05 October 2012

EMA/PRAC/571481/2012 Final
Patient Health Protection

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of meeting 3-5 September 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)

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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 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

Acting chair: Noel Wathion (EMA), Chair elected at the meeting: June Raine

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 September 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 (Annex I); 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. 30 or more members were present in the room).

1.2. Agenda of the meeting of 3-5 September 2012

The agenda was adopted.

1.3. Minutes of the previous meeting of the PRAC 19-20 July 2012

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

Post-meeting note: the minutes were published on 7 September 2012 on the EMA website www.ema.europa.eu

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

None

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

None

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Adalimumab – HUMIRA (CAP)[1]

- Signal of dermatomyositis

Regulatory details:

PRAC Rapporteur: Ulla Wandel-Liminga (SE)

Background

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

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

During routine signal detection activities, a signal of dermatomyositis was identified by the EMA based on 14 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 review of the cases reported to EudraVigilance describing dermatomyositis with adalimumab. One of these cases was also described in the literature[2] In this article, the authors described that the patient re-experienced dermatomyositis following a switch from adalimumab to infliximab suggesting a potential role of the inhibition of the TNF signalling

[1] Centrally Authorised Product
[2] Riolo G, Towheed TE. Anti-tumor necrosis factor (TNF) inhibitor therapy-induced dermatomyositis and fasciitis. J Rheumatol. 2012;39(1):192-4

pathway in the genesis of the reaction. Additionally the PRAC considered a further article, describing dermatomyositis during adalimumab use[3].

The PRAC commented that some cases contained in EudraVigilance could have been confounded by various factors such as a history of autoimmune diseases. Others were insufficiently documented. Nevertheless, based on the current data, the PRAC agreed that it could not be excluded that the exposure to adalimumab had caused a worsening and/or progression of symptoms, beyond the natural history of the disease. Therefore the PRAC agreed that the signal warranted further review. Furthermore given that infliximab was also mentioned in the case described in the literature, the PRAC agreed that data available for this substance should also be reviewed.

Recommendation(s)

- The Marketing Authorisation Holder (MAH) for Humira (adalimumab) and MAH for Remicade (infliximab) should submit within 30 days a cumulative review of dermatomyositis, discuss plausible pathophysiologic mechanisms and consider labelling change. A 60 day-assessment timetable was supported to assess the results of this review, leading to a further PRAC recommendation.

The EMA will review cases of dermatomyositis reported to EudraVigilance in association with pharmacologically related substances and report back to the PRAC.

4.1.2. Cinacalcet – MIMPARA (CAP)

- Signal of QT prolongation/ventricular arrhythmias

Regulatory details:

PRAC Rapporteur: Ulla Wandel-Liminga (SE)

Background

Cinacalcet is a calcimimetic agent used in the treatment of hyperparathyroidism (HPT) of different origin.

Mimpara, a centrally authorised medicine which contains cinacalcet, has been used, in the period from 2004 until 2010, by an estimated number of more than 700,000 patients worldwide.

During routine signal detection activities a signal of QT prolongation/ventricular arrhythmias was identified by EMA based on 15 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 QT prolongation/ventricular arrhythmias reported to EudraVigilance.

The PRAC commented that despite the fact that most patients had an underlying cardiovascular disorder, which could provide an alternative explanation for the genesis of the reaction, the contribution of cinacalcet to the development of QT prolongation/ventricular arrhythmias could not be excluded, particularly considering its effect on calcium levels.

[3] Brunasso AM, Scocco GL, Massone C. Dermatomyositis during adalimumab therapy for rheumatoid arthritis. J Rheumatol. 2010;37(7):1549-50

In particular, the PRAC noted that QT prolongation/ventricular arrthymias is already included in the Risk Management Plan and considered that the new data should prompt re-evaluation of this risk with a view to strengthening risk minimisation as appropriate. On this basis and considering the nature of the suspected reaction, the PRAC agreed that the signal warranted further investigation, and that in light of the strength of the signal an update of the product information should be considered.

Recommendation(s)

- The MAH should be requested to respond to an agreed list of questions within 30 days.
- Having regard to the urgency of the matter, a type II variation should be submitted as a regulatory procedure to address the signal. A 30 day-assessment timetable was supported.

The PRAC will provide advice to the CHMP regarding the assessment of such Type II variation.

