8 May 2014
EMA/315293/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Final Minutes of the meeting on 7-10 April 2014

Chair: June Raine – Vice-Chair: Almath Spooner

Note on access to documents

Some documents mentioned in the agenda/minutes cannot be released at present following a request for access to documents under Regulation (EC) No 1049/2001 as they are subject 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 minutes items and should be read in conjunction with the minutes.

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

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

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

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

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

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

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

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

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

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

Product-related pharmacovigilance inspections
(Item 9 of the PRAC Minutes)

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

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

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

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1. Introduction

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

The Chairperson opened the meeting, welcoming all participants to the 7-10 April 2014 meeting of the PRAC.

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

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 noted that George Aislaitner was stepping down as member from GR as well as Line Michan as alternate from DK and thanked them for their contribution to the work of the PRAC since its establishment.

1.2. Adoption of agenda of the meeting of 7-10 April 2014

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 3-6 March 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 3-6 March 2014 EMA/PRAC/253432/2014 were published on the EMA website on 28 April 2014.

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

2.1. Newly triggered procedures

2.1.1. Methadone medicinal products for oral use containing povidone (NAP)

- Review of the benefit-risk balance following notification by Norway of a referral under Article 107i of Directive 2001/83/EC, based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
PRAC Co-Rapporteur: Karen Pernille Harg (NO)

Administrative details:
MAH(s): Martindale Pharma, various
Triggering MS: NO

Background

The Norwegian Medicines Agency (NOMA) sent a letter of notification on 2 April 2014 along with an assessment report for triggering a referral procedure under Article 107i of Directive 2001/83/EC for methadone-containing medicinal products for oral use containing povidone. The notification was transmitted following receipt of 16 cases from several parts of Norway where the injection of a drug - in place of the recommended oral use – containing the excipient polyvinylpyrrolidone (more commonly known as povidone) and leading to kidney failure (including three fatal cases) had been suspected. Because of the high amount of povidone K90 (11.7 mg/ml) contained in Methadone Martindale Pharma 2 mg/ml, this was strongly suspected as the causal drug by the reporters.

Discussion

The PRAC noted the rationale provided by Norway and noted that the product information for Methadone Martindale Pharma specifies that the product is for oral administration only and that under no circumstances this product should be injected as injecting it may cause serious and permanent damage to the body with possible fatal consequences. The PRAC discussed whether the safety concern could be common to other related products and it was agreed that all methadone-containing medicinal products for oral use containing povidone should be included in the review. The PRAC also discussed lists of questions to be addressed during the procedure as well as a timetable for conducting the review. Finally the PRAC agreed that input from additional experts should also be sought within the review by means of an ad-hoc expert group meeting.

The PRAC appointed Qun-Ying Yue (SE) as Rapporteur and Karen Pernille Harg (NO) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

- A list of questions should be addressed by the MAHs (published on the EMA website EMA/PRAC/186318/2014) and data will be gathered from the stakeholders (healthcare professionals, patients' organisations and the general public) by means of responses to a list of questions (EMA/PRAC/222825/2014). The procedure will follow the adopted timetable (EMA/PRAC/186319/2014).
- An ad-hoc expert group meeting should be convened within the procedure.
- The PRAC agreed that all methadone-containing products for oral use containing povidone should be included in the review.

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

3.1. Newly triggered Procedures

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

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

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

Administrative details:
MAH(s): Boehringer Ingelheim, various
Triggering MS: BE

Background

The Belgian Medicines Agency (AFMPS) sent a letter of notification on 4 April 2014 triggering a referral procedure under Article 31 of Directive 2001/83/EC for a review of all ambroxol and bromhexine containing medicines. The letter follows the identification of new safety concerns which had emerged through the assessment of a work-sharing PSUR and signal detection activities for ambroxol containing products. Although immediate hypersensitivity reactions (including anaphylactic reactions), were already considered a known risk associated with ambroxol, they have been increasingly reported over the last two years and cases of delayed-type hypersensitivities associated with severe cutaneous adverse reactions (SCARs) have also been reported. Moreover, further to the assessment of the cumulative review on efficacy and safety of ambroxol hydrochloride in children under 6 years of age, the Belgian agency reached the conclusion that the benefit-risk balance of ambroxol within the indication 'secretolytic therapy' could no longer be considered favourable in this population. Ambroxol containing products are indicated in Europe for a number of conditions including orally as expectorants, as well as to relieve sore throat. Some formulations are used to treat breathing disorders in premature and newborn babies.

Discussion

The PRAC noted the safety concerns identified by Belgium for ambroxol containing products. Since ambroxol is a major metabolite of bromhexine, the PRAC agreed that products containing bromhexine should also be included in the review. Finally the PRAC discussed a list of questions to be addressed by relevant MAHs during the procedure as well as a timetable for conducting the review.

The PRAC appointed Margarida Guimarães (PT) as Rapporteur and Harald Herkner (AT) and Jean-Michel Dogné (BE) as Co-Rapporteurs for the procedure.

Summary of recommendation(s)/conclusions

- A list of questions should be addressed by the MAHs (published on the EMA website EMA/PRAC/189078/2014) and the procedure will follow the adopted timetable (EMA/PRAC/189079/2014).

3.1.2. Codeine (NAP)

- Review of the benefit-risk balance of codeine indicated for the treatment of cough and/or cold in paediatric patients following notification by Germany of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Martin Huber (DE)

Administrative details:
MAH(s): various
Triggering MS: DE

Background

The German Medicines Agency (BfArM) sent a letter of notification on 4 April 2014 triggering a referral procedure under Article 31 of Directive 2001/83/EC for the review of codeine-containing medicines indicated for the treatment of cough and cold in paediatric patients. The letter follows the conclusion of the review for codeine containing medicines used for pain in the same population finalised in June 2013 under an Article 31 procedure. The risk minimisation measures introduced following the Article 31 procedure for codeine used for pain relief included restrictions on use in children under 12 years of age, contraindication to use in patients known to be CYP2D6 ultra-rapid metabolisers and also that its use is not recommended for paediatric patients in whom respiratory function is compromised. Codeine is also widely used as an antitussive agent in children and adolescents below the age of 18 years. The posology is similar in both the pain and cough indication and therefore further consideration of whether similar risk minimisation measures might be needed for products with the cough and cold indication is warranted.

Discussion

The PRAC noted the notification letter from the German Medicines Agency and discussed a list of questions to be addressed by relevant MAHs during the procedure as well as a timetable for conducting the review. The PRAC requested interaction and involvement of the EMA Paediatric Committee (PDCO) in the review.

The PRAC appointed Julie Williams (UK) as Rapporteur and Martin Huber (DE) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

- A list of questions should be addressed by the MAHs (EMA/PRAC/180085/2014 published on the EMA website) and the procedure will be conducted in accordance with the adopted timetable (EMA/PRAC/180087/2014).

3.1.3. Testosterone (NAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)
PRAC Co-Rapporteur: Maia Uusküla (EE)

Administrative details:
MAH(s): various
Triggering MS: EE

Background

Following discussion at the PRAC in March 2014, the Estonian Medicines Agency (State Agency of Medicines) sent a letter of notification on 27 March 2014 along with a rationale for triggering a referral under Article 31 of Directive 2001/83/EC for a review of testosterone-containing medicines, used as replacement therapy in male hypogonadal disorders caused by either pituitary or testicular disorders or in hypogonadism following orchiectomy, as well as to promote masculinisation in hypogonadal adolescent boys, and in the prevention of osteoporosis in hypogonadal men, in the context of a possible increased risk of cardiovascular events and myocardial infarction in men who have pre-existing heart disease.

Discussion

The PRAC noted the notification letter from the Estonian Medicines Agency following discussion on the same signal at the March 2014 meeting (see related PRAC minutes) and discussed a list of questions to be addressed during the procedure as well as a timetable for conducting the review.

The PRAC appointed Doris Stenver (DK) as Rapporteur and Maia Uusküla (EE) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

- A list of questions should be addressed by the MAHs (published on the EMA website EMA/PRAC/178703/2014) and the procedure will follow the adopted timetable (EMA/PRAC/178709/2014).

Post-meeting note: Torbjörn Callréus (DK) took over Doris Stenver as Rapporteur for the procedures after being nominated as alternate for DK after the April PRAC meeting.

3.2. Ongoing Procedures

3.2.1. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide (NAP)

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

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)
PRAC Co-Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number: EMEA/H/A-31/1387
MAH(s): sanofi-aventis GmbH, various
Triggered by: UK

Background

A referral procedure under Article 31 is ongoing for valproate and medicines containing related substances (see PRAC minutes 7-10 October 2013). The PRAC (Co)-Rapporteurs prepared an assessment report on the responses received to the list of questions from the MAHs, for discussion at the PRAC.

