12 February 2015
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Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 6-9 January 2015

Chair: June Raine – Vice-Chair: Almath Spooner

Disclaimers

Some of the information contained in this agenda is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the PRAC meeting highlights once the procedures are finalised. The start of referrals will also be announced in the meeting highlights.

Note on access to documents

Some documents mentioned in the agenda cannot be released at present following a request for access to documents under Regulation (EC) No 1049/2001 as they relate to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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Explanatory notes

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

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 agenda)

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 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.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. 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 summary of product characteristics and the package leaflet.

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

The RMP describes what is known and not known about the side effects of a medicine and states how these risks 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 agenda)

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 summarises data on the benefits and risks of a medicine and includes 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 agenda)

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 management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections
(Item 9 of the PRAC agenda)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

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

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1. Introduction

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

The Chairperson opened the 6-9 January 2015 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Amelia Cupelli as the new alternate for Italy. In addition, the PRAC welcomed the new Latvian presidency of the Council of the EU.

1.2. Adoption of agenda of the meeting of 6-9 January 2015

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

1.3. Minutes of the previous PRAC meeting on 1-4 December 2014

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

Post-meeting note: the PRAC minutes of the meeting held on 1-4 December 2014 were published on the EMA website on 14 January 2015 (EMA/PRAC/786812/2014).

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

None

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

3.1. Newly triggered Procedures

None

3.2. Ongoing Procedures

None

3.3. Procedures for finalisation

3.3.1. **Ambroxol** (NAP); **bromhexine** (NAP)

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

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)
PRAC Co-Rapporteurs: Jean-Michel Dogné (BE), Harald Herkner (AT)

Administrative details:
MAH(s): Boehringer Ingelheim, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC for ambroxol and bromhexine-containing medicines (see minutes of the PRAC 1-4 December 2014 meeting for background) is to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs as well as the available evidence on the risks of serious cutaneous adverse reactions (SCARs) associated with the use of ambroxol and bromhexine-containing medicines and aspects relating to paediatric use of these products taking into account the advice provided by the PDCO. The PRAC considered that ambroxol and bromhexine are associated with hypersensitivity reactions, including anaphylactic reactions and that there is reasonable possibility of a risk of SCARs associated with these products based on spontaneous case reports. Overall, the PRAC considered that such reactions were likely to be very rare given the extensive exposure to ambroxol and bromhexine-containing medicines over many years. The PRAC was of the view that the risk of SCARs should be addressed by its inclusion in the product information accompanied by a warning in order for patients and caregivers to recognise the prodrome of SCARs and discontinue treatment immediately in the event of such signs. In addition, the PRAC agreed that all product information for these medicines should reflect the current knowledge on the risk of immediate hypersensitivity reactions. Finally, the PRAC considered that the available data were insufficient to justify the introduction of new age restrictions, therefore no recommendation was made regarding changes to existing age restrictions in the different Member States.

Summary of recommendation(s)/conclusions

The PRAC adopted by majority[1] a recommendation, to be considered by the CMDh, to vary the marketing authorisations for ambroxol and bromhexine-containing medicines – see 'PRAC considers risk of severe allergic reactions with ambroxol- and bromhexine-containing medicines to be small' EMA/796499/2014. The PRAC also agreed key messages that could be used for communication at national level, via preferred routes to be decided by individual MSs: e.g. bulletins, webpage or direct healthcare professional communication (DHPCs).

[1] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded. CMDh position planned for the February 2014 meeting

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

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Denosumab – PROLIA** (CAP), **XGEVA** (CAP)

- Signal of deafness

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

Administrative details:
EPITT 18175 – New signal
MAH(s): Amgen Europe B.V.
Lead MS: SE

Background

Denosumab is a human monoclonal antibody used for the treatment of osteoporosis, bone loss in men with prostate cancer, prevention of skeletal related events in adults with bone metastases from solid tumours and treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The exposure for centrally authorised medicines containing denosumab, is estimated to have been more that 1.2 million patient-years for Prolia and 147,000 patient-years for Xgeva from first authorisation in 2010 to 2013.

During routine signal detection activities, a signal of deafness was identified by the EMA, based on 37 cases of deafness and unilateral deafness retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of deafness and agreed that out of the 37 cases, 6 seemed possibly related to denosumab with a suspected causality, including 1 with a positive rechallenge. In other cases an association cannot be excluded but the level of detail provided was variable and so far, no cases had been reported in the literature.

Therefore the PRAC agreed that further information was needed for the assessment of this signal and, for the cases identified, a history of infections or current infection, as well as antibiotic treatment should be specifically addressed as certain antibiotics can cause hearing loss.

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

Summary of recommendation(s)

- The MAH for Prolia and Xgeva (denosumab) should submit to the EMA within 60 days a cumulative review of the signal of deafness associated with denosumab, including literature, post-marketing and clinical trials data, to be assessed within the PSURs currently under evaluation (DLP: 26/09/2014).

4.1.2. Olanzapine – **ZYPADHERA** (CAP), **ZYPREXA** (CAP), **ZYPREXA VELOTAB** (CAP)

- Signal of angle closure glaucoma

Regulatory details:
PRAC Rapporteur: Terhi Lehtinen (FI)

Administrative details:
EPITT 18159 – New signal
MAH(s): Eli Lilly Nederland B.V.
Lead MS: FI

Background

Olanzapine is an atypical antipsychotic used for the treatment of schizophrenia, for the treatment of moderate to severe manic episodes and for the prevention of recurrence in patients with bipolar disorder. As a suspension for injection, it is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or manic episodes, when oral therapy is not appropriate.

The exposure for centrally authorised medicines containing olanzapine, is estimated to have been more than 41 million patients, in the period from first authorisation in 1996 to 2014.

During routine signal detection activities, a signal of narrow-angle glaucoma was identified by the EMA, based on 13 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of glaucoma reported and noted that according to the product information, the use of olanzapine is contraindicated in patients with known risk of narrow-angle glaucoma. The PRAC also considered that some of the cases reported as new 'onset of glaucoma' had been assessed as related by the reporter since no pre-existing risk factors were present. The pathogenic mechanism by which olanzapine may induce angle closure glaucoma is based on its proposed anticholinergic effects which may cause mydriasis and therefore cause a mechanical closure of the angle in anatomically predisposed eyes, causing an increase of intraocular pressure. The PRAC acknowledged that the number of reported cases was low in absolute terms considering the wide population exposure, and noted that contraindications were already in place. However, the PRAC agreed that the signal should be fully evaluated.

Summary of recommendation(s)

- The MAH for Zyprexa (olanzapine) should submit to the EMA within 60 days a cumulative review of the signal. This should include a detailed discussion on the pathogenic mechanism, review of spontaneous cases as well as information from clinical trials and literature.

4.2. New signals detected from other sources

4.2.1. **Daclatasvir - DAKLINZA** (CAP)
Sofosbuvir - SOVALDI (CAP), **sofosbuvir, ledipasvir – HARVONI** (CAP)

- Signal of arrhythmia

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:
EPITT 18177 – New signal
MAH(s): Gilead Sciences International Ltd (Harvoni, Sovaldi), Bristol-Myers Squibb Pharma EEIG (Daklinza)
Lead MS: PT

Background

Daclatasvir and sofosbuvir are antivirals for systemic use, indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

The cumulative post-authorisation exposure for Sovaldi, a centrally authorised medicine containing sofosbuvir, in the EU is estimated to be approximately 9,600 patients, in the period from first authorisation in January 2014 to June 2014. The cumulative post-authorisation exposure for Daklinza a centrally authorised medicine containing daclatasvir is not yet available (as the first PSUR is due for submission in March 2015).

During routine signal detection activities, on the basis of a cluster of case reports[3] mainly issued from the French safety database, France identified a signal of cardiac arrhythmia with sofosbuvir and/or daclatasvir. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information available on the cluster of case reports of arrhythmia reported in the French Safety database suggesting a signal of a potential risk of cardiac arrhythmia with sofosbuvir and/or daclatasvir, notably in the presence of potentiating factors, such as concomitant use of medications inducing bradycardia, including amiodarone in some cases, or a medical history of cardiac disease. In order to fully assess the signal, the PRAC agreed that based on the available information, a comprehensive cumulative safety review on cardiac arrhythmia should be performed including an analysis of possible potentiating factors such as drug-drug interaction and carefully examine the possible influence of risk factors. Moreover, any potential relationship with the baseline degree of hepatic dysfunction should be investigated.

Summary of recommendation(s)

- The MAHs for Daklinza (daclatasvir), Sovaldi (sofosbuvir) and Harvoni (sofosbuvir/ledipasvir) should submit to the EMA within 60 days a cumulative review of all cases of cardiac arrhythmias, including bradycardia, taking into account all relevant data.

[3] 6 cases reports in patients taking sofosbuvir and daclatasvir; and 2 cases in patients taking sofosbuvir with other antivirals

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: At its February 2015 plenary meeting, the PRAC agreed to shorten the timetable for the review assessment and a follow-up discussion is planned in April 2015. The PRAC also confirmed that the dissemination of a DHPC was not warranted at this stage of the evaluation (in line with GVP Module XV – Safety communication).

4.2.2. **Benzodiazepines** (NAP)

- Signal of Alzheimer's disease

Regulatory details:
PRAC Rapporteur: N/A

Administrative details:
EPITT 18195 – New signal
MAH(s): various
Lead MS: DK

Background

Benzodiazepines are a widely prescribed class of substances approved in several indications including anxiety, insomnia, muscle spasms, epilepsy, general anaesthesia, sedation prior to surgical procedures and adjunctive therapy in psychotic illnesses. The majority of benzodiazepines are authorised through the national route.

A signal of benzodiazepines and Alzheimer's disease (AD), based on the case-control study by *Billioti et al*[4] published in the BMJ in September 2014, was brought to the attention of the PRAC by the CMDh and was evaluated by DK which confirmed that the signal needed further analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the conclusion of the study by *Billioti et al.* that the risk of AD was increased by 43-51% amongst patients who previously received benzodiazepine treatment and that the risk was increased in patients with longer exposure.

The PRAC commented on the inherent limitations of this type of study in the investigation of the research question, given its retrospective case-control design, and highlighted the challenges of research in the area. The PRAC, on one hand, acknowledged the good quality of the study but also emphasised that, as highlighted by the authors, the two main indications for benzodiazepines, namely anxiety and sleep disorder, are early symptoms of dementia. The PRAC agreed that no regulatory action was necessary based on this study report and will continue to closely monitor this issue for new evidences.

Summary of recommendation(s)

- No regulatory action was considered necessary based on this study report; however the signal should continue to be monitored closely, according to current practice, in case any new evidence arises.

[4] Billioti de Gage S, Moride Yola, Ducruet Thierry, Kurth Tobias, Verdoux Hélène, Tournier Marie et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study BMJ 2014; 349:g5205

4.2.3. **Clopidogrel – PLAVIX** (CAP)
Prasugrel – EFIENT (CAP)

- Safety of dual antiplatelet therapy

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:
EPITT 18184 – New signal
MAH(s): Eli Lilly Nederland B.V. (Efient), Sanofi Clir SNC (Plavix)
Lead MS: PT

Background

Clopidogrel and prasugrel are two antithrombotic agents belonging to the class of thienopyridines.

The exposure for centrally authorised medicine containing clopidogrel or prasugrel, is estimated to have been more than, respectively, 164 million patient (from 1998 to 2013) for clopidogrel and 2 million patients (from 2009 to 2014) for prasugrel, worldwide.