Post-meeting note: following the meeting, the MAH requested a 1-month extension of the timeline to submit the requested variation in order to allow for inclusion of additional data from the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) study, since study data were likely to allow better evaluation of the signal. The PRAC agreed to this extension request.

4.1.3. Clopidogrel – PLAVIX (CAP) & generic products

- Signal of eosinophilic pneumonia

Regulatory details:

PRAC Rapporteur: Maria Alexandra Pego (PT)

Background

Clopidogrel is an antithrombotic agent used in the prevention of atherothrombotic events in peripheral vascular diseases, stroke, acute coronary syndrome, myocardial infarction and atrial fibrillation.

Centrally authorised medicines containing clopidogrel have been used, from 1998 until 2010, by an estimated number of more than 115 millions of patients worldwide.

A signal for eosinophilic pneumonia was identified by EMA based on a review of seven cases 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 cases of eosinophilic pneumonia reported to EudraVigilance, including one published case[4]. The PRAC agreed that the risk of eosinophilic pneumonia associated with clopidogrel had been very rarely reported. However the PRAC acknowledged the importance of evaluating the possible causal role of clopidogrel in such reactions, given that stopping a medicince associated with eosinophilic pneumonia when the reaction occurs, could be critical. Therefore the PRAC agreed that the signal warranted further review.

[4] Mizuno Y, Shimizu H, Yamashita M, Horie Y and Mizoo A. A case of clopidogrel-induced eosinophilic pneumonia. The Japanese Respiratory Society Journal 2011; 49(11): 838-842.

Recommendation(s)

- The MAH for the originator products should be requested to submit within 60 days a cumulative review consisting of a scientific evaluation of the cases of eosinophilic pneumonia, hypereosinophilic syndrome, drug rash with eosinophilia and systemic symptoms and drug-induced hypersensitivity syndrome. A 30 day-timetable was supported to assess the results of this review leading to a further PRAC recommendation.

4.1.4. Duloxetine – CYMBALTA, ARICLAIM, XERISTAR, YENTREVE (CAPs)

- Signal of serotonin syndrome due to a potential interaction with aripiprazole

Regulatory details:

PRAC Rapporteur: Dolores Montero (ES)

Background

Duloxetine is a combined serotonin and noradrenaline reuptake inhibitor. Duloxetine is used in the treatment of diabetic neuropathies, depressive disorder, major anxiety disorders.

Centrally authorised medicines containing duloxetine have been used, in the period from 2004 until 2011, by an estimated number of more than 42 million patients worldwide.

During routine signal detection activities, a signal of serotonin syndrome in patients taking duloxetine and aripiprazole, both used concomitantly, was identified by the EMA based on 6 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the review of the cases of serotonin syndrome in patients taking concomitantly duloxetine and aripiprazole reported in EudraVigilance.

The PRAC noted that the current product information for products containing duloxetine contains information of serotonin syndrome. However an interaction with aripiprazole was not specifically reported.

The PRAC discussed the biological rationale of the reaction and concurred that since aripiprazole is a partial agonist of serotonin receptors, a potential for a pharmacodynamic interaction with duloxetine could not be ruled out. The PRAC agreed that the signal warranted further investigation.

Recommendation(s)

- The MAH for duloxetine products should be requested to submit within 60 days a cumulative review. A 30 day-timetable was supported to assess the results of this review, leading to a further PRAC recommendation.

4.1.5. Roxithromycin (NAPs)[5]

- Signal of hearing disorders

[5] Nationally Authorised Product

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Roxithromycin is an antimicrobial used for the treatment of infections due to sensitive microorganisms.

Medicines containing roxithromycin have been nationally authorised in the EU since 1989 and have been used, from 2008 until 2011, by an estimated number of more than 20 million patients worldwide.

During routine signal detection activities, the Italian Medicines Agency (AIFA) identified a signal based on 14 case reports, falling under the category of hearing disorders, retrieved from EudraVigilance. IT confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the cases retrieved from EudraVigilance and noted that some cases have been described in the literature, in relation to other macrolide antibacterials[6]

The PRAC acknowledged that the majority of the patients recovered fully, in accordance with the clinical outcomes commonly reported in the macrolide-related cases of ototoxicity.