Summary of recommendation(s)/conclusions

The PRAC discussed the aspects to be further clarified in the review and the areas where more information was required, and agreed on a list of outstanding issues to be addressed by the MAHs. Furthermore the PRAC supported the organisation of a Scientific Advisory Group meeting in the framework of the current procedure; this aspect will be further discussed once further information is assessed. The PRAC expressed strong support for involving representatives from patients' organisations in the review to enhance interaction and exchange of information with a focus on understanding the patients' perspective on the communication, awareness and understanding of the risks of valproate during pregnancy and in women of child bearing potential and to explore their views on options for improving risk communication. Therefore PRAC supported organising a dedicated meeting with representatives from patients' organisations.

Summary of recommendation(s)/conclusions

- A list of outstanding issues should be addressed by the MAHs and the procedure will follow the revised timetable (EMA/PRAC/606970/2013 Rev.1).
- An ad-hoc meeting with representatives from patients organisations will be organised within the review with the cooperation of the EMA's networks of eligible patients' organisations (see Patients' and consumers' organisations involved in the Agency's activities).

3.3. Procedures for finalisation

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

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

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

Administrative details:
Procedure number: EMEA/H/A-31/1370
EPITT 13359 – Follow up March 2014
PRAC Co-Rapporteurs (responsibility per substance): Margarida Guimarães (PT) (lisinopril); Carmela Macchiarulo (IT) (delapril, telmisartan, aliskiren, moexipril); Tatiana Magálová (SK) (spirapril, quinapril); Dolores Montero Corominas (ES) (fosinopril, irbesartan); Almath Spooner (IE) (benazepril, cilazapril, perindopril); Valerie Strassmann (DE) (ramipril, eprosartan, olmesartan); Menno van der Elst (NL) (trandolapril, losartan, azilsartan); Julie Williams (UK) (captopril, imidapril, zofenopril, candesartan); Qun-Ying Yue (SE) (enalapril, valsartan)
MAH(s): Actavis (Telmisartan Actavis, Actelsar HCT), Bayer Smith Kline Beecham (Kinzalmono, Kinzalkomb, Pritor, Pritor Plus), Boehringer Ingelheim (Micardis, Micardis Plus, Onduarp, Twynsta), Krka (Ifirmasta, Ifirmacombi, Tolura), Novartis (Copalia, Copalia HCT, Exforge, Exforge HCT, Dafiro, Dafiro HCT, Imprida), Novartis Europharm Ltd (Rasilamlo, Rasilez, Rasilez HCT, Rasitrio), Pharmathen S.A. (Sabervel), Sanofi-Winthrop / BMS (Aprovel, CoAprovel, Irbesartan Zentiva, Irbesartan HCT Zentiva, Karvea, Karvezide), Takeda (Edarbi, Ipreziv), Teva Pharma / Pharmachemie (Irbesartan Teva, Irbesartan HCT Teva, Telmisartan Teva, Telmisartan Teva Pharma), various

Oral explanations: *Not applicable*

Background

A referral procedure under Article 31 of Directive 2001/83/EC for agents acting on the renin-angiotensin system (see minutes of the PRAC 2-6 March 2014 meeting for background) is to be concluded. A final assessment of the data submitted was produced by the (Co)-Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs. The review included – among other data - assessment of the results of the published studies ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes) and ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints). The review also included the advice of a Scientific Advisory Group.

Clinical trial data has confirmed that dual blockade of the renin angiotensin system (RAS), through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAS-acting agent.

Overall, the Rapporteurs concluded that dual blockade of RAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is not recommended and ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

In addition, the concomitant use of ACE-inhibitors or ARBs with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) and is not recommended in all other patients.

Valsartan and candesartan remain authorised for the treatment of heart failure in combination with ACE-inhibitors in selected patients who cannot use other heart failure treatments. Treatment should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Based on these conclusions the PRAC agreed that changes should be made to the relevant product information of all medicines concerned.

Summary of recommendation(s)/conclusions

The PRAC adopted, by majority, a recommendation to vary the marketing authorisations of RAS-acting agents to be considered by the CHMP – see communication 'PRAC recommends against combined use of medicines affecting the renin-angiotensin (RAS) system' EMA/196502/2014. Key communication elements for use by the national competent authorities were also agreed.

Twenty-three members voted in favour of the recommendation together with Iceland and Norway whilst one member had a divergent view[1].

Post meeting note: The medicinal product Tolucombi EMEA/H/C/002549 is additionally included in this referral procedure (EMEA-H-A-31-1370).

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Aripiprazole – **ABILIFY** (CAP), **ABILIFY MAINTENA** (CAP)

- Signal of diplopia

Regulatory details:
PRAC Rapporteur(s): Margarida Guimarães (PT), Qun-Ying Yue (SE)

Administrative details:
EPITT 17913 – New signal

[1] Carmela Macchiarulo (IT).

[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

MAH(s): Otsuka Pharmaceutical Europe Ltd
Leading MS: PT

Background

Aripiprazole is an antipsychotic used for the treatment of schizophrenia in adults and in adolescents aged 15 years and older, for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment. Aripiprazole is also used for up to 12 weeks to treat moderate to severe manic episodes in patients aged 13 years or over.

The exposure for Abilify, a centrally authorised medicine containing aripiprazole, is estimated to have been more than 7 million patient-years worldwide, in the period from first authorisation in 2004 to 2013.

During routine signal detection activities, a signal of diplopia 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 diplopia and noted that some of cases included evidence on a positive dechallenge. In some other cases, alternative explanations or potential confounders could be found.
The product information for aripiprazole containing medicines currently included some eye related disorders but not diplopia. The PRAC commented that different plausible biological mechanisms could be considered as underlying the suspected reaction, either involving the nuclei controlling coordination of conjugate eye movement in the basal ganglia, the cerebral peduncles and the pons or the oculomotor cranial nerves or the effector muscles, and concluded that it would be useful to gather further data to conclude on the signal.

Summary of recommendation(s)

- The MAH for Abilify/Abilify Maintena (aripiprazole) should submit to the EMA, within 90 days, a cumulative review of all diplopia and diplopia related events presenting the available data from clinical trials, post-marketing experiences, and literature.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. Imatinib - GLIVEC (CAP), NAP

- Signal of decreased estimated glomerular filtration rate (eGFR)

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

Administrative details:
EPITT 17946 – New signal
MAH: Novartis Europharm Ltd

Background

Imatinib is protein-tyrosine kinase inhibitor used for the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) and Ph+ acute lymphoblastic leukaemia (ALL) in adult and paediatric patients, malignant gastrointestinal stromal tumours (GIST) and dermatofibrosarcoma protuberans (DFSP) in selected patients.
A signal of decreased estimated glomerular filtration rate (eGFR) was identified by ES, triggered by an article published in Annals of Oncology by Marcolino et al[3]. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the signal of decreased eGFR and noted that according to current product information for imatinib-containing medicines, acute renal failure is currently identified as an adverse reaction. However, evidence regarding the effect of long-term treatment on renal function and the occurrence of chronic progressive renal failure in these patients was lacking.

In the observational study by Marcolino et al., 105 CML patients were treated with imatinib during a median follow-up of 4.5 years. Estimated GFR decreased with imatinib treatment duration. The mean estimated GFR was 94 ± 21 mL/min/1.73m2 at baseline and 81 ± 22 mL/min/1.73m2 at the last follow-up measure (p<0.001). In this study, 12% of patients who had a baseline estimated GFR >60 mL/min/1.73m2 developed chronic renal failure during a median follow-up of 4.5 years.

The PRAC noted that results from a recent clinical trial (Study 3000-WW[4]) with bosutinib and imatinib, were consistent with these findings and provided evidence of declining renal function over time, based upon increase in serum creatinine and reduction of eGFR over time.

Summary of recommendation(s)

- The MAH for Glivec (imatinib) should submit to the EMA, within 60 days, supplementary information on the signal by providing a response to a list of questions including a cumulative review of all cases reported in clinical trials with information relevant to assess renal function and an analysis of the populations at greater risk for renal impairment.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Sodium containing formulations of effervescent, dispersible and soluble medicines (NAP)

- Signal of association with cardiovascular events

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 17931 – New signal
MAH: various
Leading MS: UK

[3] Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients. Marcolino MS, Boersma E, Clementino NC, Macedo AV, Marx-Neto AD, Silva MH, van Gelder T, Akkerhuis KM, Ribeiro AL. Ann Oncol. 2011 Sep;22(9):2073-9. doi: 10.1093/annonc/mdq715. Epub 2011 Feb 10.

[4] Cortes JE, KimDW, KantarjianHMet al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronicmyeloid leukemia:Results from the BELA trial. J Clin Oncol 2012;30:3486–3492.

