbol is part of a global project of "active pharmacovigilance". The symbol is not included in the product information but it is included in the Belgian medicines agency website and in the national therapeutic guide; currently no survey on the effectiveness of the inverted black triangle on the spontaneous reporting rate is available in Belgium.

The PRAC agreed that an abstract symbol not linked to any meaning/connotation is less likely to cause confusion/wrong interpretation or alarm to patients. Furthermore, the black symbol does not necessarily have to have a meaning or to directly allude to an action as long as the accompanying text is clear enough and conveys the right message.

EMA stated that the PRAC will be presented with the final template of the product information including the explanatory statement accompanying the black symbol following its agreement by the Quality Review of Documents group. In parallel to the preparation for the publication of the revised template, particular emphasis will be given to the preparation of the communication campaign.

The EMA will put forward a specific request to the relevant project team for coordination of a communication campaign. The PRAC will begin discussion on a communication strategy at their 29-31 October 2012 meeting.

The PRAC asked to be provided with the template for product information updated to include the black symbol and the explanatory statement which accompanies the symbol as soon as agreed.

Advice

The PRAC agreed the following Advice to the European Commission:

- The black inverted triangle should be the symbol for products subject to additional monitoring (▼). The Committee adopted the PRAC recommendation by consensus.
- The symbol should be black and be proportional to the font size of the subsequent standardised text. In all cases its size should be not less than 5 mm per side.

11.6. EudraVigilance Database

None

11.7. Risk Management Plans and Effectiveness of risk Minimisations

None

11.8. Post-authorisation Safety Studies

None

11.9. Community Procedures

11.9.1. Referral Procedures for Safety Reasons

11.9.1.1. Q&A on Practical Implementation of Urgent Union Procedure

The EMA circulated a draft Q&A on "Practical Implementation of Urgent Union Procedure" (Article 107i of the Directive 2001/83/EC). This version already reflects the views of the Committees/Referrals Project Team for the implementation of the pharmacovigilance legislation (including Member States).

11.10. Risk communication and Transparency

11.10.1. Public Participation in Pharmacovigilance

None

11.10.2. Safety Communication

11.10.2.1. Process for review of Direct Healthcare Professional Communications (DHPCs) by EMA

EMA presented a process for the review of DHPCs and in particular when PRAC involvement is foreseen. EMA clarified that the establishment and operation of the PRAC as well as the new responsibilities of the CMDh necessitate changes in the way DHPCs are to be handled by national competent authorities and by the EMA.

For topics being discussed at the PRAC, the PRAC will be responsible for the review of the related DHPC (although the review of all DHPCs will be finalised by CHMP/CMDh). A review of the DHPC may be finalised by PRAC in case of interim measures. Where assessment of the related procedure requiring the DHPC does not fall within the remit of the PRAC (e.g. shortage not linked to safety, transitional period), PRAC will not be involved in the review process.

Regarding the practicalities of the review process it was proposed that PRAC could give advice on key messages and on the communication plan and that this consideration by PRAC should be informed by initial review of the DHPC text by a team of 'DHPC reviewers' including selected PRAC members, PRAC and CHMP Rapporteurs, Lead Members States and relevant EMA staff. EMA will provide editorial support and support the process at the stage of developing the communication plan. The final DHPC text will be circulated through the currently used Early Notification System.

The PRAC supported the proposal in principle but recommended that awareness of the details of the initiative is promoted amongst all Member States involved.

11.11. Continuous pharmacovigilance

None

11.12. Inter Status with EMA Committees and Working Parties

11.13. Inter Status within the EU regulatory network

11.14. Contacts of the PRAC with external parties and inter Status of the EMA with interested parties

None

12. Any other business

None

ANNEX I – List of Abbreviations

For a [List of the abbreviation used in the PRAC minutes](#), see:

www.ema.europa.eu

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12.1.1.

ANNEX II – List of Participants: *including any restrictions with respect to involvement of members / alternates / experts following evaluation of Declared interests for the 3-5 October 2012 meeting.*

PRAC member PRAC alternate	Country	Outcome restriction applying to the topics of the current meeting following evaluation of electronic Declaration of Interest (e-DoI)	Product/ substance
Bettina Schade	Austria	Full involvement	
Jean-Michel Dogne	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	codeine, mirtazapine, trazodone
Virginie Chartier	Belgium	Full involvement	
Yuliyani Eftimov	Bulgaria	Full involvement	
Christos Petrou	Cyprus	Full involvement	
Jana Mlada	Czech Republic	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uuskula	Estonia	Full involvement	
Katrin Kiisk	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Isabelle Robine	France	Full involvement	
Evelyn Falip	France	Full involvement	
Martin Huber	Germany	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer reviewer for:	codeine, trazodone
Julia Pallos	Hungary	Full involvement	
Gudrun Kristin Steingrimsdottir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Fernanda Ferrazin	Italy	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 Elst	Netherlands	Full involvement	
Ingebjorg Buajordet	Norway	Full involvement	
Pernille Harg	Norway	Full involvement	
Alexandra Pego	Portugal	Full involvement	
Margarida Guimaraes	Portugal	Full involvement	
Nicolae Fotin	Romania	Full involvement	
Anna Harcarova	Slovakia	Full involvement	
Dolores Montero	Spain	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
June Munro Raine	United Kingdom (Chair)	Full involvement	
Julie Williams	United Kingdom	Full involvement	
Julia Dunne	United Kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	Country	Outcome restriction applying to the topics of the current meeting following evaluation of e-DoI	Product/ substance
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise (Marieke) De Bruin		Full involvement	
Stephen Evans		Full involvement	
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Involvement in discussion only for:	golimumab
Lennart Waldenlind		Full involvement	

Additional European experts participating to the meeting for specific Agenda items	Country	
Ilaria Passarani (BEUC)	<i>Not applicable</i>	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items.
Rikke Jensen	Denmark	
Eleanor Carey	Ireland	
Katarina Andersson	Sweden	
Charlotte Backman	Sweden	
Alison Banner-Simpson	United Kingdom	
Kathryn Ord	United Kingdom	
Jonathan Rowell	United Kingdom	
Karen Slevin	United Kingdom	
Anya Sookoo	United Kingdom	