The PRAC focused on the severity and outcome of the signal concerned (irreversible hearing damage) and concurred that although rare, ototoxicity from the use of some macrolide antibacterials is a well-recognised adverse drug reaction. Therefore the PRAC agreed that the signal warranted further investigation, and that in light of the strength of the signal an update of the product information should be considered.

Recommendation(s)

The Committee appointed Carmela Macchiarulo (IT PRAC member) as PRAC Rapporteur.

- The MAH for the originator product should be requested to submit a cumulative review of cases of 'hearing disorders' associated with roxithromycin within 60 days.
- A 60 day-type II variation should be submitted as a regulatory procedure to address the signal.

The PRAC will provide advice to the relevant Member States on the assessment of such Type II variation.

4.1.6. Roxithromycin (NAPs)

- Signal of rhabdomyolysis secondary to interaction with statins

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Roxithromycin is an antimicrobial used for the treatment of infections due to sensitive microorganisms.

[6] Periti P, Mazzei T, Mini E, Novelli A. Adverse effects of macrolide antibacterials. Drug Saf. 1993 Nov;9 (5):346-64;; J Coulston, N Balaratnam. Irreversible sensorineural hearing loss due to clarithromycin. Postgrad Med J 2005;81:58–59)

Medicines containing roxithromycin have been nationally authorised in the EU since 1989 and have been used, from 2008 until 2011, by an estimated number of more than 20 million patients worldwide.

During routine signal detection activities the Italian Medicines Agency (AIFA) identified a signal based on 14 case reports of rhabdomyolysis, retrieved from EudraVigilance, describing roxithromycin co-prescribed with statins. IT confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed information arising from the review of the cases describing rhabdomyolysis associated with roxithromycin and co-administered statins.

The PRAC discussed the time-to-onset of the reaction and commented that in several cases rhabdomyolysis occurred when roxithromycin was added to an existing treatment with statins. The PRAC also discussed a possible biological rationale which could explain the reaction and considered that, based also on data from the literature, a potential for drug-drug interaction was plausible. Therefore the PRAC agreed that the signal warranted further investigation.

Recommendation(s)

The Committee appointed Carmela Macchiarulo (IT PRAC member) as PRAC Rapporteur.

The Committee agreed the following recommendation:

- The MAH for the originator product containing roxithromycin should be requested to submit within 60 days a cumulative review of cases of rhabdomyolysis associated with roxithromycin with a particular focus on concomitant administration with statins taking into consideration data on patient exposure. A 60 day-timetable was supported to assess the results of this review leading to a further PRAC recommendation.

EMA will review EudraVigilance data on the therapeutic class concerned and relevant pharmacogenomic information, within the same agreed timeframe and report back to the PRAC.

4.1.7. Sitagliptin - JANUVIA, RISTABEN, TESAVEL, XELEVIA (CAP)

- Signal of rhabdomyolysis

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Sitagliptin is used in the treatment of Type II diabetes mellitus.

Centrally authorised medicines containing sitagliptin have been used by an estimated number of more than 7.1 million patient-years from 2007 until 2011 worldwide.

During routine signal detection activities a signal of rhabdomyolysis in patients taking sitagliptin was identified by the EMA arising from 41 case reports reported to EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the review of the cases reported to EudraVigilance. The PRAC emphasised that a large number of the individual cases, including some published cases, was reported in co-administration with statins, for which rhabdomyolysis is a known adverse drug reaction. The PRAC commented that, in several cases, rhabdomyolysis developed in elderly patients (often with renal insufficiency) in whom sitagliptin was added to an existing multi-therapeutic regimen.

The PRAC also discussed a possible biological rationale for the reaction, and considered the potential for drug-drug interactions and agreed that more information should be gathered on these aspects. in conclusion, given the severity and outcome of the reaction, as well as the observed occurrence of the reaction in patients with impaired renal failure, the PRAC agreed that the signal warranted further investigation.

Recommendation(s)

- The MAH for sitagliptin originator products should be requested to submit within 60 days a cumulative review of cases of rhabdomyolysis associated with sitagliptin with a particular focus on concomitant administration of statins, paying special attention to those patients with impaired renal function, taking into consideration available pre-clinical data and categorisation of rhabdomyolysis cases. The review will be assessed in the framework of an upcoming PSUR procedure.