Background

Some oral dispersible, soluble and effervescent formulations of medicinal products might contain high level of sodium used as an excipient to aid solubility. Following the publication of the results of a nested case-control study in the BMJ[5] , which had highlighted that patients exposed to effervescent, dispersible, and soluble medicines containing sodium were at a greater risk of adverse cardiovascular events compared with patients taking the same medicines in standard non-soluble formulations, UK raised this issue as a signal for analysis and prioritisation at the PRAC, with a view to improving current excipient labelling guidelines.

Discussion

The PRAC discussed the strengths and limitations of the above mentioned study. The PRAC commented that in the study the association between hypertension and soluble medicines was strong (OR 7.18) supporting a limited role for confounding. However, it was emphasised that a cohort study design would have been more appropriate as the outcomes examined were relatively common; there was a lack of adjustments for duration of treatment in the analysis conducted in a heterogeneous group of patients, including both those with intermittent use of the medicinal products and those with prolonged use; patients' dietary intake was not available and hence had not been included in the analysis. Despite the limitations of the study, however, the PRAC concurred that it is well established that high sodium intake (most commonly as dietary sodium chloride (salt)), is associated with cardiovascular events particularly hypertension and stroke. Therefore the association seen in the study between soluble medicines containing sodium and non-fatal stroke can be considered plausible.

The PRAC noted that sodium is listed in the guideline 'Excipients in the label and package leaflet of medicinal products for human use' and that there are provisions in place for labelling of sodium containing medicines for oral use where sodium is > 1mmol* / dose; reporting: '*This medicinal product contains x mmol (or y mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet'*. The PRAC debated on whether this wording could be further expanded and clarified and agreed that this should be further investigated.

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

Summary of recommendation(s)

- The PRAC recommended that there should be engagement with the EMA Excipients guideline group to consider whether updates could be made to the labelling of sodium within the 2003 Guideline in order to make the sodium labelling clearer and more meaningful for patients. In particular, how the labelling can more clearly express sodium content in medicines in the context of 'dietary salt'. EMA secretariat will work closely with the PRAC Rapporteur and present a follow-up to the PRAC, which is expected in September 2014.

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab - HUMIRA (CAP)

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

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

[5] George J, Majeed W, Mackenzie IS, MacDonald TM, Wei L. Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study. BMJ 2013;347:f6954

Administrative details:
EPITT 17701 – Follow up November 2013
MAH: AbbVie Ltd.

Background

For background information, see PRAC minutes of 4-7 November 2013. The MAH replied to the request for information on the signal of possible missed dose due to malfunction of the pre-filled pen device and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the responses received. The complaint rates for the pre-filled pen (0.05-0.1%) during the cumulative review period were deemed to be very low in absolute terms. The PRAC noted that there is a procedure in place for the MAH to follow the complaint rate over time and several actions to improve the pen device had been taken. However, details of a procedure for replacement of any device that has failed to deliver the drug needed to be clarified.

Several types of improvements have been or are being put in place by the MAH to address the concerns about pen malfunctioning and it is considered that these interventions have already contributed to or will produce over time a significant decrease of the complaint rate.

More specifically the introduction in France of a new cap design for the pre-filled pen has resulted in a reduction there of the complaint rate of approximately 20%. Similar trends are expected in other EEA countries where the new cap design is available.

No evidence of significant clinical risk associated with the complaints described has emerged. The major problem for the user is to know how much of the dose was actually administered, and decide whether to use another pen immediately or not. For this purpose, the PRAC felt it appropriate to clarify to the users the role of the yellow indicator present in the device, and the significance in case the latter has not appeared at all in the specifically designed device's window. Regarding this aspect the PRAC suggested expanding the text currently present in the package leaflet.

Summary of recommendation(s)

- The MAHs for Humira (adalimumab)[6] should be requested to submit to the EMA within 60 days a variation to update the product information of the relevant presentation to expand the 'Giving the Injection' section of the package leaflet.
- The MAH should provide with this submission details concerning the procedure for replacement of a device that has failed to deliver the drug, and clarification as to how this information is communicated to patients and prescribers.
- The MAH should address in the next PSUR (DLP 31/12/2016) all complaints due to device malfunction from the EU, including provision of complaint rates per number of devices sold over time.

For the full PRAC recommendations, see EMA/PRAC/229812/2014 published on the EMA website.

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

4.3.2. Clindamycin (NAP)

- Signal of drug interaction with warfarin leading to increase in the international normalised ratio (INR)

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 17700 – Follow up December 2013
MAHs: Pfizer, various

Background

For background information, see PRAC minutes of 2-5 December 2013.
The MAH replied to the request for information on the signal of drug interaction with warfarin leading to increase in the international normalised ratio (INR) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the data presented. Two potential mechanisms have been suggested to explain an effect on the coagulation parameters: the first, more probable, is an effect on gut flora synthesis and absorption of vitamin K inhibited by clindamycin, but a pharmacokinetic interaction between clindamycin and the R enantiomer of warfarin has also been proposed. Overall, the information presented including published literature reports in addition to spontaneous data, seemed to confirm a causal relationship between the administration of clindamycin and an increase in INR in patients maintained on vitamin K antagonists such as warfarin, acenocoumarol and fluindione. Therefore, the PRAC agreed that the product information for clindamycin containing-medicines should be updated regarding this interaction.

Summary of recommendation(s)

- The MAH for the reference, centrally authorised medicine [7] should be requested to submit to the EMA within 60 days a variation to update the product information.
- The MAHs of generic products should then be requested to submit to the EMA or to the national competent authorities of the MSs, as applicable, a variation to align their product information to that of the originator.

For the full PRAC recommendations, see EMA/PRAC/229812/2014 published on the EMA website.

4.3.3. Fentanyl, transdermal patch (NAP)

- Signal of accidental exposure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

[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

Administrative details:
EPITT 17778 – Follow up December 2013
MAHs: Janssen-Cilag, various
Leading MS: NL

Background

For background information, see PRAC minutes of 2-5 December 2013.
The MAH replied to the request for information on the signal of accidental exposure and the responses were assessed by the Rapporteur.

Discussion

The PRAC was reassured that in the product information for fentanyl patches, warnings and precautions for use regarding accidental exposure and instructions on the handling and disposal of used and unused patches are included. However, it was noted that cases of accidental exposure and medication error still occurred and in some instances with a fatal outcome, including in children. The lack of patch visibility may have played a role in these cases.
Therefore the PRAC proposed to explore implementation of risk minimisation measures in line with those imposed in the USA, i.e. improve patch visibility of all fentanyl transdermal patches. The MAH should assess the effectiveness of these risk minimisation measures once implemented and, based on the outcome of that evaluation, further measures might be warranted.
The PRAC discussed the usefulness of a DHPC as a further risk minimisation measure in order to highlight to Healthcare Professionals the risk of accidental exposure (especially in children) and to highlight and reinforce awareness regarding accidental exposure and proper disposal of the patches, and this was endorsed. Remaining routine pharmacovigilance measures were considered sufficient to monitor accidental exposure and medication error reported with fentanyl Transdermal Therapeutic System (TTS).

Summary of recommendation(s)

- The MAH for Fentanyl TTS brand leader should submit to the National Competent Authority (NCA) within 30 days proposals on how to improve patch visibility and timelines for implementation, a strengthened wording in their Product Information (PI) to warn of the risks associated with accidental exposure in children, to inform about the criticality of safe disposal, storing and handling. The MAHs of generic products containing fentanyl TTS should update their Product information in line with that of the reference product.
- A DHPC was supported as additional risk minimisation measure. The MAHs should monitor in the PSUR the effectiveness of the above risk minimisation measures (update SmPC, PL, DHPC and improved visibility) on prevention of accidental exposure. Based on the outcome of the evaluation, further measures including the introduction of educational materials might be warranted.

For the full PRAC recommendations, see EMA/PRAC/229812/2014 published on the EMA website.

4.3.4. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP)

- Signal of complex regional pain syndrome (CRPS) linked to the process of vaccination

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

Administrative details:
EPITT 17644 – Follow up December 2013
MAHs: GlaxoSmithKline Biologicals

Background

For background information, see PRAC minutes of 2-5 December 2013. The MAHs for Cervarix and Gardasil/Silgard replied to the request for information on the signal of complex regional pain syndrome (CRPS) linked to the process of vaccination and the responses were assessed by the Rapporteurs.

Discussion

The PRAC discussed the analysis of the currently available information from spontaneous reporting and from clinical trials as well as from the published literature, which was considered not sufficient to support any causal relationship between the administration of human papillomavirus vaccine and onset of CRPS.
However the PRAC agreed to keep the signal under monitoring for appropriate collection of further information. The MAHs should continue surveillance for cases suggestive of CRPS with a commitment to perform specific active surveillance.