The EMA was informed by the FDA of a recent literature article by *Mauri et al.*[5] published in the New England Journal of Medicine (NEJM) describing the benefits and risks of continuing dual antiplatelet therapy beyond 1 year, after the placement of a drug eluting coronary stent. The study was conducted to assess the optimal duration of use of dual antiplatelet therapy based on a thienopyridine drug (clopidogrel or prasugrel) and aspirin. At the same time, the FDA published a drug safety communication entitled: *FDA reviews long-term antiplatelet therapy as preliminary trial data shows benefits but a higher risk of non-cardiovascular death*. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the findings of the dual antiplatelet therapy (DAPT) study, a randomized, placebo controlled, double blind trial that evaluated efficacy and safety of 12 *vs* 30 months of dual antiplatelet treatment, involving approximately 10,000 patients. Amongst patients who continued with thienopyridine therapy from 12 to 30 months there was a lower risk of stent thrombosis, myocardial infarction (MI) and of major adverse cardiac or cerebrovascular events (MACCE) (composite endpoint of death, MI and stroke).
On the contrary, overall death was increased in subjects receiving 30 months of dual antiplatelet therapy compared to those receiving 12 months of therapy, driven by an increase in non-cardiovascular death. The increase in nonvascular deaths seemed to relate only to the clopidogrel treated group, but not to the prasugrel one.

The PRAC discussed the strengths and limitations of the study and noted that, according to the authors, there might have been an imbalance at the time of randomisation due to chance, with a higher proportion of patients with known cancer included in the dual antiplatelet arm.

In addition, some of the findings may be a result of multiple testing problems, and, amongst other issues, the population enrolled in DAPT had several pre-existing cardiovascular risk factors, namely diabetes, and were also treated with other medications that may have not been controlled to avoid

[5] Mauri, L., Kereiakes, D. J., Yeh, R. W., Driscoll-Shempp, P., Cutlip, D. E., Steg, P. G., Massaro, J. M. (2014). Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. The New England Journal of Medicine, 141116134515006. doi:10.1056/NEJMoa1409312

bias. However, given the significant sample size, the pragmatic 'real life' approach and the relevance of the adverse event, the PRAC agreed that the signal should be further investigated, first taking into account any relevant information from the routine regulatory exchange with FDA.

Summary of recommendation(s)

- Follow-up discussion will take place at the April/May 2015 PRAC plenary meeting after further review and clarification on the signal are gathered.

4.2.4. Leflunomide – ARAVA (CAP)

- Signal of colitis

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
EPITT 18189 – New signal
MAH(s): Sanofi-aventis Deutschland GmbH (Arava, Leflunomide Winthrop), Teva B.V.(Repso), Teva Pharma B.V. (Leflunomide Teva), Medac Gesellschaft fur klinische Spezialpraparate GmbH (Leflunomide medac), Ratiopharm GmbH (Leflunomide ratiopharm)
Lead MS: NL

Background

Leflunomide is a disease-modifying anti-rheumatic drug (DMARD) used in the treatment of rheumatoid arthritis and psoriatic arthritis.

The exposure for centrally authorised medicines containing leflunomide is estimated to have been over 2 million patient-years worldwide in the period from first authorisation in 1999 until 2014.

During routine signal detection activities, a signal of colitis and related terms was identified by the EMA, based on 16 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of colitis reported which included colitis microscopic, colitis ulcerative, ischaemic and haemorrhagic enterocolitis.

The cases seemed to suggest a pattern of patients with rheumatoid arthritis, without previous history of gastrointestinal issues, who started treatment with leflunomide and within months or years developed severe diarrhoea and dehydration, amongst other ADRs. In about 50% of cases this resulted in significant weight loss.
Patients were treated with intravenous fluids, and empirical antibiotic therapy. Cholestyramine wash-out was performed in some cases. Biopsies were also performed in a number of cases and the results were consistent with different types of colitis. The PRAC noted that some cases were also described in the literature and agreed that further information was needed in order to progress in the evaluation of the signal.

Summary of recommendation(s)

- The MAH for Arava (leflunomide) should submit to the EMA within 60 days a cumulative review of cases of colitis (excluding infective) associated with leflunomide.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.5. Sildenafil – **REVATIO** (CAP), **VIAGRA** (CAP)

- Signal of pulmonary haemorrhage in off label paediatric use

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

Administrative details:
EPITT 18183 – New signal
MAH(s): Pfizer Limited (Revatio, Viagra), Actavis Group PTC ehf (Sildenafil Actavis), Ratiopharm GmbH (Silendafil Ratiopharm), Teva Pharma B.V. (Sildenafil Teva)
Lead MS: NL

Background

Sildenafil is phosphodiesterase type 5 (PDE5) inhibitor used for the treatment of erectile dysfunction in men and for the treatment of pulmonary arterial hypertension.

The exposure for centrally authorised medicines containing sildenafil is estimated to have been, in the period from first authorisation in 1999 to 2014, more than 376,000 patient-years in the pulmonary hypertension indication and 68 million patients in the erectile dysfunction indication.

During routine signal detection activities, a signal of pulmonary haemorrhage was identified by the EMA, based on a recent publication by *Steiner et al*[6] which triggered a further search in EudraVigilance resulting in a total of 30 cases identified. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the recent publication by *Steiner et al.* describing pulmonary haemorrhage in two very premature babies (<30 weeks gestational age) treated, off-label, with sildenafil for respiratory failure and patent ductus arteriosus.

The PRAC also discussed the information on the other paediatric cases reviewed. Several cases had a time-to-onset suggestive for an association with the treatment and did not report other suspected concomitant medications which could have provided an alternative explanation for the development of the reaction.

Therefore the PRAC concluded that the role of sildenafil in the occurrence of pulmonary haemorrhage could not be ruled out. Moreover the PRAC noted that the RMP of Revatio lists epistaxis/bleeding amongst important identified risks and the product information includes a warning of bleeding in combination with risk factors for haemorrhage.
Therefore the PRAC agreed that the signal warranted further investigation.

Summary of recommendation(s)

- The MAH for Revatio (sildenafil) should submit to the EMA within 60 days a cumulative review (of clinical studies, post-marketing reports and literature) of sildenafil and pulmonary

[6] Steiner M, Salzer U, Baumgartner S, Waldhoer T, Klebermass-Schrehof K, Wald M, Langgartner M, Berger A. Intravenous sildenafil i.v. as rescue treatment for refractory pulmonary hypertension in extremely preterm infants. Klin Padiatr. 2014 Jul; 226(4):211-5

haemorrhage in the paediatric population taking into account the off-label age and indication use. This review should include data within and outside the approved indication (i.e. unblinded data from an ongoing study in persistent pulmonary hypertension of the newborn if available).

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. **Gadoversetamide – OPTIMARK** (CAP)
gadodiamide (NAP), **gadopentetic acid** (NAP)

- Signal of nephrogenic systemic fibrosis (NSF) in patients with acute kidney injury

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
EPITT 18141 – Follow-up November 2014
MAH(s): Mallinckrodt Deutschland (Optimark), various

Background

For background information, see PRAC Minutes November 2014.
The MAH replied to the request for information on the signal of nephrogenic systemic fibrosis (NSF) in patients with acute kidney injury and the responses were assessed by the Rapporteur.

Discussion

The PRAC noted that although no new EU cases of nephrogenic systemic fibrosis (NSF) have been reported, there is a possibility that changes in estimated glomerular filtration rate (eGFR) may lag behind renal impairment in acute kidney injury (AKI). Consequently, vulnerable patients might not be optimally protected from NSF by the existing renal contraindications in product information of gadolinium-containing contrast agents (GdCAs) designated as 'high risk' in relation to NSF. The PRAC also took into account that in the United States, all of the high risk GdCAs (Omniscan (gadodiamide), Optimark (gadoversetamide) and Magnevist (gadopentetic acid)) contained the additional contraindication 'acute kidney injury' (AKI). The American College of Radiology Manual on Contrast Media (2013) noted that between 12-20% of confirmed cases of NSF have occurred in patients with AKI, often superimposed on chronic kidney disease and that the European Society of Urogenital Radiology guidelines (2013) stated that gadolinium-containing contrast agents with the highest risk of NSF are contraindicated in patients with acute renal insufficiency.

Having considered the evidence submitted, the PRAC agreed that there is a need to further clarify the wording already present in the current EU product information of 'high risk' GdCAs as well as to bring them in line with the global prescribing data information regarding acute kidney injury, therefore the PRAC supported a further update of the product information.

Summary of recommendation(s)

- The MAHs for Omniscan (gadodiamide), Magnevist (gadopentetic acid) and Optimark (gadoversetamide) should submit a variation within 60 days to the EMA/NCAs of the EU Member States as applicable to update the product information regarding acute kidney injury. Following the variation of the marketing authorisations for these products, MAHs for any

medicinal products containing the same active substances should submit respective variation application to the NCAs.

For the full PRAC recommendations see EMA/PRAC/734433/2014 published on the EMA website.

4.3.2. **Latanoprost** (NAP)

- Signal of increased reporting of eye disorders, in particular eye irritation, after change of formulation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 18068 – Follow-up September 2014
MAH(s): Pfizer (Xalatan), various

Background

For background information, see PRAC Minutes September 2014. The MAH for the originator product replied to the list of question on the signal of increased reporting of eye disorders, in particular eye irritation, following a change of formulation and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered that the data submitted by the MAH confirmed a clear increase in the number of reports of eye irritation following the launch of the new formulation of Xalatan in most of the EU countries, particularly in the UK and Germany.

A possible explanation for the increased ocular irritation may be the lower pH of the new formulation but based on the information available, it was not possible to conclude that this was the reason. The PRAC noted that reports of eye irritation tended to decrease after the new formulation had been on the market for a while to a level similar to that prior to its launch but considered that this did not necessarily imply that the event no longer occurs or patients adjust to the new formulation as many factors will influence reporting rates.

In most of the reports of eye irritation describing both outcome of the reaction and action taken, patients either continued Xalatan without resolution of their symptoms or discontinued the product. There were also a few reports of adverse events suggesting a loss of efficacy in temporal association with the switch to the new formulation of Xalatan, although it was difficult to draw any conclusions on efficacy implications from spontaneous data alone.

Summary of recommendation(s)

- The PRAC recommended that further exploration and evaluation of relevant data sources is necessary to fully evaluate the signal and to inform its discussions on the need for and nature of any regulatory action. In particular, the Committee agreed on some aspects to be further explored by the Rapporteur. Feedback will be provided to PRAC at the March 2015 plenary meeting.

4.3.3. **Lithium** (NAP)

- Signal of solid renal tumours

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
EPITT 18090 – Follow-up September 2014
MAH(s): various

Background

For background information, see PRAC Minutes September 2014.
The MAHs replied to the request for information on the signal of solid renal tumours and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the results of the review performed. The majority of the cases identified were literature cases and described renal cysts, but a small number of cases reported renal cancer, renal cell carcinoma and renal oncocytoma. The diagnosis was mainly done by ultrasound. These tumours occurred in patients on long-term lithium therapy (mean duration: 21 years) and were at different degrees of renal insufficiency at the time of diagnosis. Most of the patients diagnosed with a renal cancer underwent a nephrectomy and recovered while lithium was continued unchanged. No relapses were observed after a follow-up of at least 1 year. The histology and histochemistry tests showed that the origin of these tumours was the collecting duct.

Following the assessment of the individual cases and literature review submitted, the PRAC agreed that it was appropriate to update the product information to reflect that long-term use of lithium may induce microcysts, oncocytomas and collecting duct renal carcinomas. Moreover, options for better characterisation of the risk were contemplated and the PRAC concluded that routine pharmacovigilance will be appropriate.

Summary of recommendation(s)

- The MAHs of lithium-containing medicinal products[7] should submit to the NCAs of the EU Member States, within 60 days, a variation to amend the product information to reflect that cases of microcysts, oncocytomas and collecting duct renal carcinoma have been reported in patients with severe renal impairment who received lithium for more than 10 years.
- In addition, routine pharmacovigilance should continue to be performed in order to better characterise the risk.

Homeopathic products containing lithium are not affected by this PRAC recommendation.

For the full PRAC recommendations, see EMA/PRAC/734433/2014 published on the EMA website.