The EMA will review data from EudraVigilance on the products concerned to support the assessment of the Rapporteur taking account of methodological approaches to detect the effect of drug-drug association on drug-event association (bystander bias).

Based on the outcome of the current assessment on the possible association between sitagliptin and rhabdomyolysis the PRAC will give consideration on the need for a review of the therapeutic class of the DPP-4 inhibitors. Products involved in such a review and the appropriate legal framework for this will be further discussed.

4.1.8. Somatropin – NUTROPINAQ, OMNITROPE (CAPs, NAPs)

- Signal of convulsions (SMQs – Standardised MedDRA Queries)

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Background

Somatropin is a potent metabolic hormone used to treat various conditions including Prader-Willi syndrome, pituitary dwarfism, Turner syndrome.

Medicines containing somatropin have been authorised in the EU since 2001. Somatropins have been used by a large number of patients worldwide.

During routine signal detection activities a signal for a possible association of convulsions with somatropins was identified by the EMA arising from 228 cases reported to EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the review of the cases, describing reactions falling under the category of convulsions. The PRAC reflected on the fact that a number of literature articles described a potential association between somatropin and convulsions and that the product information of some somatropins already lists raised intracranial pressure as an adverse effect. However, the PRAC agreed that the signal warranted further investigation with a view to strengthening risk minimisation as appropriate.

Recommendation(s)

The Committee appointed Sabine Straus (NL) as PRAC Rapporteur.

- The MAHs for all authorised products should be requested to perform within 120 days a cumulative review of case reports from all sources and available - literature of 'SMQ Narrow (Standardised MedDRA Queries, narrow scope) Convulsions' associated with somatropin. A 60 day-timetable was supported to assess the results of this review leading to a further PRAC recommendation.

4.1.9. Sunitinib - SUTENT (CAP)

- Signal of cholecystitis

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Background

Sunitinib is an antineoplastic agent used in the treatment of pancreatic neuroendocrine tumours, gastrointestinal stromal tumors (GIST) and metastatic renal cell carcinoma.

Sutent, a centrally authorised medicine which contains sunitinib, has been used, from 2006 to 2012, by an estimated number of more than 160,000 patients, worldwide.

During routine signal detection activities, a signal of cholecystitis was identified by the EMA based on 17 cases of cholecystitis and related disorders 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 reported in EudraVigilance. The PRAC commented that some of the cases diagnosed as cholecystitis may have been confounded by a coexistent perihepatitis, but also took into consideration that neither cholelithiasis nor metastases had been described in the cases reviewed. Moreover, the PRAC remarked that cases of acalculous and emphysematous cholecystitis had also been described in the literature, postulating a plausible biological rationale related to anti-angiogenic activity, and emphasised that a positive de-challenge was identified in the same cases. Therefore, the PRAC agreed that the signal warranted further investigation.

Recommendation(s)

- The MAH should be requested to perform within 60 days a cumulative review of cases of cholecystitis and related terms associated with sunitinib with particular focus on acalculous and

emphysematous cholecystitis. A 30 day-timetable was supported to assess the results of this review leading to a further PRAC recommendation.

4.1.10. Varenicline - **CHAMPIX** (CAP)

- Signal of convulsions

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Background

Varenicline is indicated for smoking cessation in adults.

The patient exposure for Champix, a centrally authorised medicine containing varenicline since 2006 has been estimated to be more than 450,000 patients-years worldwide, in the period from 2011 until 2012[7].

Following a search of the UK Yellow Card Database[8], UK identified a signal of convulsions with varenicline, based on 85 case reports. EMA contributed by reviewing EudraVigilance data. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information arising from the review of the cases reported for 'convulsions' (Standardised MedDRA Queries, narrow scope). In many of the cases reported other risk factors accounting for convulsions were present or there was insufficient information provided. Nevertheless, in a very small number of cases, it was more difficult to exclude a possible causal association. Therefore the PRAC agreed that the signal warranted further review.

Recommendation(s)

- The PRAC Rapporteur should assess the UK cases in the ongoing PSUR procedure (start: 2 August 2012); the Rapporteur will present the PSUR Assessment Report at the 26-29 November 2012 PRAC meeting.

In addition, the UK will provide a report to the PRAC Rapporteur on the nicotinic receptor mutation and further explore the background incidence of epilepsy as appropriate.