Summary of recommendation(s)

- The analysis of the currently available information does not support a causal relationship between the use of Cervarix and Gardasil/Silgard and CRPS onset.
- The signal of CRPS should be closely monitored by the MAHs of Cervarix and Gardasil/Silgard during each PSUR evaluation with a discussion of all the suspected CRPS cases reported, accompanied with a quantitative analysis for causality assessment (disproportionality analysis, analysis of temporality and observed versus expected analysis).

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

- Signal of complex regional pain syndrome (CRPS) linked to the process of vaccination

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

Administrative details:
EPITT 17645– Follow up December 2013
MAHs: Sanofi Pasteur MSD, SNC (Gardasil), Merck Sharp & Dohme Limited (Silgard)

See above 4.3.4. CERVARIX

4.3.6. Levonorgestrel-releasing intrauterine device (IUD) (NAP)

- Signal of risk of uterine perforation – Final study results of EURAS-IUD study

Regulatory details:
PRAC Rapporteur: *to be appointed*

Administrative details:
EPITT 2706 – Follow up PhVWP March 2012
MAHs: Bayer, various
Leading MS: DE

Background

The "European Active Surveillance Study for Intrauterine Devices" (EURAS-IUD) was a large, multinational, controlled, non-interventional, prospective, active surveillance study following two cohorts of women with a newly inserted IUD (Mirena: a levonorgestrel-releasing intrauterine system nationally authorised in most Member States), or copper IUDs.

This prospective cohort study had been set up in 2006 investigating the risk of uterine perforation associated with Mirena and copper IUDs as a national measure upon request from BfArM after a signal was triggered following receipt of numerous spontaneous reports on uterine perforation associated with Mirena. The study protocol was endorsed by the former Pharmacovigilance Working Party (PhVWP) in 2007 and interim results were discussed by the PhVWP in 2012.

Final study results of EURAS-IUD were submitted to BfArM on 13 December 2013. DE presented this as a signal follow-up for discussion by the PRAC.

Discussion

The PRAC discussed the assessment of the results of the study. The primary statistical variable was the risk ratio for perforation (RR) between LNG-IUS and copper IUD. 61,448 women were recruited (70% LNG-IUS, 30% copper IUDs). In total, 61 perforations with LNG-IUS (1.4 per 1000 insertions (95% CI: 1.1-1.8)) and 20 with copper IUD (1.1 per 1,000 insertions (95% CI: 0.7-1.7)) occurred. The adjusted risk ratio was 1.61 (95% CI: 0.96 – 2.70). Breastfeeding and post-partum status were confirmed as risk factors for uterine perforation. PRAC noted that further data and discussion on the methods and results of the study should be provided by the MAH, and was informed by DE that a work-sharing variation to update the PI of the LNG-IUS IUS Mirena with results from EURAS-IUD is expected in May 2014.

Summary of recommendation(s)

- The MAH for Mirena should be requested to submit an update of the product information to reflect the final results of the EURAS IUD study and should submit additional data and information. This should be done within a work-sharing variation procedure to be submitted within 60 days. The requested additional data and information should be submitted to the appointed RMS (SE) for the work-sharing variation within that variation procedure.

For the full PRAC recommendations, see EMA/PRAC/229812/2014 published on the EMA website.

4.3.7. Simvastatin (NAP)

- Signal of myopathy and rhabdomyolysis associated with high doses

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 13849 – Follow up November 2013
MAHs: Bayer various

Background

For background information, see PRAC minutes of 4-7 November 2013.

Following discussion at the November 2013 PRAC meeting further information on the overall pattern of statin use, especially at high doses in the EU, was investigated; information on the potential

importance of genetic polymorphisms (such as variants of the SLCO1B1 gene) which may help identifying patients predisposed to myopathy/rhabdomyolysis with statin use, was also requested from the MAH. This new information was assessed by the Rapporteur.

Discussion

The PRAC discussed the data received on pattern of usage of statins which showed a diverse pattern across Europe. The use of simvastatin 80mg appeared overall to be a very small proportion of all statin use in all member states.

A number of potential biomarkers for myopathies in association with statin use have been identified. The genetic polymorphism SLCO1B1*5 has been mostly associated with cases of rhabdomyolysis seen with simvastatin use. Some, but not all, studies have found an increased risk of rhabdomyolysis with other statins when this variant of SLCO1B1 is present. Conversely, SLCO1B1*5 polymorphisms appear to account for about 40 to 50% of cases of rhabdomyolysis with simvastatin. Thus, a significant number of cases are not associated with this polymorphism. A number of other potential biomarkers for myopathy have been proposed but the evidence supporting them is sparse.

The genetic polymorphism SLCO1B1*5 is associated with an increased risk of myopathy, due to increased plasma levels of simvastatin. SLCO1B1*5 occurs in ~15-18% of Europeans and was found in about 45% of myopathy cases seen with simvastatin in the SEARCH trial, and accounted for 50-60% of myopathy cases seen in the 'SEARCH' and 'HPS' clinical trials. Screening for SLCO1B1*5 is not recommended for routine clinical practice.

The PRAC agreed, regarding SLCO1B1 genotypes that it would be appropriate to include information on genetic subpopulations as a risk factor for myopathy in the simvastatin label and also highlight the importance of considering the impact of the SLCO1B1 genotype, and in particular, advising that, where the patient's genotype is already known, the presence of the C allele, should be considered as part of an individual benefit-risk assessment prior to prescribing 80 mg simvastatin and high doses avoided in those found to carry the CC genotype.

Summary of recommendation(s)

- The MAHs for the reference, nationally authorised[8] simvastatin containing medicine should be requested to submit to the NCAs of the MS within 60 days a variation to update the product information to include information on the SLCO1B1 gene allele as requested by the PRAC.
- The MAHs of generics products should at the same time be requested to submit to the EMA or to the national competent authorities of the MSs, as applicable, a variation to align their product information to that of the originator.

For the full PRAC recommendations, see EMA/PRAC/229812/2014 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

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

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

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

5.1.1. 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: Reduction of thrombotic cardiovascular events (including stent thrombosis) in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI); Maintenance of P2Y12 inhibition in adult patients with acute coronary syndromes or in patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 therapy is interrupted due to surgery ('bridging') during the pre-operative period

5.1.2. Ketoconazole

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

Administrative details:
Product number(s): EMEA/H/C/003800, *Orphan*
Intended indication: Treatment of Cushing's syndrome

5.1.3. Obinutuzumab

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

Administrative details:
Product number(s): EMEA/H/C/002799, *Orphan*
Intended indication: Treatment of chronic lymphocytic leukaemia
Applicant: Roche Registration Ltd

5.1.4. Safinamide

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

Administrative details:
Product number(s): EMEA/H/C/002396
Intended indication: Treatment of Parkinson's disease (PD)

5.1.5. Tadalafil

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

Administrative details:
Product number(s): EMEA/H/C/003787, *Generic*
Intended indication: Treatment of erectile dysfunction in adult males

5.1.6. Tolvaptan

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

Administrative details:
Product number(s): EMEA/H/C/002788, *Orphan*
Intended indication: Treatment of autosomal dominant polycystic kidney disease (ADPKD)

5.1.7. Vorapaxar

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

Administrative details:
Product number(s): EMEA/H/C/002814
Intended indication: Reduction of atherothrombotic events

5.2. Medicines already authorised

RMP in the context of a variation[9] – PRAC-led procedures

See section 14.

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

5.2.1. Denosumab – PROLIA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/001120/II/0030
Procedure scope: Extension of indication to add treatment of osteoporosis in men at increased risk of fracture. As a consequence the MAH proposes to update SmPC sections 4.1 and 5.1
MAH(s): Amgen Europe B.V.

Background

Prolia is a centrally authorised product containing denosumab, a monoclonal antibody used in the treatment of osteoporosis in postmenopausal women at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

The CHMP is evaluating a type II variation procedure for Prolia to add treatment of osteoporosis in men at increased risk of fracture. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 8 for Prolia (denosumab) in the context of the variation under evaluation by the CHMP was not yet considered acceptable pending some minor modifications to be introduced to the summary of the risk management plan.

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

5.2.2. Denosumab – PROLIA (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/001120/II/0036
Procedure scope: Update of SmPC section 4.4 upon request by PRAC following the assessment of PSU/027, to revise the warnings on osteonecrosis of the jaw (ONJ)
MAH(s): Amgen Europe B.V.

Background

Prolia is a centrally authorised product containing denosumab, a monoclonal antibody used in the treatment of osteoporosis in postmenopausal women at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

The CHMP is evaluating a type II variation procedure for Prolia, submitted to revise the warnings on osteonecrosis of the jaw (ONJ) in the product information as recommended by the PRAC following assessment of the latest PSURs. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 0.1 for Prolia (denosumab) in the context of the variation under evaluation by the CHMP was not yet considered acceptable. It was considered that a DHPC, which addresses the risks of ONJ and of hypocalcaemia, should be disseminated, following finalisation of the above mentioned variation, and of an ongoing parallel procedure on hypocalcaemia (see below 5.2.4.).