4.3.4. **Paroxetine** (NAP)

- Signal of aggression

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
EPITT 18089 – Follow-up September 2014
MAH(s): GlaxoSmithKline, various

Background

For background information, see PRAC Minutes September 2014.
The MAH replied to the request for information on the signal of aggression and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the review performed on reports of paroxetine and aggressive behaviour/violence from clinical trials, published medical literature (including epidemiology data), post-marketing experience and preclinical toxicology studies results.

Paroxetine clinical trial data collected from adult placebo controlled studies, showed no difference in incidence of hostility events in the paroxetine group versus placebo group. In adult active-controlled trials, hostility events occurred at a lower incidence in the paroxetine group than in the active comparator group although this difference was not statistically significant. In the paediatric placebo-controlled trials, the incidence of hostility events observed on paroxetine therapy was 3.7% compared to 0.6% in the placebo group and this difference was statistically significant.

Further to these results, however, there were a number of cases reports where possible causality could not be excluded based on dechallenge and rechallenge information or by the fact that paroxetine was the only reported drug. Moreover, there is a possible biological explanation based on serotonin function. Product information for the other substances of the same class of medicinal products reflects that this adverse drug reaction can occur. A warning regarding aggression associated with the use of paroxetine in children and adolescents younger than 18 years old, based on the Article 31 referral dated 2003 on selective serotonin re-uptake inhibitors (SSRIs) had been previously introduced. The PRAC agreed that the product information should be updated to reflect that cases of aggression in adults have been observed in post marketing experience.

Summary of recommendation(s)

- The MAHs for paroxetine-containing products[8] should submit a variation within 60 days to the NCAs of the EU Member States to update the product information regarding aggression[9].

For the full PRAC recommendations, see EMA/PRAC/734433/2014 published on the EMA website.

[8] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to
[9] SmPC section 4.8 and package leaflet

4.3.5. Pravastatin – **PRAVAFENIX** (CAP)
Atorvastatin, fluvastatin, lovastatin, pitavastatin, rosuvastatin, simvastatin (NAP)

- Signal of immune-mediated necrotizing myopathy (IMNM)

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
EPITT 18140 – Follow-up November 2014
MAH(s): various

Background

For background information, see PRAC Minutes November 2014.
The Rapporteur performed a further review of the evidence available and of previous regulatory assessments and actions in the EU.

Discussion

Since the conclusions of the PhVWP in 2012 on rosuvastatin and immune-mediated necrotizing myopathy (IMNM), a number of articles have been published about different statins and IMNM. IMNM has meanwhile been well described as a rare risk of statins.
Progressive autoimmune necrotizing myopathy is characterised by progressive muscle weakness, elevated muscle enzymes, specific auto-antibodies against the target hydroxymethylglutaryl-coenzyme A reductase (HMGCR), and progression of symptoms and signs despite discontinuation of statins. Muscle biopsy typically shows a necrotizing myopathy without severe inflammation.

As concluded by authors of a number of studies published, recognizing IMNM is important because, unlike patients with self-limited statin myopathy, those with statin-associated autoimmune myopathy might require immunosuppressive therapy to control the disease. Therefore, the PRAC agreed that the product information of statins should be updated to inform of the possibility of IMNM in statin-treated patients, in line with the previously PhVWP's recommended wording for rosuvastatin.

Summary of recommendation(s)

- The MAHs for medicinal products containing atorvastatin, simvastatin, pravastatin, fluvastatin, pitavastatin or lovastatin should submit a variation within 60 days to the NCAs of the Member States (or EMA as applicable) to amend the product information to include immune-mediated necrotizing myopathy (IMNM)[10].

For the full PRAC recommendations see EMA/PRAC/734433/2014 published on the EMA website.

4.3.6. Recombinant Factor VIII:
Antihemophilic factor (recombinant) (NAP)
Moroctocog alfa – REFACTO AF (CAP)
Octocog alfa – ADVATE (CAP), **HELIXATE NEXGEN** (CAP), **KOGENATE** (CAP)

- Signal of inhibitor development in previously untreated patients

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

[10] SmPC sections 4.4 and 4.8 and package leaflet

Administrative details:
EPITT 18134 – Follow-up December 2014
MAH(s): Baxter AG (Advate, Recombinate), Bayer Pharma AG (Kogenate, Helixate NexGen), Pfizer Limited (ReFacto AF), various

Background

For background information, see PRAC Minutes December 2014.
The EMA secretariat and the Rapporteurs made contact with relevant investigators on the results of the studies discussed at the previous meeting.

Discussion

Following further communication with the study authors in December 2014, the PRAC acknowledged the confirmation of the availability of their data for further analysis. The PRAC agreed that an analysis of recent study data using meta-analysis techniques could increase the precision of the results, obtain risk estimates comparing individual factor VIII products. It was discussed whether to include three selected studies[11], currently considered the most representative ones, or further studies. It was agreed to focus on the three for conducting a further analysis. An action plan was discussed and supported.

Summary of recommendation(s)

- An analysis of the data from the three studies should be performed and led by the Rapporteur according to an agreed action plan. The PRAC will assess the protocol and the results of the study when they become available.

4.3.7. Teriparatide – FORSTEO (CAP)

- Signal of non-uraemic calciphylaxis (NUC)

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 18056 – Follow-up September 2014
MAH(s): Eli Lilly Nederland B.V.

Background

For background information, see PRAC Minutes September 2014.
The MAH replied to the request for information on the signal of non-uraemic calciphylaxis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the review of spontaneous reports of non-uraemic calciphylaxis (NUC) noting complex medical histories and aetiological/predisposing factors for NUC and that the literature including nonclinical studies suggested preventive effects in vascular calcification. The lack of histologic

[11] Gouw SC, et al. PedNet and RODIN Study Group. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013;368:231-9.
Calvez T et al. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A, Blood. 2014 Sep 24. pii: blood-2014-07-586347. [Epub ahead of print]
Collins PW et al. Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe haemophilia A, 2000-2011. Blood. 2014 Oct 22. pii: blood-2014-07-580498

evidence of vascular mineralisation or other changes in toxicology studies with teriparatide was highlighted. It was also noted that in many of the cases teriparatide was used to treat corticosteroid-related osteoporosis and the PRAC noted that corticosteroids were a possible risk factor for NUC.

Given the current level of evidence based on analysis of individual cases, an association of teriparatide with calciphylaxis was considered by the PRAC to be weak and insufficient to support an update of the product information. However, it was pointed out that even if all cases describing corticosteroid use were excluded, there was still a substantial number of cases of calciphylaxis in which use of corticosteroid was not reported and the PRAC concurred that, given the rarity of the condition in the general population, such a number might be considered relatively high. Therefore the PRAC supported further investigation of whether teriparatide may represent an additional risk factor which in rare cases can trigger the onset of calciphylaxis in the presence of other risk factors, either disease states or concomitant medications.

Summary of recommendation(s)

- The MAHs for Forsteo (teriparatide) should keep non-uraemic calciphylaxis under close monitoring through routine pharmacovigilance, and 'non-uraemic calciphylaxis' should be added to the RMP as an important potential risk at the next regulatory opportunity.

4.3.8. **Valproate and related substances** (NAP)

- Signal of mitochondrial toxicity

Regulatory details:
PRAC Rapporteur*:* Martin Huber (DE)

Administrative details:
EPITT 17956 – Follow-up October 2014
MAH(s): Neuraxpharm Arzneimittel GmbH, Sanofi-Aventis, various

Background

For background information, see PRAC Minutes October 2014.
The MAH replied to the request for information on the signal of mitochondrial toxicity and the responses were assessed by the Rapporteur. Moreover, advice from the Pharmacogenomics Working Party (PgWP) was received.

Discussion

The PRAC considered the review of the spontaneous case reports, a literature review and a standard reference work.

The PgWP advised that polymerase gamma (POLG) is the most frequent nuclear DNA encoded mitochondriopathy that can be diagnosed by human molecular genetic testing. According to the experts' opinion, a quality-accredited human molecular genetic laboratory that performs human molecular genetic diagnostics in patients would be able to perform this testing in clinical practice.

The PRAC confirmed that the evidence, cumulatively, was sufficient to support a causal association between valproate and aggravation of underlying mitochondrial diseases, including the risk of hepatotoxicity occurring mainly in patients suffering from POLG mutations/Alpers-Huttenlocher syndrome. Therefore, the PRAC concluded that there was sufficient evidence to justify a contraindication in patients known to have mitochondrial disorders caused by POLG mutations and

supported a contraindication for children under two years of age who are suspected of having a POLG-related disorders.

Summary of recommendation(s)

- The MAHs for valproate-containing medicines[12] should be requested to submit to the NCAs of the Member States within 60 days a variation to update the product information to include a contraindication in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG)[13] as well as children under two years of age who are suspected of having a POLG-related disorders.

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the CHMP on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

Please refer to the CHMP pages for upcoming information (http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights).

See also ANNEX I Risk Management Plans

5.2. Medicines already authorised

RMP in the context of a variation[14] – PRAC-led procedure

5.2.1. **Micafungin – MYCAMINE** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000734/II/0026
Procedure scope: Revised RMP to update the important identified risk of drug interaction; include a second survey to be conducted in Q1 2015 to further assess the effectiveness of risk minimisation measures as requested by the PRAC in May 2014
MAH(s): Astellas Pharma Europe B.V.

[12] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to
[13] SmPC section 4.3 and 4.4 and package leaflet
[14] In line with the revised variation regulation for submissions as of 4 August 2013

Background

Micafungin is an antifungal product indicated for the treatment of invasive candidiasis, of oesophageal candidiasis in patients for whom intravenous therapy is appropriate and for the prophylaxis of Candida infection, in patients undergoing allogeneic haematopoietic stem cell transplantation.

The CHMP is evaluating a type II variation procedure for Mycamine, a centrally authorised product containing micafungin, to update the RMP according to new information that had become available. The PRAC is responsible for providing advice to the CHMP on these proposed modifications.

Summary of advice

- The RMP version 14 for Mycamine (micafungin) in the context of the variation under evaluation by the CHMP was considered acceptable provided that supplementary information is submitted before finalisation of the variation procedure by the CHMP. The MAH is reminded of its obligation with regard to the labelling and conditions of the marketing authorisation(s) and should provide a proposal to improve the distribution of the checklist and the administration and monitoring guide prior to prescription.
- The PRAC acknowledged that the use of Mycamine occurs in a very specific therapeutic field and in that context, a DHPC was not deemed necessary.
- Furthermore, the PRAC considered that off-label use is a safety concern based on the grounds for restriction of the indication but should not be added to the RMP as a separate important risk because of the likely specialist supervision of use. The PRAC endorsed a further request for information to be addressed by the MAH.

5.2.2. Oseltamivir – TAMIFLU (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000402/II/0114
Procedure scope: Proposal for a new and alternative study BV29684 assessing the 'safety of prenatal exposure to oseltamivir' as a category 3 study (MEA 099) to replace the agreed 2-year extension of the Danish-Swedish registry (NV25577)
MAH(s): Roche Registration Ltd

Background

Oseltamivir is a selective inhibitor of influenza virus neuraminidase enzymes, indicated for the treatment and prevention of influenza in individuals of 1 year of age or older, during a pandemic influenza outbreak; also for treatment and post-exposure prevention of influenza in infants less than 1 year of age.

The CHMP is evaluating a type II variation procedure for Tamiflu in order to propose a new and alternative study BV29684 assessing the 'safety of prenatal exposure to oseltamivir' as a category 3 study to replace the agreed 2-year extension of the Danish-Swedish registry (NV25577: assessing the safety of oseltamivir exposure in pregnant women in Denmark and Sweden). The extension of this registry was requested by the PRAC in May 2013 after the interim results of the study (period 2008-2010) were examined. The PRAC is responsible for providing advice to the CHMP on this proposal.