4.1.11. Vemurafenib - **ZELBORAF** (CAP)

- Signal of pancreatitis

Regulatory details:

PRAC Rapporteur: Ulla Wandel Liminga (SE)

[7] Based on data contained in the latest PSUR submitted
[8] The Yellow Card Scheme, run by the Medicines and Healthcare products Regulatory Agency (MHRA) and the UK Commission on Human Medicines, is used to collect information from both health professionals and the general public on suspected side effects

Background

Vemurafenib is an antineoplastic medicine used in the treatment of unresectable or metastatic melanoma.

Zelboraf, a centrally authorised medicine containing Vemurafenib since February 2012, has been used until June 2012, by an estimated number of more than 5,000 patients worldwide.

During routine signal detection activities, a signal relating to a possible association of pancreatitis with vemurafenib, was identified by EMA based on 9 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 preliminary analysis of the cases reported and agreed that it provided sufficient information to warrant further analysis of the data. The PRAC was informed that in this case the MAH had already been requested to perform a cumulative review of all cases of pancreatitis and related terms to be included in the next PSUR, with data lock point 17 August 2012, submission expected in October 2012.

The MAH should include in the analyses the review of time to onset and time to resolution of pancreatitis in the melanoma patient population.

Recommendation(s)

- The Rapporteur should assess the cumulative review of pancreatitis and related terms within the next PSUR due for submission in October 2012 according to the related timetable.

The EMA will support closely the monitoring in EudraVigilance of any new cases of pancreatitis reported in association with vemurafenib and communicate to the Rapporteur as appropriate.

4.2. New signals detected from other sources

4.2.1. **Codeine** (NAPs)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Codeine is a widely used opioid medicine for pain relief. It is also used in the treatment of coughs.

On 15 August 2012, the US FDA published a Drug Safety Communication warning that codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death (http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm). These children had evidence of being “ultra-rapid metabolizers” of substrates of cytochrome P450 2D6 (CYP2D6), including codeine.

In response to this communication, EMA performed a search in EudraVigilance for paediatric cases from the EEA with fatal outcome reported in association with codeine use. In the absence of a Lead Member State the EMA confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted that, in some EU Member States, the product information for codeine-containing products already included a reference to the risk of administration of codeine to CYP2D6 ultra-rapid metaboliser patients.

The PRAC then discussed the outcome of the search performed in EudraVigilance which found 2 serious cases in paediatric subjects known to be extensive CYP2D6 metabolisers. Additional cases reported did not investigate CYP2D6 phenotype but high blood levels of codeine and its metabolites were recorded.

The PRAC concurred on the severity of the observed reactions and agreed that the available information of the cases suggested that codeine had reached toxic blood levels. Therefore the PRAC emphasised that further consideration of risk minimisation measures was necessary. Furthermore such measures, in principle, should be consistently applied across all codeine-containing products in all Member States of the EU, especially for those products authorised in the paediatric population for post-operative pain relief.

The PRAC concluded that the signal required further review with the aim to discuss risk minimisation measures. Follow-up discussion was provisionally planned for the 1-3 October 2012 meeting following a rapid information gathering exercise directed towards all Member States regarding the authorisation status of codeine containing medicines.

Recommendation(s)

The Committee appointed Julie Williams (UK) as Rapporteur for this signal.

- The Rapporteur should conduct a survey on the authorisation status in EU of codeine-containing products indicated in children to make an informed decision on the mechanism for follow up of the signal , for further discussion at the 1-3 October 2012 PRAC meeting.

4.3. Signals follow-up and prioritisation

4.3.1. Pandemic influenza vaccine – **PANDEMRIX** (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Background

Pandemrix is a pandemic influenza vaccine, H1N1. Pandemrix had been the subject of a previous referral procedure (European Medicines Agency recommends restricting use of Pandemrix published on 21 July 2011), in which the CHMP concluded that there was a 6 to 13-fold increased risk of narcolepsy in vaccinated children and adolescents and recommended the restriction of the use of the vaccine to adults over 20 years of age.

Pandemrix has been authorised since 2008, and it is estimated that more than 31 million patients had been vaccinated so far[9]. However the last doses of Pandemrix were distributed during March 2011 and

[9] From the Marketing Authorisation until 2012, based on data from national authorities

the product had a shelf life of 2 years. It is therefore unlikely that currently Pandemrix remains in use in the EU.