5.2.3. Denosumab – PROLIA (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/001120/II/0037
Procedure scope: Update of the SmPC, upon request by PRAC following the assessment of PSU 027, to refine the warnings on hypocalcaemia including a description of the clinical manifestations of severe symptomatic hypocalcaemia and increases in parathyroid hormone in sections 4.4 and 4.8, and to add musculoskeletal pain as an identified risk in section 4.8 further to post-marketing experience
MAH(s): Amgen Europe B.V.

Background

Prolia is a centrally authorised product containing denosumab, a monoclonal antibody used in the treatment of osteoporosis in postmenopausal women at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

The CHMP is evaluating a type II variation procedure for Prolia, to refine the warnings on hypocalcaemia, including a description of the clinical manifestations of severe symptomatic hypocalcaemia, and increases in parathyroid hormone as recommended by the PRAC following assessment of the latest PSUR. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 0.1 for Prolia (denosumab) in the context of the variation under evaluation by the CHMP was not yet considered acceptable. It was considered that a DHPC, which addresses the risks of ONJ and of hypocalcaemia, should be disseminated, following finalisation of the above mentioned variation and of an ongoing parallel procedure on ONJ (see above 5.2.3.).

5.2.4. Denosumab – XGEVA (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/002173/II/0027
Procedure scope: Update of the SmPC, upon request by PRAC following the assessment of PSU/014, to revise the warnings in section 4.4 on osteonecrosis of the jaw (ONJ), and to add information in sections 4.4 and 4.8 on the incidence of ONJ based on duration of exposure
MAH(s): Amgen Europe B.V.

Background

Xgeva is a centrally authorised product containing denosumab, a monoclonal antibody, used in the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

The CHMP is evaluating a type II variation procedure for Xgeva, to revise the warnings on osteonecrosis of the jaw (ONJ). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 0.1(revised) for Xgeva (denosumab) in the context of the variation under evaluation by the CHMP was not yet considered acceptable. It was considered that a DHPC, which addresses the risks of ONJ and of hypocalcaemia, should be sent, following finalisation of the above mentioned variation and of the parallel procedure on hypocalcaemia (see below 5.2.5.). Further, the MAH should discuss the need for an additional risk minimisation measure, including the value of a patient reminder card given that Xgeva is normally administered under the responsibility of a healthcare professional and the patient may not have access to the information contained in the package leaflet raising awareness about relevant risk factors for ONJ and related risk minimisation measures.

5.2.5. Denosumab – XGEVA (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/002173/II/0028
Procedure scope: Update of the SmPC, upon request by PRAC following the assessment of PSU 014, to refine the warnings on hypocalcaemia including a description of the clinical manifestations of severe symptomatic hypocalcaemia and increases in parathyroid hormone in sections 4.4 and 4.8, and to add musculoskeletal pain as an identified risk in section 4.8 further to post-marketing experience. Further, sections 4.2 and 5.3 of the SmPC have been updated with respect to recommendations for monitoring of calcium levels, and information regarding patients with renal impairment
MAH(s): Amgen Europe B.V.

Background

Xgeva is a centrally authorised product containing denosumab, a monoclonal antibody, used in the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

The CHMP is evaluating a type II variation procedure for Xgeva, to refine the warnings on hypocalcaemia including a description of the clinical manifestations of severe symptomatic hypocalcaemia and increases in parathyroid hormone. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 8.1 (revised) for Xgeva (denosumab) in the context of the variation under evaluation by the CHMP was not yet considered acceptable. It was considered that a DHPC, which addresses the risks of ONJ and of hypocalcaemia, should be sent following finalisation of the above mentioned variation and of a parallel procedure on ONJ.

5.2.6. 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
MAH(s): Takeda Pharma A/S

Background

Rienso is a centrally authorised medicine containing ferumoxytol, an anti-anaemic preparation indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD).
The CHMP is evaluating an extension of the therapeutic indication for Rienso, to extend the indication to all cause iron deficiency anaemia when oral therapy is ineffective or inappropriate or where there is a need for rapid iron repletion. 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 3.1 for Rienso (ferumoxytol) submitted in the context of the extension of indication should be revised before finalisation of the procedure and the related CHMP opinion. In particular, in line with the recent Article 31 referral for iron containing intravenous (IV)

medicinal products (see CHMP AR, EMA/549569/2013) educational material for prescribers as well as for patients highlighting the risks of hypersensitivity reactions and warnings should be integrated in all relevant parts of the RMP and implemented as a condition for marketing authorisation (Annex II condition). Additional risk minimisation measures for the risk of hypersensitivity with targeted follow-up questionnaires were considered necessary.

- The PRAC noted that further analysis on the risk of hypersensitivity reactions will be provided in the upcoming PSUR procedure due for PRAC recommendation in July 2014.

5.2.7. Fingolimod – **GILENYA** (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002202/II/0021
Procedure scope: Modification of SmPC section 4.1 to extend the patient population from patients with high disease activity despite treatment with a beta-interferon (IFN) to patients with high disease activity despite treatment with a disease modifying therapy (DMT)
MAH(s): Novartis Europharm Ltd

Background

Gilenya is a centrally authorised product containing fingolimod, an immunosuppressant, indicated as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis for patients with high disease activity despite treatment with a beta-interferon, and patients with rapidly evolving severe relapsing remitting multiple sclerosis.
The CHMP is evaluating an extension of the therapeutic indication for Gilenya, to include the patient population of patients with high disease activity despite treatment with a disease modifying therapy (DMT). 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 7.1 for Gilenya (fingolimod) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable.
- The next update of the RMP should take into account some additions and clarifications requested by the PRAC with regards to the proposed amended protocol for the on-going post-authorisation safety study FTY720D2406 to evaluate the safety and efficacy of Gilenya in patients switching from other disease modifying agents.

5.2.8. Insulin lispro – **HUMALOG** (CAP), **LIPROLOG** (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000088/X/0125, EMEA/H/C/000393/X/0092
Procedure scope: Addition of a new strength (200 U/ml KwikPen presentation)
MAH(s): Eli Lilly Nederland B.V.

Background

Humalog and Liprolog are centrally authorised medicines containing insulin lispro, indicated in the treatment of diabetes mellitus.
The CHMP is evaluating a line extension for Humalog and Liprolog to include a new strength. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The updated RMP version 4 for Humalog and Liprolog (insulin lispro) in the context of the 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.
  The update should take into account some additions proposed by the PRAC, such as an expansion of the measures to address the potential risk of medication errors, to better reflect possible types of medication errors that might occur.
- The need for a DHPC and patient communication materials ensuring a focus on the key messages regarding medication errors in clinical practice was supported.
- Interaction with relevant patient groups in the framework of user testing of the patient information was recommended.

5.2.9. Zoledronic acid – ZOLEDRONIC ACID TEVA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002439/X/0008
Procedure scope: Addition of a new pharmaceutical form, solution for infusion with three new presentations
MAH(s): Teva Pharma B.V.

Background

Zoledronic Acid Teva is a centrally authorised generic medicine zolendronic acid, a bisphosphonate, indicated in the prevention of skeletal-related events and treatment of tumour-induced hypercalcaemia.
The CHMP is evaluating a line extension for Zoledronic Acid Teva to include a new pharmaceutical form. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The updated RMP version 4 for Zoledronic Acid Teva in the context of variation for a line extension under evaluation by the CHMP could be considered acceptable pending revision in accordance with some necessary modifications to the sections relating to important identified risks, important potential risks and missing information. These sections need to be in line with the RMP of other products containing zoledronic acid. The pharmacovigilance plan and risk minimisation activities need to be updated accordingly.

RMP evaluated in the context of a PSUR procedure

See also Bivalirudin under 6.1.3. , Eculizumab under 6.1.5. , Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil under 15.1.11. , Etravirine under 15.1.12. , Fingolimod under 6.1.7. , 6.1.19., Glycopyrronium bromide under 6.1.8. , Ritonavir under 15.1.23. , Strontium ranelate under 6.1.15. , Trastuzumab under 15.1.29. , Vinflunine ditartrate under 6.1.19.

RMP evaluated in the context of PASS results

See also Dolutegravir under 16.4.1. , Ivacaftor under 16.4.2. ; Retigabine under 16.4.3.

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

See Annex 14.2

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[10]

6.1.1. Aliskiren – RASILEZ (CAP)
aliskiren, amlodipine – RASILAMLO (CAP)
aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/PSU 035, EMEA/H/C/002073/PSU 008, EMEA/H/C/000964/PSU 032
MAH(s): Novartis Europharm Ltd

Background

Aliskiren and aliskiren-combinations act on the renin-angiotensin system and are indicated for the treatment of hypertension.