Summary of advice

- The revised RMP version 11 for Tamiflu (oseltamivir) replacing the 2 year extension of study NV25577 with the proposed new study was not considered acceptable as it was not a suitable replacement for the requested extension of study NV 25577. The new study BV 29684 could be considered an optional and additional study but the PRAC considered that the results of NV 25577 should be assessed before making a recommendation on the need to perform additional studies. A request for further information to be addressed by the MAH was agreed before the procedure is concluded.

5.2.3. Rivaroxiban – XARELTO (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000944/II/0034
Procedure scope: Amendment to Annex II of the marketing authorisation to extend and expand the ongoing epidemiological rivaroxaban PASS programme to fulfil the CHMP objective on the post-approval programme for the acute coronary syndrome (ACS) indication
MAH(s): Bayer Pharma AG

Background

For background, see PRAC Minutes October 2014.

The MAH responded to a request of amendments of the RMP requested by the PRAC together with a proposal for amendment of the Annex II that were assessed by the Rapporteur.

Summary of advice

- The revised RMP version 8 for Xarelto (rivaroxaban) in the context of the variation under evaluation by the CHMP was considered acceptable and the PRAC acknowledged the need for a pragmatic adaptation of the definition of clinically relevant bleeding in the proposed PASS programme. However, some further minor amendments are required before finalisation of the procedure, including an amendment to the obligation in Annex II, proposed in order to better meet the underlying objective of the obligation.

RMP in the context of a variation – CHMP-led procedure

5.2.4. Ferumoxytol – RIENSO (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002215/II/0008
Procedure scope: Extension of indication to all cause iron deficiency anaemia when oral therapy is ineffective or inappropriate or where there is a need for rapid iron repletion. As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 are updated. The package leaflet is updated accordingly. The MAH

took the opportunity to propose minor editorial changes to the SmPC and to propose the update of the product information in line with the latest version of the QRD template (9.0)
MAH(s): Takeda Pharma A/S

Background

For background see 6.1.3. Rienso PSUR.

A revised RMP has been submitted as part of a proposed extension of indication of Rienso to include all cause iron deficiency anaemia when oral therapy is ineffective or inappropriate or where there is a need for rapid iron repletion. This RMP version had been developed based on version 3.3, submitted together with the current PSUR.

Summary of advice

- The RMP version 3.4 for Rienso (ferumoxytol) submitted in the context of the proposed extension of indication under evaluation by the CHMP was considered acceptable in relation to the content specific for this extension of indication only. Therefore a further RMP version should be submitted for this variation procedure - prior to finalisation at the CHMP level - based on current version 3.4 but excluding all content related to the assessment of version 3.3, which is still under discussion within the ongoing PSUR procedure. For other comments, see 6.1.3. Rienso PSUR.

5.2.5. Insulin glargine – OPTISULIN (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000309/X/0079/G
Procedure scope: Extension of the marketing authorisation to register additional strength 300 U/ml, grouped with a type IA variation to vary the invented name from Optisulin to Toujeo
MAH(s): Sanofi-aventis Deutschland GmbH

Background

For background information, see PRAC Minutes September 2014. Further information as requested by the PRAC was received and assessed by the PRAC Rapporteur.

Summary of advice

- The updated RMP version 4.1 for Optisulin (insulin glargine) in the context of a variation for a line extension under evaluation by the CHMP was considered acceptable provided that an update is submitted in response to a request for supplementary information to be adopted by CHMP. Given that the 300 U/ml and 100 U/ml formulations are not bioequivalent, a change of the dose of the basal insulin may be required, and close metabolic monitoring is to be recommended during a switch and in the initial following weeks. Therefore, the PRAC considered that educational materials for healthcare professionals and for patients and/or carers need to be developed to address the risk(s) of medication error (switching between 100U/ml and 300U/ml without dose adjustment).

5.2.6. Ustekinumab – STELARA (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000958/II/0042
Procedure scope: Extension of indication to add the treatment of moderate to severe plaque psoriasis in paediatric patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. As a consequence, SmPC sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 and the package leaflet are updated. A revised RMP (version 12) is assessed as part of the application
MAH(s): Janssen-Cilag International N.V.

Background

Stelara is a centrally authorised medicine containing ustekinumab, indicated for the treatment of plaque psoriasis and psoriatic arthritis. The CHMP is evaluating an extension of the therapeutic indication for Stelara to add the treatment of moderate to severe plaque psoriasis in paediatric patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 12 for Stelara (ustekinumab) submitted in the context of the extension of indication under evaluation by the CHMP was considered acceptable provided an updated RMP and satisfactory responses to a number of questions raised by the PRAC are submitted. In particular 'long term safety in paediatric patients' and 'long term impact on growth and development in paediatric patients' should be included in the RMP as important potential risks. The MAH should commit to performing a post-marketing study in paediatric patients, and should document this as an additional pharmacovigilance activity in the RMP.

RMP evaluated in the context of a PSUR procedure

See also Ferumoxytol – RIENSO 6.1.3. , Hydroxycarbamide – SIKLOS 15.1.13. , Liraglutide – VICTOZA 6.1.4.

RMP evaluated in the context of PASS results

See also Paliperidone – XEPLION 16.1.13.

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

See Annex 14.1

RMP evaluated in the context of a stand-alone RMP procedure

None

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[15]

6.1.1. **Ambrisentan – VOLIBRIS** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000839/PSUV/0040
MAH(s): Glaxo Group Ltd

Background

Ambrisentan is an endothelin receptor antagonist (ERA) indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Volibris (ambrisentan) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 60 days detailed incident rates in person-time of treatment emergent events relevant to renal failure/renal dysfunction from all clinical trials performed to date in PAH patients on ambrisentan only, comparator only and placebo treated patients. The MAH should also provide a detailed review of cases of renal failure, renal failure acute, renal failure chronic and renal impairment, including a discussion on a possible underlying mechanism for kidney disorders.
- In the next PSUR, the MAH should provide a detailed review of cases of menstrual disorders and vaginal haemorrhage. In addition, the MAH should consider updating the RMP by changing the risk of symptomatic hypotension from an important potential to an important identified risk.

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

6.1.2. **Dasatinib – SPRYCEL** (CAP)

- Evaluation of a PSUR procedure

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000709/PSUV/0041
MAH(s): Bristol-Myers Squibb Pharma EEIG

Background

Dasatinib is a protein kinase inhibitor indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase. Dasatinib is also indicated for the treatment of adult patients with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy as well as the treatment of adult patients with Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Sprycel (dasatinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add Stevens-Johnson syndrome as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should closely monitor cases of renal failure and provide further analysis on disproportionality analysis of dasatinib, imatinib and nilotinib. In addition, the MAH should closely monitor cases of severe renal impairment. Moreover, the MAH should provide detailed reviews of toxic skin reactions, bone marrow failure including cases of pancytopenia and myelosuppression. Furthermore, the MAH should provide detailed reviews of thrombocytopenia and should propose to update the product information accordingly as warranted. Finally, the MAH should suggest an update of the product information with growth and development disorders and bone mineral metabolism disorders in the paediatric population in line with the agreed risk minimisation measures.

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

6.1.3. **Ferumoxytol – RIENSO** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002215/PSUV/0015 (with RMP version 3.3)
MAH(s): Takeda Pharma A/S

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

Background

Ferumoxytol is a colloidal iron-carbohydrate complex indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rienso, a centrally authorised medicine containing ferumoxytol, and issued a recommendation on its marketing authorisation(s) (see also PRAC Minutes December 2014).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy within the PSUR, and following an oral explanation by the MAH addressing questions from the PRAC, the PRAC agreed, by majority vote, that the risk-benefit balance of Rienso (ferumoxytol) remains favourable provided the terms of the marketing authorisation(s) are varied and that additional risk minimisation measures and conditions are imposed. The Committee adopted a recommendation for consideration by the CHMP. Nineteen members/alternates out of 36 eligible to vote, together with Iceland and Norway, voted in favour of the recommendation, while fourteen[17] members/alternates had divergent views (see EMA website Home>Find medicine>Human Medicines - PRAC PSUR assessment report to be published following EC decision).
- The product information should be updated to add a warning on the likelihood of a more serious outcome of severe hypersensitivity reactions in elderly patients or with co-morbidities. Moreover, the conditions of the marketing authorisation should be changed to ensure that prior to the use of ferumoxytol, the MAH agrees with individual NCAs the content and format of the educational programme, aiming at highlighting the risks and warnings on hypersensitivity reactions and the monitoring of patients during and after administration. This includes communication media, distribution modalities, and any other aspects of the programme. The MAH shall ensure that in each MS where ferumoxytol is marketed, all HCPs and patients/carers expected to use ferumoxytol have access to/are provided a healthcare professional checklist and patient alert card. Finally, the MAH is required to conduct a study to investigate the mechanism of hypersensitivity associated with the exposure to ferumoxytol, according to a protocol agreed by the CHMP by 31 October 2016. In addition, the warning on interference with magnetic resonance imaging (MRI) should be amended to reflect that interpretation of tissue MRI may be affected for up to 6 months after administration of ferumoxytol.
- Therefore the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should provide a revised synopsis for a study investigating the risk of hypersensitivity in EU chronic kidney disease (CKD) patients comparing ferumoxytol with iron sucrose as a comparator. The MAH should provide also a revised protocol for a study to measure the effectiveness of the new risk minimisation measures as previously agreed by the PRAC with a retrospective chart review design. In addition, the MAH should provide an update on the progress of the study to investigate the mechanism of hypersensitivity associated with exposure to ferumoxytol. The MAH should also provide the full study report for the phase I of the chronic disease research group (CDRG) study, and should submit the protocol for the phase II of the CDRG study. Moreover, the MAH should submit three monthly and within each

[17] The relevant AR containing the divergent positions will be published on the EMA website once the procedure is fully concluded, following EC decision
[18] Update of SmPC section 4.4 and Annex II. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

PSUR detailed reviews of hypersensitivity case reports, all fatal cases and all pregnancy cases, together with usage data.

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

6.1.4. Liraglutide – VICTOZA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001026/PSUV/0029 (with RMP version 4.0)
MAH(s): Novo Nordisk A/S

Background

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Victoza (liraglutide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated in relation to the information related to overdose and to reflect a possible adverse reaction of diarrhoea based on post-marketing case reports. Therefore the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide detailed reviews of cases of lipase increased, cholecystitis and cholelithiasis. In addition, the MAH should include a comparison of patients with weight decrease *versus* without weight decrease taking into account the study report of the LEADER[20] trial. Minor revisions were recommended to be taken into account for the RMP update at the next regulatory opportunity.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.5. Mirabegron – BETMIGA (CAP)

- Evaluation of a PSUR procedure

[19] Update of SmPC section 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[20] Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results – a long term evaluation

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

Administrative details:
Procedure number(s): EMEA/H/C/002388/PSUV/0015
MAH(s): Astellas Pharma Europe B.V.

Background

Mirabegron is a selective beta 3-adrenoceptor agonist indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence in adult patients with overactive bladder (OAB) syndrome.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Betmiga (mirabegron) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add nausea as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide detailed reviews of cases of urinary retention and cases of increased blood pressure, and should propose to update the RMP and product information accordingly as warranted. The MAH should also provide detailed reviews of cases of anticholinergic syndrome, psychiatric disorders, chest discomfort, oedema and cases of cardiac failure or worsening of cardiac failure. In addition, the MAH should provide a comparative analysis between serious adverse drug reactions (ADRs) collected in the elderly (>65 years old) and the serious ADRs collected in non-elderly patients. Moreover, the MAH should provide more information about study 178-JC-BE0003 in order to know if this study could address the important missing information about the safety of mirabegron in patients with pre-existing cardiovascular disease. Finally, the MAH is requested to closely monitor cerebrovascular events and report of lack of efficacy.

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

6.1.6. **Nepafenac – NEVANAC** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000818/PSUV/0029
MAH(s): Alcon Laboratories (UK) Ltd

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

Background

Nepafenac is a non-steroidal anti-inflammatory (NSAID) and analgesic prodrug indicated in adults for the prevention and treatment of postoperative pain and inflammation associated with cataract surgery and for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Nevanac (nepafenac) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add corneal perforation as an undesirable effect with an unknown frequency, together with a cross-reference in the warning section. Therefore, the current terms of the marketing authorisation(s) should be varied[22].In the next PSUR, the MAH should provide detailed reviews of corneal disorders and of off-label use.