EMA was informed that new preliminary information on the risk of narcolepsy, arising from the results of a French study, had become available for regulatory review. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

A researcher from the University of Bordeaux presented the preliminary results of the French case-control study. The expected date of publication of the study at the time of the meeting was mid-September 2012.

An association between narcolepsy and H1N1 vaccine was found for the whole study population that received Pandemrix as the main vaccine compared with another vaccine used as a control. Given that during the period analysed media attention was estimated to be low, publication bias was not considered an issue in the study. The risk difference between subjects aged under 19 and subjects aged 19 or over was difficult to estimate. The European Centre for Disease Prevention and Control (ECDC) was planning to communicate on the Vaccine Adverse Event Surveillance & Communication (VAESCO) studies results mid-September 2012. The French National Agency (ANSM) was also planning to communicate on H1N1 vaccination and narcolepsy (French pharmacovigilance updated data, VAESCO studies results, French case-control results) in mid-September 2012.

A researcher from the Health Protection Agency (HPA), London, presented the preliminary results of a study recently submitted for peer-reviewed publication (Risk of narcolepsy in children receiving an AS03 adjuvanted AH1N1 (2009) influenza vaccine in England).

The PRAC discussed a summary of findings from the EU Pandemrix and narcolepsy studies (children and adolescents) and a proposal for an update of the product information for Pandemrix.

Recommendation(s)

Given that there was no ongoing utilisation in the EU and further data/analyses are anticipated, the PRAC agreed awaiting the Rapporteur's assessment of the French study prior to concluding on the nature of any change to the product information based on the available epidemiological study data on the risk of narcolepsy.

Further discussion is scheduled for the 29-31 October 2012 PRAC meeting.

Post-meeting note: communications on VAESCO study results and French results of the case-control study were released on 20 September 2012 by ECDC and the French Medicines Agency (ANSM) respectively.

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

5.1.1. Phentermine/topiramate

- Evaluation of the RMP in the framework of a full application for a Marketing Authorisation Application

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

The PRAC discussed the RMP for a medicine containing phentermine and topiramate in the framework of a full application for a centralised Marketing Authorisation Application, and provided advice to the CHMP.

Full information relating to PRAC discussions on products in the pre-authorisation phase will be released once the CHMP has reached an opinion for such medicines.

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

5.2. Medicines already authorised

None

6. Assessment of Periodic Safety Update Reports (PSURs)

None

7. Post-authorisation Safety Studies (PASS)

7.1. Post-authorisation safety studies protocols

None

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

9.1. Safety related variations

None

9.2. Renewals

None

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

10.1. Safety related variations

None

10.2. Renewals

None

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

None

10.4. Other

None

11. Organisational, regulatory and methodological matters

11.1. Mandate and organisation of the PRAC

11.1.1. Election of the Chair and Vice-Chair of the PRAC

June Raine was elected as Chair, for a term of 3 years. Almath Spooner was elected as vice-Chair for the same term.

11.1.2. Rules of Procedure of the PRAC

The EMA updated the PRAC on the process for finalisation of the PRAC Rules of Procedure adopted at its inaugural meeting. The PRAC Rules of Procedure, as adopted by the PRAC at its July 2012 meeting will be in use awaiting the favourable opinion of both the European Commission and the EMA Management Board. Both the European Commission and the EMA Management Board are now being consulted and the Management Board will discuss the PRAC Rules of Procedure at their 4 October 2012 meeting (for details see *www.ema.europa.eu* Home>About Us>Who we are>Management Board>Meetings). An update of the discussion will be given at the 29/31 October meeting of the PRAC.

11.2. Pharmacovigilance audits and inspections

None

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

11.3.1. Periodic Safety Update Reports

None

11.3.2. PSURs Repository

None

11.3.3. Union Reference Date List (EURD List)

11.3.3.1. Consultation on the draft List, version September 2012

The EURD list has been prepared by the EMA in collaboration with the National Competent Authorities and MAHs. It consists of a comprehensive list of active substances/combinations of active substances subject to different marketing authorisations and for which the PSUR submission frequencies have been allocated following a risk based approach. The list also includes the Union Reference Dates (EURD) of the substances, the Data Lock Points (DLP) that will drive the PSUR submission, and a statement whether PSURs are required for Generic, Well Established Use (WEU), Homeopathic, Traditional Herbal medicinal products containing each of the active substances/combinations of active substances listed in the document.