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of aliskiren, aliskiren/hydrochlorothiazide (HCT) and aliskiren/amlodipine-containing products and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of aliskiren, aliskiren/HCT, aliskiren/amlodipine and aliskiren/amlodipine/hydrochlorothiazide-containing products in the approved indication(s) remains favourable.

[10] 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

- Nevertheless, the product information should be updated to add nausea, vomiting and vertigo as undesirable effects with unknown frequencies. Therefore the current terms of the marketing authorisation(s) should be varied[11].
- The MAH should submit to EMA within 60 days a detailed analysis of cases of gastritis and the corrective action and preventive action (CAPA) taken to avoid coding errors. The MAH should provide a discussion on the potential impact on the overall benefit-risk of the medicinal products and propose an update of the product information as warranted.
- In the next PSUR, MAHs should provide a detailed analysis of cases of dyspnoea; hypertension and blood pressure inadequately controlled, and propose to update the product information as warranted. The MAH should also provide a discussion on the impact of the results of study CSPP100A2413[12] on the product information which currently states that 'aliskiren should be taken with a light meal'. In addition, the MAH should continue to closely monitor several adverse drug reactions, in particular, cases of pancreatitis, ischemic colitis and microalbuminuria.

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. Aztreonam – CAYSTON (CAP), NAP

- Evaluation of a PSUSA[13] procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00000283/201309
MAH(s): Gilead Sciences International Ltd (Cayston), A. Menarini Industrie Farma (Primbactam), Bristol-Myers Squibb (Azactam)

Background

Aztreonam is an antibacterial agent indicated for inhalation use for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older. Aztreonam is also indicated for parenteral use for the treatment of urinary tract infections (UTI), lower respiratory tract infections (RTI), bacteremia/septicemia, meningitis, bone and joint infections, skin and skin-structure infections, intra-abdominal infections, gynecologic infections, and gonorrhea. It is also indicated as adjunctive therapy to surgery in the management of infections caused by susceptible organisms and for the elective and specific use in severe bacterial infections that are known or believed to be caused by gram-negative pathogens, in particular in debilitated or immune-depressed patients.

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of aztreonam-containing products for inhalation and parenteral use and issued a recommendation on their marketing authorisation(s).

[11] 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
[12] 8-week randomized, open-label, multicentre study to evaluate the efficacy and safety of oral aliskiren 300 mg once daily under light meal versus fasted condition in patients with hypertension
[13] PSUR single assessment, referring to CAP, NAP

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of aztreonam-containing products in the approved indication(s) remains favourable.
- With regard to aztreonam-containing products for parenteral use, the current terms of the marketing authorisation(s) should be maintained.
- With regard to aztreonam for inhalation use (Cayston), the product information should be updated to refine the warning on allergic reactions. Therefore the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR for Cayston, the MAH should closely monitor fatal cases and cases of dizziness.
- In the next PSUR for aztreonam for parenteral use, MAHs should add to their safety specification the development of resistance to aztreonam as an important potential risk and Use in pregnancy, use in low birth weight infants and use in neonates younger than one week as missing information.

The assessment of safety data for aztreonam-containing products for inhalation use should be assessed separately from other aztreonam-containing products for parenteral use, to allow a risk proportionate evaluation. The next PSUR for aztreonam-containing products for inhalation use 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 PSUR submission for aztreonam-containing products for parenteral use PSURs should be changed from yearly to 5-yearly and the list of Union reference dates (EURD list) is updated accordingly.

6.1.3. Bivalirudin – ANGIOX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000562/PSU 024 (with RMP version 11)
MAH(s): The Medicines Company UK Ltd.

Background

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

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Angiox (bivalirudin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a more comprehensive analysis of the data on the number of cases of acute stent thrombosis reported in the EUROMAX study[15]. In addition, the MAH should provide a detailed analysis on the need to strengthen the wording relating to prolonged infusion following PCI in STEMI patients in the posology and method of administration section of the product information.

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

6.1.4. Deferiprone – FERRIPROX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000236/PSU 060
MAH(s): Apotex Europe BV

Background

Deferiprone is an iron chelating agent indicated for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ferriprox, a centrally authorised medicine containing deferiprone, 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 Ferriprox (deferiprone) 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 90 days a protocol synopsis for a study aiming at assessing compliance in the EU with the SmPC recommendations under clinical practice conditions and collecting longitudinal safety data in newly treated patients, further details on the newly conducted studies in rodents and monkeys, and a discussion on the need to update the product information accordingly.
- In the next PSUR, the MAH should provide a comprehensive review on the possible pathophysiological mechanism of the occurrence of leukocytoclastic vasculitis and update the product information as warranted. The MAH should also provide a detailed review of increased serum liver enzymes following a single administration of deferiprone and of off-label use especially when deferiprone is concomitantly administered with other iron chelators. Some

[15] European Ambulance Acute Coronary Syndrome (ACS) Angiography Trial (EUROMAX)

other issues should continue to be closely monitored or need to be addressed. The MAH should also consider updating the product information regarding concomitant use with other iron chelators. Finally, the MAH should submit an updated RMP.

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

6.1.5. Eculizumab – SOLIRIS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000791/PSU 044 (with RMP version 10.0)
MAH(s): Alexion Europe SAS

Background

Eculizumab is a recombinant humanised monoclonal $IgG_{2/4k}$ antibody indicated in adults and children for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uremic syndrome (aHUS).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Soliris, a centrally authorised medicine containing eculizumab, 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 Soliris (eculizumab) 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 30 days a variation providing all available evidence on whether immune response in neonates following maternal exposure to eculizumab could be affected, and include a thorough discussion on the appropriateness of an update to the product information accordingly to address the risk of potential adverse reactions in neonates.
- In the next PSUR, the MAH should provide further information, including, clarification on the number of patients exposed to eculizumab in clinical trials, in particular those with generalised myasthenia gravis (gMG). In addition, the MAH should ensure that appropriate follow up of pregnancy outcome is in place to capture suspected adverse reactions in neonates after delivery date. The length of follow-up should take into account that infection by Group B Streptococci may have an early or late onset.
- The MAH should submit an updated RMP to reflect the serious infections in neonates after maternal exposure as an important potential risk in the framework of an upcoming procedure and/or no later than with the next PSUR procedure.

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. Everolimus – VOTUBIA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002311/PSU 005
MAH(s): Novartis Europharm Ltd

Background

Everolimus is a selective serine-threonine kinase inhibitor indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) and for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Votubia, a centrally authorised medicine containing everolimus, 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 Votubia (everolimus) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add the risk of angioedema as a warning following concomitant use of everolimus and angiotensin-converting-enzyme (ACE) inhibitors. Therefore the current terms of the marketing authorisation(s) should be varied[16].

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

6.1.7. Fingolimod – GILENYA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002202/PSU 021 (with RMP version 7.0)
MAH(s): Novartis Europharm Ltd

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated as single disease-modifying therapy in highly active relapsing remitting multiple sclerosis under certain conditions.

[16] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Gilenya, a centrally authorised medicine containing fingolimod, 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 Gilenya (fingolimod) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add hypersensitivity and rash as undesirable effects with unknown frequencies. Therefore the current terms of the marketing authorisation should be varied[17].
- In the next PSUR, the MAH should provide additional information, in particular on progressive multifocal leukoencephalopathy (PML), skin cancers, multiple sclerosis relapses and sudden unexplained deaths (SUD). Thrombocytopenia (including immune thrombocytopenic purpura) and pancytopenia should be kept as signals under review. In addition, the MAH should provide a detailed review of cases of brain and cervical cancers and a discussion on the need to update the product information to reflect the higher risk of serious infections when leucopenia is associated with lymphopenia.
- In addition, the MAH should submit to EMA an updated RMP to upgrade hypersensitivity from a potential to an identified risk in the framework of the next procedure opportunity.

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

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002691/PSU 007 (with RMP version 3.1), EMEA/H/C/002430/PSU 007 (with RMP version 3.1), EMEA/H/C/002690/PSU 007 (with RMP version 3.1)
MAH(s): Novartis Europharm Ltd

Background

Glycopyrronium bromide is an inhaled long-acting muscarinic receptor antagonist (anticholinergic) indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Enurev Breezhaler, Seebri Breezhaler and Tovanor Breezhaler, centrally authorised medicines containing glycopyrronium bromide, and issued a recommendation on their marketing authorisation(s).

[17] 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.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Enurev Breezhaler, Seebri Breezhaler and Tovanor Breezhaler (glycopyrronium bromide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the advice on method of administration to target possible inadequate use of the medicine or medical device. Hypersensitivity should be also added as a warning to ensure glycopyrronium bromide treatment is discontinued immediately if such reactions are experienced and alternative therapy instituted. In addition, hypersensitivity and angioedema should be added as undesirable effects with uncommon frequencies. Therefore the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should provide a detailed review of cases of paradoxical bronchospasm. The MAH should also submit an updated RMP to reflect minor changes.