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

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000746/PSUV/0044, EMEA/H/C/002105/PSUV/0016
MAH(s): Janssen-Cilag International N.V.

Background

Paliperidone is an antipsychotic indicated for the treatment of schizophrenia under certain conditions. The oral pharmaceutical form is also indicated for the treatment of psychotic or manic symptoms of schizoaffective disorder in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Invega and Xeplion, centrally authorised medicines containing paliperidone, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

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

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

- For Invega (prolonged-release tablet), the current terms of the marketing authorisation(s) should be maintained.
- For Xeplion (prolonged-release suspension for injection), the product information should be updated to clarify in the method of administration section that the third injection should be administered one month after the second injection. Therefore the current terms of the marketing authorisation(s) should be varied[23].

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

6.1.8. Roflumilast – **DALIRESP** (CAP), **DAXAS** (CAP), **LIBERTEK** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002658/201407
MAH(s): Takeda GmbH

Background

Roflumilast is a phosphodiesterase 4 (PDE4) inhibitor indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Daliresp, Daxas and Libertek, centrally authorised medicines containing roflumilast, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Daliresp, Daxas and Libertek (roflumilast) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add panic attack as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide detailed reviews of cases of gastrointestinal haemorrhage, pneumonia, and renal failure. Moreover, the MAH should continue to review all fatal cases including an assessment of lack of efficacy.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

[23] Update of SmPC section 4.2. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[24] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.2. Follow-up to PSUR procedures[25]

6.2.1. Nilotinib – TASIGNA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000798/LEG 047
Procedure scope: MAH's response to PRAC recommendation on PSUV/0069 as adopted in September 2014
MAH(s): Novartis Europharm Ltd

Background

Following the most recent assessment of a PSUR for the above mentioned medicine, the PRAC requested the MAH to submit further data on abortions and foetotoxicity (see PRAC Minutes September 2014). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusions

Based on the review of the data submitted by the MAH, the PRAC agreed that, in the light of the current knowledge, there was no need to update the product information section on fertility, pregnancy and lactation as the SmPC sections dedicated to preclinical safety data and contraindication remain unchanged. The MAH should ensure that adequate follow-up reports are reported in the annual PSURs.

7. Post-authorisation Safety Studies (PASS)

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

See Annex 16

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

7.2.1. Agomelatine – THYMANAX (CAP), VALDOXAN (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Ingebjørg Buajordet (NO)

Administrative details:
Procedure number(s): EMEA/H/C/000916/MEA 023, EMEA/H/C/000915/MEA 023
Procedure scope: Evaluation of a PASS protocol for a study using databases in four European countries to assess the incidence of hospitalisation for liver injury in current medical practice in comparison with other antidepressant drugs
MAH(s): Servier (Ireland) Industries Ltd., Les Laboratoires Servier

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

Background

Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist indicated in adults for the treatment of major depressive episodes.

As part of the RMP for Valdoxan/Thymanax, centrally authorised products containing agomelatine the MAH was required to conduct a PASS using databases in four European countries in order to assess the incidence of hospitalisation for liver injury in current medical practice in comparison with other antidepressant drugs. The MAH submitted a protocol for such study (PASS for agomelatine and the risk of hospitalisation for acute liver injury (ALI)) which was assessed by the Rapporteur.

Summary of advice

- The study protocol for the proposed PASS for Valdoxan/Thymanax (agomelatine) could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA within 30 days. In particular, since the expected number of exposed patients remains low as per the inclusion criteria, suggestions aiming at strengthening the study were made intended to control the potentially significant impact of exposure/outcome misclassification.
- A 30 days assessment timetable will apply.

7.2.2. Agomelatine – THYMANAX (CAP), **VALDOXAN** (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Ingebjørg Buajordet (NO)

Administrative details:
Procedure number(s): EMEA/H/C/000916/MEA 024, EMEA/H/C/000915/MEA 024
Procedure scope: Evaluation of a PASS protocol for a non-interventional post-authorisation safety study/pharmacogenomic study to explore the potential liver injury and potential associated risk factors, risk of hepatotoxic reactions associated with agomelatine in reasonable timelines. Pharmacogenomic study: further explore the potential liver injury and potential associated risk factors, specific investigations are implemented for patients who exhibit abnormal liver enzymes (ALAT, ASAT or ALP value > 3 x upper limit of normal (ULN) or total bilirubin > 2 ULN) in the ongoing and planned clinical trials with agomelatine, with close follow-up of abnormalities until resolution, and determination of key variables in liver function assessment and appropriate etiological investigations. DNA should be taken allowing for search of the influence of different genetic polymorphisms
MAH(s): Servier (Ireland) Industries Ltd., Les Laboratoires Servier

Background

Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist indicated in adults for the treatment of major depressive episodes.

As part of the RMP for Valdoxan/Thymanax, centrally authorised products containing agomelatine, the MAH was required to conduct a pharmacogenomic study to explore the potential for liver injury and potential associated risk factors with DNA samples to be taken allowing for investigation of the influence of different genetic polymorphisms. The MAH submitted a protocol for such study (human leukocyte antigen (HLA) alleles as genetic risk factors for evaluation of aminotransferases in patients treated with agomelatine) which was assessed by the Rapporteur.

Summary of advice

- The proposed study protocol for the for Valdoxan/Thymanax (agomelatine) pharmacogenetic study could be acceptable provided an updated protocol with the changes regarding sampling, sequencing, handling of missing data, inclusion of serious cases is submitted to the EMA within 30 days.

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

None

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

See Annex 16

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

See Annex 16

7.6. Other matters relating to PASS

7.6.1. **Efavirenz, emtricitabine, tenofovir – ATRIPLA** (CAP)

- Evaluation of a feasibility study

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000797/MEA 038.1
Procedure scope: Interim report on the antiretroviral pregnancy registry (APR)
MAH(s): Bristol-Myers Squibb and Gilead Sciences Ltd.

Background

Atripla is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate. It is indicated for use alone as a single tablet regimen or in combination with other antiretroviral agents for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults.

An interim report of data from the antiretroviral pregnancy registry (APR) whose purpose is to detect and provide an early signal of any major teratogenic effect of HIV drugs to which pregnant women are exposed was submitted by the MAH and assessed by the Rapporteur.

Summary of advice

Based on the assessment of the data received the PRAC acknowledged that in spite of the teratogenic concern seen in animal studies and some human studies, the totality of human data from different

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

sources is somewhat reassuring regarding the use in women of child bearing potential and pregnant women.

The PRAC also acknowledged the different approaches in handling the data in the national and WHO guidelines. In the light of the 2013 WHO consolidated guidelines on "the use of antiretroviral drugs for treating and preventing HIV infection", the MAH is requested to provide some additional information within the forthcoming PSUR, including a review on the safety of efavirenz-containing products during pregnancy taking into account all available clinical and non-clinical data, with the aim to confirm whether the current EU product information is still justified or requires modification regarding the contraindication for use in women of child bearing potential as well as during pregnancy.

7.6.2. Interferon beta-1a – REBIF (CAP)

- Evaluation of a feasibility study

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

Administrative details:
Procedure number(s): EMEA/H/C/000136/LEG 040
Procedure scope: Feasibility assessment of the case control study comparing the risk of thrombotic microangiopathy (TMA) with different Rebif formulations
MAH(s): Merck Serono Europe Limited

Background

For further background, see PRAC Minutes July 2014.

Further to the PRAC advice provided in relation to a variation to update the product information to include thrombotic microangiopathy (TMA), the CHMP considered that the MAH had to submit additional safety data in order to evaluate the feasibility of a case-control study comparing the risk of TMA with different Rebif formulations. The MAH provided a response which was assessed by the Rapporteur.

Summary of advice

Based on the assessment of the data and explanations received from the MAH, the PRAC concluded that a case-control study comparing the risk of TMA with different Rebif formulations was probably not feasible at this time. However, the PRAC reiterated that cooperation by the MAH with the National Institute for Biological Standards and Control (NIBSC) in providing any samples of formulations or specific batches as required, to support investigation of the biological basis for a possible difference in risk of TMA between the Rebif formulations is encouraged.

Moreover, monitoring of TMA should be performed and discussed in future PSURs, taking into account exposure of patients to Rebif, overall reporting rate of ADRs and reporting rate of TMA analysed separately by regions/countries where old or new Rebif formulations are available.
Future PSURs should also provide an updated discussion concerning the feasibility of a case-control study. This should be based on updated calculations and considerations as far as possible based on data from available data sources.

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

See Annex 17

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. On-going or concluded pharmacovigilance inspection

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 agenda.

9.3. Others

None

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

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

None

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

None

10.3. Other requests

None

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Azithromycin oral and intravenous formulations (NAP)

- PRAC consultation on a safety-related variations upon Finland's request

Regulatory details:
Lead member: Terhi Lehtinen (FI)

Administrative details:
Procedure number: FI/H/XXXX/WS/23

Procedure scope: PRAC consultation on a variation procedure evaluating the draft PASS protocol (A0661209) for a non-imposed non-interventional study in the Kaiser Permanente databases to examine the effects of azithromycin use on cardiovascular outcome
MAH(s): Pfizer (Zithromax)

Background

For background, see PRAC minutes July 2014.

Following the latest PRAC advice on the signal of cardiovascular events associated with azithromycin the MAH submitted to Finland (RMS for the originator product) a draft PASS protocol (A0661209) for a non-imposed non-interventional study in the Kaiser Permanente databases to examine the effects of azithromycin use on cardiovascular outcome. FI requested the advice of the PRAC on a draft protocol.

Summary of advice

The PRAC agreed in principle with the proposed study protocol. The MAH should also investigate methods to ascertain the severity of indication, by using proxy variables. However, the PRAC acknowledged that such variables might be hard to identify and the results of the study would have to be carefully interpreted.

The PRAC also supported further review of the additional feasibility study from the US Veterans Affairs database, expected to be submitted by the MAH.

11.1.2. **Domperidone** (NAP)

- PRAC consultation on a safety-related variation upon Belgium's request

Regulatory details:
Lead member: Jean-Michel Dogné (BE)

Administrative details:
Procedure number: BE/H/0106/01-04,08-09/II/044
Procedure scope: PRAC consultation on a variation procedure evaluating a RMP as required in the conditions to the marketing authorisation(s) following Article 31 referral for domperidone containing products (Annex IV of Commission Decision dated 14 July 2014)
MAH(s): Zentiva (Motilium)

Background

For background see PRAC Minutes March 2014.

The MAH submitted a type II variation to fulfil the conditions to the marketing authorisations following the outcome of an Article 31 referral for domperidone-containing products that was finalised following a Commission Decision dated 14 July 2014. Belgium as RMS for the reference domperidone containing product assessed this RMP which will serve as a model for RMPs of all domperidone-containing products and requested PRAC advice on this.

Summary of advice

The PRAC recommended some changes to the RMP and endorsed a request for supplementary information for the MAH. The PRAC further advised that, as the RMP will serve as a model for RMPs of all domperidone-containing products, core elements of the RMP - once finally agreed - should be made public by the RMS/CMDh for future reference.

11.1.3. **Ibuprofen** (NAP)

- PRAC consultation on a safety-related variations upon Malta's request

Regulatory details:
Lead member: Amy Tanti (MT)

Administrative details:
Procedure number: MT/H/0101/001-004/II/007
Procedure scope: PRAC consultation on a variation procedure evaluating the MAH's request to add Kounis syndrome to the product information
MAH(s): Actavis (Ibuprofen Actavis)

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activities, contained in ,nationally-approved medicines[31]. Following the evaluation of their own signal, the MAH for an ibuprofen-containing medicine submitted a type II variation to the NCAs with the scope to propose a change in their product information concerning Kounis syndrome (concurrence of acute coronary syndromes with conditions associated with mast cell activation, such as allergies or hypersensitivity and anaphylactic or anaphylactoid reactions). Malta, as RMS, requested the advice of the PRAC on this variation procedure.