The PRAC adopted the final draft EURD list with some minor refinements. The list will be transmitted to September 2012 CHMP and CMDh for adoption.

Post-meeting note: The EURD list was published on the EMA website on 1 October 2012 (www.ema.europa.eu Home>Regulatory>Human medicines>Pharmacovigilance> Guidance European Union reference dates and frequency of submission of periodic safety update reports (PSUR)).

11.4. Signal Management

11.4.1. Signal Management

11.4.1.1. List of substances subject to signal management worksharing

The PRAC was reminded of the legal obligation for the EMA to publish a list of the active substances that are subject to worksharing for signal management together with the appointed lead Member States and co-leaders. The view was expressed that it would be logical for the same Member State to assess the signal detection and PSURs for the same active substance to support development of knowledge of benefit risk throughout the product lifecycle. The benefits were acknowledged and this might be aimed for in future. Further comments should be sent to EMA lead person by 12 September 2012.

The list will be sent to CMDh, for appointment of lead Member State, during their September 2012 meeting. It was highlighted that substances not yet allocated are to be monitored by all Member States. The list will be updated on a regular basis.

11.5. Adverse Drug Reactions reporting and additional reporting

11.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

None

11.5.2. Additional Monitoring

None

11.5.3. List of Products under Additional Monitoring

11.5.3.1. Creation and maintenance of the List

The PRAC was reminded of the list of products under additional monitoring which will include all medicinal products approved in the EU subject to additional monitoring irrespective of the approval procedure (i.e. centrally or nationally authorised). It was explained that the National Competent Authorities can link to the EMA list on their website or publish a list of nationally authorised products only. The deadline to answer the Non Urgent Request of Information was extended until 20 September 2012. The full criteria for filling in the list will be re-circulated by EMA.

The Committee noted that the draft templates and procedures will be presented at the September 2012 CMDh meeting.

11.5.3.2. Selection of symbol for products subject to additional monitoring

The members were informed about discussions at the Quality Review of Documents (QRD) group on the work undertaken by the EMA on the identification of the black symbol for products subject to additional monitoring.

The QRD proposed two symbols to the PRAC: an inverted black triangle and a magnifying glass. The members discussed the advantages and disadvantages of both symbols. BE and UK agreed to provide further information on the value of the use of the inverted triangle at national level in advance of the October 2012 PRAC meeting.

A trend vote was taken on the two symbols and a majority in favour of the inverted black triangle was observed (20 in favour of the triangle out of 31, Iceland and Norway supported the majority).

Further discussion and conclusion are expected at the October 2012 PRAC meeting.

11.6. EudraVigilance Database

None

11.7. Risk Management Plans and Effectiveness of risk Minimisations

11.7.1. Risk Management Systems

11.7.1.1. Draft PRAC Rapporteur RMP Assessment Report template

The members were informed about the draft PRAC Rapporteur RMP Assessment Report template. Comments on the template should be sent to the EMA topic leader by 20 September 2012.

11.7.1.2. Draft PRAC Advice template

The members noted the draft PRAC Advice template. Comments on the template should be sent to the EMA topic leader by 20 September 2012.

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

None

11.8. Post-authorisation Safety Studies

11.8.1.1. Draft PRAC Rapporteur PASS protocol Assessment Report template

The members noted the draft templates for the study protocol of a non-interventional Post-authorisation safety study (PASS) and for the PASS protocol PRAC Rapporteur's assessment report.

Comments on the template for the study protocol of a non-interventional PASS should be sent to the EMA topic leader by 7 September 2012 and on the PRAC Rapporteur PASS protocol assessment report template by 20 September 2012.

11.9. Community Procedures

None

11.10. Risk communication and Transparency

None

11.11. Continuous pharmacovigilance

11.11.1. Continuous Pharmacovigilance, Ongoing Benefit-Risk Evaluation, Regulatory Status and Planning of Public Communication

None

11.11.2. Incident Management

None

11.12. General regulatory matters

11.12.1.1. Good Vigilance Practice (GVP)

The PRAC was provided by the EMA with an update on the GVP development. Following finalisation of the first seven modules, further modules are under preparation. For population of later chapters and for product type-specific issues, guidance is also planned. The current focus however is on finalising the draft modules on inspections, audits, additional monitoring and safety communication as well as on drafting module XI on public participation, module XII on continuous pharmacovigilance (with the integration of benefit-risk evaluation/communication, planning/decision making in regulatory action) and module XVI on risk minimisation. The PRAC will be consulted on mature drafts of all modules pre- and/or post-public consultation, as applicable.