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.

6.1.9. Iloprost – VENTAVIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000474/PSU 035
MAH(s): Bayer Pharma AG

Background

Iloprost is a synthetic prostacyclin analogue indicated for the treatment of adult patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ventavis, a centrally authorised medicine containing iloprost, 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 Ventavis (iloprost) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The PRAC noted that the final report of study 15762[19] was currently assessed in the context of the line extension procedure X/43[20] and recommended considering adding flushing as an

[18] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.
[19] randomized, open-label, single centre, crossover study to compare the pharmacokinetics of iloprost following inhalation of Ventavis 10 or Ventavis 20 solution with the I-Neb nebulizing device in healthy male volunteers under the condition of an extended inhalation time
[20] Scope of procedure: addition of a new strength (20 microgram/ml nebuliser solution)

undesirable effect to the product information as part of this procedure. In addition, the PRAC considers that the warnings on veno-occlusive disease and pulmonary oedema should be refined as part of X/43 to be in line with other medicinal products indicated in PAH.

- In the next PSUR, the MAH should provide further information, including detailed reviews of left heart failure and misuse. Some other issues should continue to be closely monitored or need to be addressed. In addition, the MAH should provide a description of safety findings from the Patient Support Programme conducted in Turkey.

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.

6.1.10. Infliximab – REMICADE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000240/PSU 143
MAH(s): Janssen Biologics B.V.

Background

Infliximab is a chimeric human-murine monoclonal antibody indicated for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Remicade, a centrally authorised medicine containing infliximab, 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 Remicade (infliximab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning to mention that some cases of active tuberculosis have been reported in patients treated with infliximab during and after treatment for latent tuberculosis. In addition, the warning and undesirable sections should be updated to reflect that the vast majority of hepatosplenic T-cell lymphoma (HSTCL) cases have occurred in patients with Crohn's disease or ulcerative colitis. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- The MAH should submit to EMA within 60 days a detailed review of cases of benign monoclonal hypergammaglobulinemia and a review of cases of hematophagic histiocytosis.
- In the next PSUR, the MAH should closely monitor cases of anterior uveitis.

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.

[21] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

6.1.11. Ipilimumab – YERVOY (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002213/PSU 022
MAH(s): Bristol-Myers Squibb Pharma EEIG

Background

Ipilimumab is a T-cell potentiator indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yervoy, a centrally authorised medicine containing ipilimumab, 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 Yervoy (ipilimumab) 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 90 days a variation to include the following listed events to the product information section on undesirable effects: nephritis, myositis/polymyositis, eye oedema, myasthenia gravis, psoriasis, proctitis, erythema multiforme, thyroiditis, blood thyroid hormone decreased, thyroxine decreased, temporal arteritis, autoimmune central neuropathy, hematuria and proteinuria. The MAH should determine the frequency category in line with the observed incidence of adverse drug reactions across clinical studies.
- In the next PSUR, the MAH should provide a cumulative review of cases of convulsion and propose an update of the product information as warranted. In addition, the MAH should provide an updated detailed cumulative review of second malignancies.

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.

6.1.12. Leflunomide – ARAVA (CAP), LEFLUNOMIDE MEDAC (CAP), LEFLUNOMIDE RATIOPHARM (CAP), LEFLUNOMIDE TEVA (CAP), LEFLUNOMIDE WINTHROP (CAP), REPSO (CAP), NAP

- Evaluation of a PSUSA[22] procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001837/201309
MAH(s): Sanofi-aventis Deutschland GmbH (Arava, Leflunomide Winthrop), Medac (Leflunomide Medac), Ratiopharm GmbH (Leflunomide Ratiopharm), Teva Pharma B.V. (Lefunomide Teva, Repso), Aptil Pharma Limited (Leflunomide), Apotex Europe B.V. (Leflunomide), Cipla (EU) Limited

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

(Leflunomide), Generics UK Ltd (leflunomide), Hexal AG (Leflunomide), Laboratorios Normon, S.A. (Leflunomide), Pharmathen S.A. (Leflon), Sigapharm GmbH (Fevol), Stada Arzneimittel AG (Leflunomide)

Background

Leflunomide is a selective immunosuppressant indicated for the treatment of adult patients with active rheumatoid arthritis as a 'disease-modifying antirheumatic drug' (DMARD) and for the treatment of active psoriatic arthritis under certain conditions.

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of leflunomide-containing products and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of leflunomide-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The PRAC noted that the recommended update to the product information to add the risk of reactivation of tuberculosis (TB) associated with leflunomide as a warning will be addressed in the context of the ongoing grouped variations WS560/G[23] for Arava (originator product). The MAHs for generic products-containing leflunomide should update their product information accordingly once the grouped variation for the originator product is finalised.
- In the next PSUR, the MAH for the originator product should provide information on the exposure in elderly patients and should continue to closely monitor cases of hepatic disorders, progressive multifocal leukoencephalopathy (PML), as well as any cases with pregnancy exposure.
- MAHs for generic products should update their product information in line with that of the originator products, thus a variation should be submitted to EMA and/or relevant National Competent Authorities, as per the submissions rules applying to each marketing authorisation as appropriate. Moreover, MAHs for generic products should closely monitor the same safety concerns as those monitored by the originator products as detailed in the PRAC assessment report.

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

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

6.1.13. Orlistat – ALLI (CAP), XENICAL (CAP), NAP

- Evaluation of a PSUSA[24] procedure

[23] Scope of procedure: worksharing variations grouped as follows: Update of sections 4.3 and 4.4 of the SmPC contraindicating and including a warning on teriflunamide the active metabolite of leflunomide; Update of section 4.5 of the SmPC for leflunomide related to the study reports HWA486/1032/001 (interaction cimetidine) and -HWA486/2F0.1 (interaction with methotrexate); Update of section 4.5 of the SmPC for teriflunomide related to the following Study reports INT11697-INT11720-INT12503-INT12500-INT10564-INT6040; Inclusion of DRESS syndrome in the RMP as requested by PRAC

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002220/201308
MAH(s): Glaxo Group Ltd (alli), Roche Registration Ltd (Xenical), Teva Pharmaceuticals Europe BV (Orlistat 123ratio), Sanofi (Orlsitat Zentiva), Teva Pharmaceuticals Polska Sp. z.o.o (Orlistat Teva), Hexal AG (Orlistat Sandoz, Orlistat Hexal 60and 120mg), Zentiva (Orlistat Zentiva), ZF Polpharma SA (Orlistat Polpharma, Slimella 60/120mg, Orlimax 120mg)

Background

Orlistat is indicated for weight loss in adults who are overweight or obese and should be taken in conjunction with a mildly hypocaloric diet under certain conditions.

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of orlistat-containing products and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of orlistat-containing products (orlistat) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, MAHs should closely monitor cases of vasculitis and continue to closely monitor cases of hepatic disorders, oxalate nephropathy and renal insufficiency, malignancies, drug interactions, exposure during pregnancy and off-label use. In addition, MAHs of orlistat 60 mg products should provide a detailed review of possible drug interactions between non-prescription orlistat and antidepressants and antipsychotics and propose to update the product information as warranted. Some other issues should continue to be closely monitored or need to be addressed.

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

6.1.14. Rivaroxaban – XARELTO (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000944/PSU 031
MAH(s): Bayer Pharma AG

Background

Rivaroxaban is a direct factor Xa inhibitor is indicated in combination for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xarelto, a centrally authorised medicine containing rivaroxaban, 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 Xarelto (rivaroxaban) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a detailed review of cases of vasculitis and propose an update of the product information and RMP as warranted. In addition, the MAH should provide a review on the relationship between PK (pharmacokinetics) and PD (pharmacodynamics) regarding the increase in bleeding risk and relationship with dose. The MAH should also provide a revised analysis of the risk of bleeding in patients who may be at particular risk such as those with impaired hepatic function or renal patients taking concomitant potent CYP3A4 inhibitors. Finally, the MAH should provide a detailed analysis of cases of serious bleeding in patients who may be at particular risk but who are not contraindicated.

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.

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000561/PSU 036 (with RMP version 13.0), EMEA/H/C/000560/PSU 036 (with RMP version 13.0)
MAH(s): Les Laboratoires Servier

Background

Strontium ranelate is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures and the treatment of severe osteoporosis in adult men at increased risk of fracture.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Osseor and Protelos, centrally authorised medicines containing strontium ranelate, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Osseor, Protelos (strontium ranelate) in the approved indication(s) remains favourable.