Summary of advice

The PRAC's view on the evidence and assessment presented was that Kounis syndrome should be interpreted as not being an adverse drug reaction in itself, but rather a consequence of hypersensitivity to the product, hypersensitivity being already labelled for ibuprofen-containing products. Therefore, based on the review of the available information, the PRAC considered that the signal identified by the MAH and the data submitted did not justify designation of Kounis syndrome as a new adverse event to be listed individually in the ibuprofen product information.

11.2. Renewals of the Marketing Authorisation

None

11.3. Other requests

11.3.1. **Imipenem, cilastatin** (NAP)

- PRAC consultation on a PSUR worksharing procedure upon Norway's request

Regulatory details:
Lead member: Ingebjørg Buajordet (NO)

Administrative details:
Procedure number: NO/H/PSUR/0003/002
Procedure scope: PRAC consultation on a PSUR worksharing procedure on the addition of drug reaction with eosinophilia and systemic symptoms (DRESS) to the product information
MAH(s): various

[31] Except one CAP with an orphan designation

Background

Imipenem is a semi-synthetic derivate of thienamycin antibiotic and cilastatin is a competitive, reversible and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolizes and inactivates imipenem. The association imipenem/cilastatin belongs to the pharmacotherapeutic group; antibacterials for systemic use, and is approved for a number of serious infections caused by susceptible organisms. Hypersensitivity reactions in the form of immediate allergic reactions and anaphylaxis is a known identified important risk associated with imipenem/cilastatin. Moreover, delayed hypersensitivity reactions such as serious cutaneous adverse reactions (SCARs) i.e. Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, have been reported and are listed in the product information. Following assessment performed within a PSUR work-sharing procedure, drug reaction with eosinophilia and systemic symptoms (DRESS) was also considered for inclusion in the product information and Norway as RMS for the imipenem/cilastatin product requested the advice from the PRAC on this assessment.

Summary of advice

Based on the review of the available information, the PRAC considered the evidence reviewed was insufficiently robust to recommend a change to the product information for products containing imipenem/cilastatin to include DRESS. Therefore the PRAC recommended that other data should be explored to substantiate the signal: this should include EudraVigilance cases of DRESS with imipenem/cilastatin. Other data to be considered may include data from the RegiSCAR registry.

11.3.2. **Apomorphine** (NAP)

- PRAC consultation on concomitant use of apomorphine with domperidone following the completion of Article 31 referral for domperidone, upon Germany's request

Regulatory details:
Lead member: Martin Huber (DE)

Administrative details:
Procedure number: *Not applicable*
Procedure scope: PRAC consultation on the concomitant use of apomorphine with domperidone contraindicated with QT-prolonging drugs following the completion of Article 31 referral for domperidone containing products (Commission Decision dated 14 July 2014)
MAH(s): various

Background

Apomorphine is a non-selective dopamine agonist indicated for the treatment of disabling motor fluctuations in patients with Parkinson's disease under certain conditions.

In the framework of the recent Article 31 procedure for domperidone-containing products (EMEA/H/A-31/1365), the PRAC noted that there are apomorphine-containing products approved in the EU for which the product information makes reference to the use of domperidone to prevent nausea, vomiting and orthostatic hypotension. Following the recommendations resulting from the domperidone referral procedure, and concerns raised by learned societies, DE addressed a request for PRAC advice in order to reconsider the combined use of apomorphine and domperidone (as included in the apomorphine product information) as the co-administration with QT-prolonging drugs is a contraindication for domperidone, and the recommended dosing regimen for domperidone stated in the apomorphine SmPCs (3 x 20 mg per day) is not compatible any longer with the new recommendations for domperidone (maximum daily dose is 30 mg).

In September 2014, Germany sent a request for non-urgent information (NUI) to all EU Member States to get a status update of the authorised medicinal products as well as the current recommendations and guidelines in place in each country.

Summary of advice

Based on the review of the available information, the PRAC confirmed that the current dose recommendation for domperidone and the information on QT prolongation in the apomorphine product information should be reviewed, and concurred that the most appropriate regulatory option to do so is to assess the data in a PSUR single assessment procedure (PSUSA). The PRAC request to have apomorphine added to the EURD list with a data lock point (DLP) in May 2015. Denmark (as the lead MS in the signal management worksharing list) will coordinate the efforts to communicate the data needed to the MAHs. The PRAC recommended consulting the EMA Scientific Advisory Group on Neurology (SAG-neurology) for expert advice in the course of the PSUSA procedure.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Pharmacovigilance audits and inspections

None

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

12.3.1. PSUR Repository

- PSUR repository implementation plan

The EMA Secretariat updated the PRAC on the deployment of the PSUR repository, with proposed detailed timelines for its full implementation. Follow-up discussion will take place at the February 2015 PRAC meeting.

12.3.2. Union Reference Date (EURD) List

- Consultation on the draft list, version January 2015

The PRAC endorsed the draft revised EURD list version January 2015 reflecting the PRAC comments impacting the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC Minutes April 2013).

Post-meeting note: following the PRAC meeting in January 2015, the updated EURD list was adopted by the CHMP and CMDh at their January 2015 meeting and published on the EMA website on 05/02/2015, see:

Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.4. Signal Management

12.4.1. Signal Management

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

In January 2015, the SMART Working Group was updated on the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) project which aims to help the EU regulatory network to operate the pharmacovigilance process in accordance with the EU legislation and at improving skills and capability. The SCOPE project aims to support Member States in operating their pharmacovigilance systems effectively as part of the EU network, making the best use of experience and practices to support best uses of available resources. A further update on SCOPE to the SMART WS1 will be provided in Q2 2015.

It was also noted that GVP module IX (signal management) will be updated in 2015, in particular, to further clarify definitions and processes.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Additional Monitoring

- Additional monitoring: optional scope

The PRAC discussed the process for requesting the inclusion of a medicinal product in the list of additional monitoring under the 'optional scope' defined in Article 23(1a) of Regulation (EC) No 726/2004 and noted the possible feasibility issues when the request is solely based on the imposition of educational material (Article 9(4)(c) and (ca) of Regulation (EC) No 726/2004 or Article 21a(a) and (d) of Directive 2001/83/EC).

The PRAC endorsed the process to be presented to the CMDh for information. A form has also been agreed to be used by NCAs to request the inclusion of centrally authorised products outside a regulatory procedure and of nationally authorised products.

12.5.2. List of Products under Additional Monitoring

- Consultation on the draft list, version January 2015

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on 28/01/2015 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of risk Minimisations

None

12.8. Post-authorisation Safety Studies

None

12.9. Community Procedures

None

12.10. Renewals, conditional renewals, annual reassessments

None

12.11. Risk communication and Transparency

None

12.12. Continuous pharmacovigilance

- Pharmacovigilance programme and revised implementation governance

The PRAC was updated on the revised implementation governance of the pharmacovigilance legislation, adopted by the Heads of Medicines Agencies (HMA), and the pharmacovigilance programme. The PRAC will receive updates on a regular basis.

12.13. Interaction with EMA Committees and Working Parties

None

12.14. Interaction within the EU regulatory network

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

- Feedback from the ENCePP plenary meeting, November 2014

The PRAC representative in the ENCePP Steering Group circulated a report from the November 2014 plenary meeting where the ENCePP Guide on Data Integration of observational studies of harm was discussed, as well as a study analysing PASS submitted for PRAC review in the first 24 months of the operation of the Committee. The need for increased collaboration and communication between ENCePP, EMA committees and other stakeholders was also emphasised.

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

None

13. Any other business

13.1. Guidance to applicants on responses to questions received from EMA Scientific Committees during the evaluation within the centralised procedure

Following the consultation of the PRAC, CAT and CHMP in December 2014 on the draft 'guidance on meetings with applicants on the responses to questions received from European Medicines Agency Scientific Committees during the evaluation within the centralised procedure', the guidance was finalised in January 2015 (EMA/636600/2014) and published on the EMA website on 01/02/2015.

14. ANNEX I - Risk Management Plans

14.1. Medicines in the pre-authorisation phase

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

14.1.1. Cangrelor

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

Administrative details:
Product number(s): EMEA/H/C/003773
Intended indication(s): Reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)

14.1.2. Cobimetinib

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

Administrative details:
Product number(s): EMEA/H/C/003960
Intended indication(s): Treatment of metastatic melanoma

14.1.3. Duloxetine

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

Administrative details:
Product number(s): EMEA/H/C/003981, *Generic*
Intended indication(s): Treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder

14.1.4. Duloxetine

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

Administrative details:
Product number(s): EMEA/H/C/004009, *Generic*
Intended indication(s): Treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder

14.1.5. Duloxetine

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

Administrative details:
Product number(s): EMEA/H/C/003935, *Generic*
Intended indication(s): Treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder

14.1.6. Dinutuximab

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

Administrative details:
Product number(s): EMEA/H/C/002800*, Orphan*
Intended indication(s): Treatment of neuroblastoma

14.1.7. Edoxaban

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

Administrative details:
Product number(s): EMEA/H/C/002629
Intended indication(s): Prevention of stroke, embolism and treatment of venous thromboembolism

14.1.8. Evolocumab

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

Administrative details:
Product number(s): EMEA/H/C/003766
Intended indication(s): Treatment of hypercholesterolaemia, mixed dyslipidaemia and homozygous familial hypercholesterolaemia

14.1.9. Fentanyl

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

Administrative details:
Product number(s): EMEA/H/C/002715
Intended indication(s): Treatment of acute moderate to severe post-operative pain

14.1.10. Human fibrinogen, human thrombin

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

Administrative details:
Product number(s): EMEA/H/C/002807
Intended indication(s): Supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis

14.1.11. Lamivudine, raltegravir

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

Administrative details:
Product number(s): EMEA/H/C/003823
Intended indication(s): Treatment of human immunodeficiency virus (HIV-1)

14.1.12. Lenvatinib

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

Administrative details:
Product number(s): EMEA/H/C/003727, *Orphan*
Intended indication(s): Treatment of papillary thyroid cancer and follicular thyroid cancer
Applicant: Eisai Ltd

14.1.13. Mercaptamine

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

Administrative details:
Product number(s): EMEA/H/C/003769, *Orphan*
Intended indication(s): Treatment of cystinosis
Applicant: Orphan Europe S.A.R.L.