11.13. Inter Status with EMA Committees and Working Parties

None

11.14. Inter Status within the EU regulatory network

None

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

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

None

12. Any other business

None

ANNEX I – List of Participants: *including any restrictions with respect to involvement of members / alternates / experts following evaluation of Declared interests.*

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI	Topics on the current Committee Agenda for which restriction applies
			Product / substance
Harald Herkner	Austria	Full involvement	
Bettina Schade - *apologies*	Austria	Not applicable	
Jean-Michel Dogne	Belgium	Cannot act as Rapporteur or Peer reviewer	Roxithromycin,Codeine
Virginie Chartier	Belgium	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Yuliyan Eftimov	Bulgaria	Full involvement	
Christos Petrou - *apologies*	Cyprus	Not applicable	
Jana Mlada	Czech Republic	Full involvement	
Eva Jirsova - *apologies*	Czech Republic	Not applicable	
Doris Stenver	Denmark	Full involvement	
Jens Ersboll - *apologies*	Denmark	Not applicable	
Maia Uuskula	Estonia	Full involvement	
Katrin Kiisk - apologies	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Terhi Lehtinen	Finland	Cannot act as Rapporteur or Peer reviewer, involvement in discussions only (i.e. no part in final deliberations and voting as appropriate), for:	Duloxetine
Isabelle Robine	France	Full involvement	
Evelyn Falip - *apologies*	France	Not applicable	
Martin Huber	Germany	Full involvement	
Birgitta Kutting	Germany	Full involvement	
George Aislaitner	Greece	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer reviewer for:	Roxithromycin, Sunitinib, Varenicline, Codeine
Julia Pallos	Hungary	Full involvement	
Melinda Palfi	Hungary	Full involvement	
Gudrun Kristin Steingrimsdottir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Donal Og Donovan – *apologies*	Ireland	Not applicable	
Carmela Macchiarulo	Italy	Full involvement	
Fernanda	Italy	Full involvement	

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI	Topics on the current Committee Agenda for which restriction applies Product / substance
Ferrazin			
Andis Lacis	Latvia	Full involvement	
Inguna Adovica	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Rita Dzetaveckiene - *apologies*	Lithuania	Not applicable	
Jacqueline Genoux-Hames - *apologies*	Luxembourg	Not applicable	
Amy Tanti	Malta	Full involvement	
Suzanne Magri Demajo - *apologies*	Malta	Not applicable	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjorg Buajordet	Norway	Full involvement	
Pernille Harg	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Alexandra Pego - *apologies*	Portugal	Not applicable	
Margarida Guimaraes	Portugal	Full involvement	
Nicoalae Fotin	Romania	Cannot act as Rapporteur or peer reviewer,, involvement in discussions only (i.e. no part in final deliberations and voting as appropriate) for:	Roxithromycin
Daniela Pomponiu	Romania	Full involvement	
Tatiana Magalova	Slovakia	Full involvement	
Anna Harcarova	Slovakia	Full involvement	
Milena Radoha-Bergoc	Slovenia	Full involvement	
Dolores Montero	Spain	Full involvement	
Miguel-Angel Macia	Spain	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Ulla Wandel Liminga	Sweden	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	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		Full involvement	
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Full involvement	
Lennart Waldenlind		Full involvement	

Additional European experts participating to the meeting for specific Agenda items	Country	
Benedicte Lunddahl	Denmark	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Antoine Pariente	France	
Christel Saussier	France	
Scheherazade Ouaret	France	
Sinead Curran	Ireland	
Charlotte Backman	Sweden	
Michael Foy	United Kingdom	
Catherine Tregunno	United Kingdom	
Phil Tregunno	United Kingdom	
Nick Andrews	United Kingdom	
Kristina Dunder (CHMP member) participation via teleconference	Sweden	

ANNEX II – List of Abbreviations

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

www.ema.europa.eu

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