14.1.14. Netupitant, palonosetron

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

Administrative details:
Product number(s): EMEA/H/C/003728
Intended indication(s): Prevention of chemotherapy-induced nausea and vomiting (CINV)

14.1.15. Nivolumab

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

Administrative details:
Product number(s): EMEA/H/C/003840
Intended indication(s): Treatment of cancer after prior chemotherapy

14.1.16. Nivolumab

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

Administrative details:
Product number(s): EMEA/H/C/003985
Intended indication(s): Treatment of advanced (unresectable or metastatic) melanoma in adults

14.1.17. Oritavancin

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

Administrative details:
Product number(s): EMEA/H/C/003785
Intended indication(s): Treatment of complicated skin and soft tissue infections (cSSTI)

14.1.18. Talimogene laherparepvec

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

Administrative details:
Product number(s): EMEA/H/C/002771
Intended indication: Treatment of adults with melanoma that is regionally or distantly metastatic

14.1.19. Tedizolid

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

Administrative details:
Product number(s): EMEA/H/C/002846
Intended indication(s): Treatment of tissue infections (cSSTI)

14.2. Medicines already authorised

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

RMP in the context of a variation[32] – PRAC-led procedure

14.2.1. Dapagliflozin – FORXIGA (CAP)
Dapagliflozin, metformin – XIGDUO (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMA/H/C/002322/WS0601/0016/G, EMA/H/C/002672/WS0601/0006/G
Procedure scope: Revised RMP with 4 revised due dates relating to pharmacoepidemiology programmes MB102103 study, MB102104 study, MB102110 study and MB102118 study
MAH(s): AstraZeneca AB

14.2.2. Dasatinib – SPRYCEL (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): MEA/H/C/000709/II/0045/G
Procedure scope: Revised RMP (version 13) to change pulmonary arterial hypertension (PAH), pregnancy-related malformative and foeto-neonatal toxicity from important potential risks to important identified risks. Addition of an important potential risk of CYP3A4 drug interactions, toxic skin reactions. Removal from important missing information of use in patients with severe renal impairment and use in patients with severe hepatic impairment
MAH(s): Bristol-Myers Squibb Pharma EEIG

14.2.3. Pregabalin – LYRICA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000546/II/0073/G
Procedure scope: Revised RMP to update the targeted report form/follow-up questionnaire for abuse, misuse, dependence and change risk of misuse, abuse and dependence from potential to identified as requested by the PRAC in the recommendation of PSUV/0069 procedure. Change of the due date of PASS A0081096.
MAH(s): Pfizer Limited

14.2.4. Temozolomide – TEMODAL (CAP)

- Evaluation of an RMP in the context of a variation

[32] In line with the revised variation regulation for submissions as of 4 August 2013

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000229/II/0072
Procedure scope: Revised RMP (version 5.0) to reclassify hepatobiliary disorders from important potential to important identified risk following the request from PRAC/CHMP in the assessment of variation II/63
MAH(s): Merck Sharp & Dohme Limited

14.2.5. **Thiotepa – TEPADINA** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/001046/II/0018
Procedure scope: Update of SmPC section 4.8 of to update the safety information on pulmonary arterial hypertension with uncommon frequency. The package leaflet is updated accordingly
MAH(s): Adienne S.r.l. S.U.

RMP in the context of a variation – CHMP-led procedure

14.2.6. **Abacavir – ZIAGEN** (CAP)
Lamivudine – EPIVIR (CAP), **LAMIVUDINE VIIV** (Art 58)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/000107/WS0578/0092, EMEA/H/W/000673/WS0578/0027, EMEA/H/C/000252/WS0578/0078
Procedure scope: Update of SmPC sections 4.2, 4.8, 5.1 and 5.2 to update the information related to the extension of the once-daily oral administration of abacavir, lamivudine (ABC, 3TC) and Lamivudine ViiV to HIV-1–infected paediatric patients aged 3 months and older, according to amended weight-band ranges, based on the final clinical study report of the ARROW study. In addition, the safety, pharmacokinetic (PK) and efficacy data support harmonisation with the WHO treatment guidelines for dosing of ABC scored tablet and 3TC scored tablet in subjects ≥ 14 kg. The package leaflet is updated accordingly
MAH(s): ViiV Healthcare UK Limited

14.2.7. **Aflibercept – EYLEA** (CAP)

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

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/002392/II/0013
Procedure scope: Extension of indication to the treatment of macular oedema following branch retinal vein occlusion (BRVO). SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 are updated with new clinical and nonclinical data. The package leaflet is updated accordingly
MAH(s): Bayer Pharma AG

14.2.8. Bevacizumab – AVASTIN (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000582/II/0072
Procedure scope: Extension of indication to the use of bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan in patient with persistent, recurrent, or metastatic carcinoma of the cervix. Consequently, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5 and the package leaflet are updated
MAH(s): Roche Registration Ltd

14.2.9. Human thrombin, human fibrinogen – TACHOSIL (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000505/II/0057
Procedure scope: Extension of indication for the use of Tachosil as suture line sealing in dura mater closure. As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8, and 5.1 of and the package leaflet are updated
MAH(s): Takeda Austria GmbH

14.2.10. Ibandronic acid – IBANDRONIC ACID ACCORD (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002638/X/0006
Procedure scope: Addition of a new strength/potency and a new pharmaceutical form 3 mg solution for injection
MAH(s): Accord Healthcare Ltd

14.2.11. Interferon alfa-2b – INTRONA (CAP)
peginterferon alfa-2b – PEGINTRON (CAP), VIRAFERONPEG (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000281/WS0611/0099, EMEA/H/C/000280/WS0611/0119, EMEA/H/C/000329/WS0611/0112
Procedure scope: Update of SmPC section 4.4 with updated information on homicidal ideation and for patients with decompensated liver disease, and update of SmPC section 4.8 with pulmonary fibrosis added as post-marketing adverse experience. The package leaflet is updated accordingly. For Intron A only, the MAH takes the opportunity to implement minor linguistic revisions in various languages arising from an internal quality check
MAH(s): Merck Sharp & Dohme Limited

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

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000963/II/0065/G
Procedure scope: Update of SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1 to include data of clinical trial sponsored by Novartis Vaccines V49_23, testing concomitant use in conventional and accelerated schedules of Ixiaro with Rabipur. Update of SmPC as recommended during the renewal procedure R/0055 with inclusion of relevant data on elderly population
MAH(s): Valneva Austria GmbH

14.2.13. Paclitaxel – ABRAXANE (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000778/II/0067
Procedure scope: Extension of indication for the use of paclitaxel in combination with carboplatin for the first-line treatment of non-small cell lung cancer (NSCLC) in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. Consequently SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of and the package leaflet are updated
MAH(s): Celgene Europe Limited

14.2.14. Ruxolitinib – JAKAVI (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002464/II/0016
Procedure scope: Extension of indication to add treatment of adult patients with polycythaemia vera resistant to or intolerant of hydroxyurea. As a result, SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 and the package leaflet are updated
MAH(s): Novartis Europharm Ltd

14.2.15. Silodosin – SILODYX (CAP), UROREC (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001209/WS0672/0018/G, EMEA/H/C/001092/WS0672/0019/G
Procedure scope: Grouped variation to 1) update SmPC sections 4.8 and 5.1 to add efficacy and safety information from a European phase IV open label clinical study undertaken in patients with benign prostate hyperplasia. The RMP is updated accordingly; 2) update of the RMP with changes requested by the PRAC in the recent renewal procedure and PSUR procedures
MAH(s): Recordati Ireland Ltd

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

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

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001242/II/0018
Procedure scope: Extension of indication including an update of SmPC sections 4.1, 4.2 and 5.1 to add the combination therapy of Teysuno with oxaliplatin (with or without epirubicin) with consequential updates to SmPC sections 4.3, 4.4, 4.5, 4.6, 4.8 and the package leaflet
MAH(s): Nordic Group B.V.

14.2.17. Vismodegib – ERIVEDGE (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002602/II/0015/G
Procedure scope: Grouped variations: 1) Following the review of GP28465 study report, update of SmPC section 4.3 to delete the contraindication with St John's wort; section 4.4 to delete the warning relating to the concomitant treatment with strong CYP inducers and section 4.5 to update the effects of concomitant medicinal products. The package leaflet is updated accordingly. 2) Following the review of GP27839 study report as well as new clinical pharmacokinetic (PK) and PK modelling data, update of SmPC section 4.2 regarding the posology information for patients with hepatic and renal impairment; section 5.2 to reflect the new PK data generated in patients with hepatic and renal impairment. 3) Finally, submission of a summary document outlining new non-clinical, clinical PK data generated since the initial marketing authorisation to complement the existing oral contraceptive drug-drug interaction data
MAH(s): Roche Registration Ltd

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

14.2.18. Filgrastim – NIVESTIM (CAP)

- Evaluation of an RMP on the context of a five year-renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/001142/R/0025
MAH(s): Hospira UK Limited

14.2.19. Leflunomide – LEFLUNOMIDE MEDAC (CAP)

- Evaluation of an RMP on the context of a five year-renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001227/R/0019
MAH(s): Medac Gesellschaft fur klinische Spezialpraparate mbH

15. ANNEX I - Periodic Safety Update Reports (PSURs)

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

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

Evaluation of PSUR procedures

15.1.1. Aminolevulinic acid hydrochloride – AMELUZ (CAP), NAP

- Evaluation of a PSUSA[33] procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00010006/201406
MAH(s): Biofrontera Bioscience GmbH, various

15.1.2. Avanafil – SPEDRA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002581/PSUV/0010
MAH(s): Menarini International Operations Luxembourg S.A.

15.1.3. Belatacept – NULOJIX (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002098/PSUV/0023
MAH(s): Bristol-Myers Squibb Pharma EEIG

[33] PSUR single assessment, referring to CAP, NAP

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:

Procedure number(s): EMEA/H/C/002246/PSUV/0018
MAH(s): MediWound Germany GmbH

15.1.5. C1 inhibitor, human – **CINRYZE** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/001207/PSUV/0027
MAH(s): ViroPharma SPRL

15.1.6. Cabazitaxel – **JEVTANA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/002018/PSUV/0025
MAH(s): Sanofi-Aventis Groupe

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/001109/PSUV/0034
MAH(s): Novartis Europharm Ltd

15.1.8. Dextromethorphan, quinidine – **NUEDEXTA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002560/PSUV/0004
MAH(s): Jenson Pharmaceutical Services Ltd

15.1.9. Emedastine – EMADINE (CAP), NAP

- Evaluation of a PSUSA[34] procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001207/201405
MAH(s): Alcon Laboratories (UK) Ltd, various

15.1.10. Galsulfase – NAGLAZYME (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000640/PSUV/0054
MAH(s): BioMarin Europe Ltd

15.1.11. Human fibrinogen, human thrombin – TACHOSIL (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001627/201406
MAH(s): Takeda Austria GmbH

15.1.12. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP), HIZENTRA (CAP), HYQVIA (CAP), KIOVIG (CAP), PRIVIGEN (CAP), NAP

- Evaluation of a PSUSA[35] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001633/201405
MAH(s): Instituto Grifols S.A., various

15.1.13. Hydroxycarbamide – SIKLOS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000689/PSUV/0025 (with RMP)
MAH(s): Addmedica

[34] PSUR single assessment, referring to CAP, NAP
[35] PSUR single assessment, referring to CAP, NAP

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000899/PSUV/0027
MAH(s): Shire Orphan Therapies GmbH

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001101/PSUV/0061, EMEA/H/C/002617/PSUV/0023
MAH(s): MedImmune LLC

15.1.16. Matrix applied characterised autologous cultured chondrocytes – **MACI** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002522/PSUV/0005
MAH(s): Aastrom Biosciences DK ApS

15.1.17. Misoprostol – **HEMOPROSTOL** (Art 58)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/W/002652/PSUV/0002
MAH(s): Linepharma France

15.1.18. Nateglinide – **STARLIX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000335/PSUV/0028
MAH(s): Novartis Europharm Ltd

15.1.19. Omalizumab – XOLAIR (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000606/PSUV/0061
MAH(s): Novartis Europharm Ltd

15.1.20. Pegaptanib – MACUGEN (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000620/PSUV/0061
MAH(s): PharmaSwiss Ceska Republika s.r.o

15.1.21. Peginterferon alfa-2a – PEGASYS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000395/PSUV/0077
MAH(s): Roche Registration Ltd

15.1.22. Pertuzumab – PERJETA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002547/PSUV/0011
MAH(s): Roche Registration Ltd

15.1.23. Ponatinib – ICLUSIG (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002695/PSUV/0014
MAH(s): Ariad Pharma Ltd

15.1.24. Pyronaridine, artesunate – PYRAMAX (Art 58)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/W/002319/PSUV/0007
MAH(s): Shin Poong Pharmaceutical Co., Ltd.

15.1.25. Ranibizumab – LUCENTIS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000715/PSUV/0049
MAH(s): Novartis Europharm Ltd

15.1.26. Sofosbuvir – SOVALDI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002798/PSUV/0009
MAH(s): Gilead Sciences International Ltd

15.1.27. Tigecycline – TYGACIL (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000644/PSUV/0088
MAH(s): Pfizer Limited

15.1.28. Tobramycin – TOBI PODHALER (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002155/PSUV/0026
MAH(s): Novartis Europharm Ltd

15.1.29. Umeclidinium, vilanterol – ANORO (CAP), LAVENTAIR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/002751/PSUV/0001, EMEA/H/C/003754/PSUV/0001
MAH(s): Glaxo Group Ltd.

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

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

16.1.1. Deferasirox – EXJADE (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number: EMEA/H/C/000670/ANX/038.5
Procedure scope: Evaluation of MAH's responses to ANX 038.4 as adopted by PRAC in July 2014 including a revised PASS protocol for study CICL670E2422: observational cohort study in paediatric non transfusion dependant-thalassaemia (NTDT) patients over 10 years
MAH(s): Novartis Europharm Ltd

16.1.2. Domperidone (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Patrick Maison (FR)

Administrative details:
Procedure number(s): EMEA/H/N/PSP/0008
Procedure scope: Evaluation of a protocol for a non-interventional post-authorisation safety study (drug utilisation study) in routine clinical practice to assess the effectiveness of the risk minimisation measures and to monitor off-label use of domperidone as per the conclusions of the Article 31 referral
MAH(s): Pierre Fabre Medicament (Domperidone Pierre Fabre, Oroperidys, Peridys)

16.1.3. Domperidone (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Patrick Maison (FR)

Administrative details:
Procedure number(s): EMEA/H/N/PSP/0009
Procedure scope: Evaluation of a protocol for a non-interventional post-authorisation safety study (drug utilisation study) in routine clinical practice to assess the effectiveness of the risk minimisation measures and to monitor off-label use of domperidone as per the conclusions of the Article 31 referral

MAH(s): Rottapharm (Domperidona Gamir)

16.1.4. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002617/MEA 004.1
Procedure scope: Evaluation of the first interim results of PASS D2560C00008: non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2-17 years of age
MAH(s): MedImmune LLC

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

- Evaluation of an imposed PASS protocol

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

Administrative details:
Procedure number: EMEA/H/C/000561/ANX 034, EMEA/H/C/000560/ANX 034
Procedure scope: Evaluation of a PASS protocol for a non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice
MAH(s): Les Laboratoires Servier

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

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:
Procedure number: EMEA/H/C/002691/ANX 001.5, EMEA/H/C/002430/ANX 001.4, EMEA/H/C/002690/ANX 001.5
Procedure scope: Evaluation of a revised PASS protocol on cardio- and cerebrovascular outcomes (multinational database cohort study to assess adverse cardiovascular outcomes in association with inhaled glycopyrronium in Europe)
MAH(s): Novartis Europharm Ltd

16.1.7. Abatacept – ORENCIA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000701/MEA 054
Procedure scope: Evaluation of a PASS protocol for a non-interventional, non-imposed protocol IM101-537 aimed at assessing the effectiveness of risk minimisation measure (patient alert card)
MAH(s): Bristol-Myers Squibb Pharma EEIG

16.1.8. Apixaban – ELIQUIS (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002148/MEA 021.1
Procedure scope: Evaluation of the MAH's response to the request for supplementary information in the PRAC assessment report on the draft protocol for a non-interventional study to assess the effectiveness of the additional minimisation measures for the prevention of bleeding (as adopted in September 2014)
MAH(s): Bristol-Myers Squibb / Pfizer EEIG

16.1.9. Bromelain enriched proteolytic enzyme preparation from ananas comosus – NEXOBRID (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002246/MEA 003.1
Procedure scope: Evaluation of a revised PASS protocol (MW2013-06-01) for a drug utilisation study to further evaluate the effectiveness of the risk minimisation activities (including evaluation of educational and training materials)
MAH(s): MediWound Germany GmbH

16.1.10. Insulin lispro – HUMALOG (CAP), LIPROLOG (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000088/MEA 025, EMEA/H/C/000393/MEA 018
Procedure scope: Evaluation of a PASS protocol for a study examining the effectiveness of risk minimisation
MAH(s): Eli Lilly Nederland B.V.

16.1.11. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/000955/MEA 041.3
Procedure scope: Evaluation of the MAH's response to MEA-041.2 request for supplementary of information as adopted in September 2014: revised registry protocol collecting long term efficacy and safety data in polyarticular juvenile idiopathic arthritis (pJIA) treatment (study WA22478)
MAH(s): Roche Registration Limited

16.1.12. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002312/II/0053 (without RMP)
Procedure scope: Submission of the clinical study report of the Eviplera/Edurant healthcare professional survey undertaken to gain an understanding of the effectiveness of the current prescribing conditions in minimising the risk associated with taking the products without food/a meal, potentially associated with the risk of development of drug resistance
MAH(s): Gilead Sciences International Ltd

16.1.13. Paliperidone – XEPLION (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002105/II/0017 (with RMP)
Procedure scope: Submission of the final study report for a drug utilisation study conducted in Europe to fulfil an additional pharmacovigilance activity in the current combined paliperidone/paliperidone palmitate risk-management plan (version 5.1). The RMP has been updated accordingly (version 5.3)
MAH(s): Janssen-Cilag International N.V.

16.1.14. Ulipristal – ELLAONE (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/001027/II/0033 (without RMP)
Procedure scope: Submission of the final clinical study report to address the CHMP request from MEA007.5 (study HRA 2914-012): prospective multicentre observational study to assess clinical follow-up and outcomes of pregnancies exposed to ella/ellaOne. No changes to the product information are proposed
MAH(s): Laboratoire HRA Pharma

16.1.15. Rilpivirine – EDURANT (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002264/II/0015 (without RMP)
Procedure scope: Submission of the clinical study report of the Eviplera/Edurant healthcare professional survey undertaken to gain an understanding of the effectiveness of the current prescribing conditions in minimising the risk associated with taking the products without food/a meal, potentially associated with the risk of development of drug resistance
MAH(s): Janssen-Cilag International N.V.

16.1.16. Darunavir – PREZISTA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000707/MEA 069.2
Procedure scope: Interim results of the observational study to assess growth abnormalities (height) in HIV-infected children and adolescents on antiretroviral therapy in Europe (PENTA study)
MAH(s): Janssen-Cilag International N.V.

16.1.17. Exenatide – BYDUREON (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002020/MEA 010.2
Procedure scope: Annual report on a study H8O-MC-B016, a modified prescription event monitoring (Modified PEM) to identify possible cases of pancreatitis, enrolling primary care patients with type 2 diabetes who receive prescription for exenatide once weekly
MAH(s): AstraZeneca AB

16.1.18. Exenatide – BYDUREON (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002020/MEA 011.3
Procedure scope: Annual report on an epidemiologic study using one or more European databases to identify possible cases of thyroid neoplasms among type 2 diabetes mellitus patients who initiate exenatide once weekly
MAH(s): AstraZeneca AB

16.1.19. Human normal immunoglobulin – PRIVIGEN (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000831/MEA 022.2
Procedure scope: First interim report on the study entitled Privigen use and haemolytic anaemia in adults and children and the Privigen safety profile in children with chronic inflammatory demyelinating polyneuropathy (CIDP): observational hospital-based cohort study in the US
MAH(s): CSL Behring GmbH

16.1.20. Infliximab – REMICADE (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000240/MEA 121.7
Procedure scope: Annual report on the adults ulcerative colitis (UC) patient registry (OPUS), including the investigation of episodic/re-treatment
MAH(s): Janssen Biologics B.V.

16.1.21. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002617/MEA 006
Procedure scope: First annual report on a post-marketing observational evaluation of the safety of live attenuated influenza vaccine (LAIV) in children and adolescents with high-risk conditions
MAH(s): MedImmune LLC

16.1.22. Rivastigmine – EXELON (CAP), PROMETAX (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000169/MEA 0036, EMEA/H/C/000255/MEA 037
Procedure scope: Interim report on the trends of multiple patch use and with CIOMS reports of medication errors and misuse
MAH(s): Novartis Europharm Ltd

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

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

17.1.1. Agalsidase alfa – REPLAGAL (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000369/S/0086 (without RMP)
MAH(s): Shire Human Genetic Therapies AB

17.1.2. Clofarabine – EVOLTRA (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000613/S/0045 (without RMP)
MAH(s): Genzyme Europe BV

17.1.3. Lapatinib – TYVERB (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

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

Administrative details:
Procedure number(s): EMEA/H/C/000795/R/0039 (without RMP)
MAH(s): Glaxo Group Ltd

17.1.4. Mecasermin – INCRELEX (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000704/S/0032 (without RMP)
MAH(s): Ipsen Pharma

17.1.5. Pixantrone – PIXUVRI (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002055/R/0020 (with RMP)
MAH(s): CTI Life Sciences Limited

17.1.6. Tafamidis – VYNDAQEL (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002294/S/0022 (without RMP)
MAH(s): Pfizer Limited

18. ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 6 - 9 January 2015 meeting.

PRAC member PRAC alternate	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting***	***Topics on the current Committee Agenda for which restriction applies Product/ substance***
June Munro Raine	Chair	Full involvement	
Harald Herkner	Austria	Cannot act as Rapporteur or Peer reviewer for:	recombinant factor VIII: antihemophilic factor (recombinant), moroctocog alfa, octocog alfa; rivaroxiban; aflibercept
Jean-Michel Dogné	Belgium	Full involvement	
Veerle Verlinden	Belgium	Full involvement	
Yuliyan Eftimov	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Nectaroula Cooper	Cyprus	Full involvement	
Eva Jirsová	Czech Republic	Full involvement	
Doris Stenver	Denmark	Full involvement	
Torbjörn Callreus	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Terhi Lehtinen	Finland	Full involvement	
Arnaud Batz	France	Cannot act as Rapporteur or Peer reviewer for:	ustekinumab; paliperidone; rilpivirine; darunavir; infliximab
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
Julia Pallos	Hungary	Cannot act as Rapporteur or Peer reviewer for:	duloxetine; domperidone
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Ruchika Sharma	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Amelia Cupelli	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product/ substance
Nadine Petitpain	Luxembourg	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Magdalena Budny	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Roxana Stroe	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Milena Radoha-Bergoč	Slovenia	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Julie Williams	UK	Full involvement	
Rafe Suvarna	UK	Full involvement	

Independent scientific experts nominated by the European Commission	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product/ substance
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer reviewer for:	paroxetine; ambrisentan; umeclidinium; vilanterol; lapatinib
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Full involvement	
Lennart Waldenlind		Full involvement	

Health care professionals and patients members	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product/substance
Filip Babylon	Not applicable	Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer for:	paroxetine; ambrisentan; umeclidinium, vilanterol; lapatinib; ustekinumab; paliperidone; rilpivirine; darunavir; infliximab; denosumab;evolocumab; talimogene; laherparepvec; dapagliflozin,metformin; exenatide; insulin lispro; amiodarone; daclatasvir; sofosbuvir, clopidogrel; prasugrel, teriparatide; japanese encephalitis vaccine; ruxolitinib; canakinumab; nateglinide; omalizumab; ranibizumab;tobramycin; nilotinib; deferasirox; glycopyrronium bromide; rivastigmine; liraglutide; sildenafil; latanoprost; moroctocog alfa; pregabalin; tigecycline; apixaban; tafamidis; azithromycin; valproate, leflunomide; insulin glargine; cabazitaxel
Marco Greco		Full involvement	

Additional European experts participating at the meeting for specific Agenda items	Country	Topics on the current Committee Agenda for which restriction applies Product/ substance
Madli Pintson	Estonia	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Corinne Fechant	France	
Thomas Grüger	Germany	
Vahid Taravati	Germany	
Annette Hinze	Germany	
Charlotte Backman	Sweden	
Darius Matusevicius	Sweden	
Rolf Gedeborg	Sweden	
Bengt Ljungberg	Sweden	

Additional European experts participating at the meeting for specific Agenda items	*Country*	*Topics on the current Committee Agenda for which restriction applies* *Product/ substance*
John-Joseph Borg	Malta	
Andrew Ruddick	United Kingdom	