- Nevertheless, the product information should be updated to add hypercholesterolaemia as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should provide a cumulative review of cases of osteonecrosis of the jaw (ONJ) as well as a detailed analysis of cases of hypertension reported in clinical trials in the severe post-menopausal osteoporosis (PMO) population without contraindications.
- The MAH should submit an updated RMP[26] according to the EC decision for the recent referral procedure under Article 20 of Regulation (EC) No 726/2004.

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.

6.1.16. Telaprevir – INCIVO (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002313/PSU 004
MAH(s): Janssen-Cilag International N.V.

Background

Telaprevir is an inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease indicated in combination for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Incivo, a centrally authorised medicine containing telaprevir, 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 Incivo (telaprevir) in the approved indication(s) remains favourable.
- The product information should be updated to revise the warning concerning the strategy for managing treatment-emergent anaemia. Therefore the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide further information, included a detailed review of cases of pancreatitis and a proposal for an update of the product information as warranted as well as a detailed review of cases of rhabdomyolysis. The MAH should also discuss the need for revision of the educational materials on anaemia to reflect the recommended management strategy of ribavirin dose reduction.

[25] The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.
[26] The requested updated RMP for Osseor (variation II/038) and Protelos (variation II/043) were submitted in April 2014
[27] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

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

6.1.17. Trabectedin – YONDELIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000773/PSU 027
MAH(s): Pharma Mar, S.A.

Background

Trabectedin is an antineoplastic agent indicated for the treatment of adult patients with advanced soft tissue sarcoma and for the treatment, in combination, of patients with relapsed platinum-sensitive ovarian cancer.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yondelis, a centrally authorised medicine containing trabectedin, 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 Yondelis (trabectedin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to further detail the risk of drug interactions between trabectedin and CYP3A4 inhibitors and inducers, by specifying interaction study results performed in adults. Therefore the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should continue to closely monitor cases of renal and urinary disorders as well as drug-drug interactions.

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.

6.1.18. Vernakalant – BRINAVESS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001215/PSU 008
MAH(s): Cardiome UK Limited

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

Background

Vernakalant is an antiarrhythmic indicated for the rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brinavess, a centrally authorised medicine containing vernakalant, 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 Brinavess (vernakalant) in the approved indication(s) remains favourable.
- The MAH should submit to EMA within 60 days a detailed review on the use of the risk minimisation tools in place in clinical practice and a review of cases of off-label use including a discussion on the impact on the benefit-risk balance of the medicinal product.
- The current terms of the marketing authorisation(s) should be maintained.

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.

6.1.19. Vinflunine ditartrate – JAVLOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000983/PSU 015 (with RMP version 13.0)
MAH(s): Pierre Fabre Médicament

Background

Vinflunine is a chemotherapy agent indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Javlor, a centrally authorised medicine containing vinflunine, 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 Javlor (vinflunine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include the risk of hyponatraemia, including cases due to the syndrome of inappropriate antidiuretic hormone secretion, and to recommend that regular monitoring of serum sodium levels is conducted in patients taking vinflunine. The list of undesirable effects is also amended to ensure consistency in the way the adverse drug reactions are coded. This does not impact the frequency categories apart from peripheral sensory neuropathy which is recategorised from common to very common and

tumour pain recategorised from not known to uncommon. The current terms of the marketing authorisation(s) should be varied[29].

- In the next PSUR, the MAH should provide additional information; in particular, a summary of all cases with a fatal outcome.

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.

6.1.20. Zoledronic acid – ACLASTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000595/PSU 032
MAH(s): Novartis Europharm Ltd

Background

Zoledronic acid (5mg) is a nitrogen-containing bisphosphonate indicated for the treatment of osteoporosis and for the treatment of Paget's disease of the bone under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aclasta, a centrally authorised medicine containing zoledronic acid, 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 Aclasta (zoledronic acid 5 mg) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to better emphasise the recommendation on the need for hydration prior to administration of zoledronic acid 5 mg and calcium intake at the beginning of the 'posology and method of administration' section. The warning and undesirable effect sections should be also updated to reflect that osteonecrosis of the jaw (ONJ) is not limited to patients taking zoledronic acid in cancer indications. In addition, anti-angiogenic drugs should be added as a concomitant risk factor for ONJ. Therefore the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH should present relevant data on atrial fibrillation from all controlled Aclasta clinical studies that are available and discuss the need for an updated RMP. The MAH should also provide a status review of the investigations aiming at minimising the risk of ONJ, in particular, those aiming at optimising the treatment regimen, including the potential beneficial effect of pausing bisphosphonate therapy before invasive dental procedures. In addition, the MAH should provide an overview of the progress and status of the different proposed experimental, preclinical, clinical and epidemiological studies as per the conclusions of the CHMP review under Article 5(3) of Regulation (EC) No 726/2004 on bisphosphonates and

[29] 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.
[30] Update of SmPC sections 4.2, 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

osteonecrosis of the jaw which was finalised in 2009. Finally, the MAH should discuss the need for revision of the product information and for additional risk minimization measures regarding the risk for ONJ as warranted.

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.

6.1.21. Zoledronic acid – ZOMETA (CAP), **ZOLEDRONIC ACID MEDAC** (CAP), **ZOLEDRONIC ACID HOSPIRA** (CAP), NAP

- Evaluation of a PSUSA[31] procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00003149/201308
MAH(s): Novartis Europharm Ltd (Zometa), Medac (Zoledronic Acid Medac), Hospira (Zoledronic Acid Hospira), PH&T (Zoledronic Acid PHT), Sandoz B.V (Zoledronic acid)

Background

Zoledronic acid (4mg and 4 mg/100ml) is a nitrogen-containing bisphosphonate indicated for the prevention of skeletal related events in adult patients with advanced malignancies involving bone and for the treatment of adult patients with tumour-induced hypercalcaemia (TIH).

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of zoledronic acid (4mg and 4 mg/100ml)-containing products and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of zoledronic acid (4mg and 4 mg/100ml)-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, MAHs should provide further information, including a detailed analysis of potential off-label use and implications for long term safety follow up/data retrieval. MAHs should also apply long term follow-up in view of the increased treatment duration with zoledronic acid due to a longer survival of zoledronic acid treated cancer patients. MAHs should also closely monitor several adverse reactions, including cases of medication error, radiation induced adverse events and vascular calcification in patients under 65 years. In addition, MAHs should comment on the status of investigations aiming at minimising the risk of ONJ, in particular, MAHs should provide an overview of investigations aiming at optimising the treatment regimen, including the potential beneficial effect of pausing bisphosphonate therapy before invasive dental procedures. MAHs are asked to present data from clinical studies on incidence of ONJ in patients who had invasive dental procedures/tooth extractions compared with those who did not. Furthermore, a summary should be provided from the clinical studies of the risk factors for ONJ (invasive dental procedures/tooth extractions, concomitant treatments, comorbidities) in patients who developed ONJ compared with subjects who did not

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

develop ONJ. Moreover, an overview of the progress and status of the different proposed experimental, preclinical, clinical and epidemiological studies should be provided as per the conclusions of the CHMP review under Article 5(3) of Regulation (EC) No 726/2004 on bisphosphonates and osteonecrosis of the jaw which was finalised in 2009. Finally, MAHs should discuss the need for revision of the product information and for additional risk minimization measures regarding the risk for ONJ as warranted.

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

6.2. Follow-up to PSUR procedures[32]

See Annex 15.2

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[33]

7.1.1. Indacaterol, glycopyrronium bromide – ULTIBRO BREEZHALER (CAP), XOTERNA BREEZHALER (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002679/ANX 002, EMEA/H/C/003755/ANX 002
Procedure scope: PASS Protocol of Study QVA149A2402: a multinational multi-database cohort study to assess RMP specified safety outcomes in association with indacaterol, glycopyrronium bromide in Europe
MAH(s): Novartis Europharm Ltd

Background

Ultibro Breezhaler and Xoterna Breezhaler are centrally authorised medicines containing indacaterol and glycopyrronium bromide. They are indicated as once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The conduct of a multinational database cohort study to assess specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe was part of the obligations in the initial marketing authorisation. A protocol for this study was assessed by the Rapporteur and presented for review by the PRAC.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 01 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that that the design of the study did not fulfil the study objectives. Data variables, study design and end-points should be revised in accordance with the recommendations of the PRAC.

The PRAC therefore recommended that:

[32] Follow up as per the conclusions of the previous PSUR procedure, assessed outside next PSUR procedure
[33] In accordance with Article 107n of Directive 2001/83/EC

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[34]

See Annex 16.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[35]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[36]

See Annex 16.4

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[37]

See Annex 16.5

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 inspections

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

[34] 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
[35] In accordance with Article 107p-q of Directive 2001/83/EC
[36] 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
[37] In line with the revised variations regulation for any submission before 4 August 2013

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

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

10.1.1. Denosumab – PROLIA (CAP), XGEVA (CAP)

- PRAC consultation on a variation worksharing procedure, on CHMP request

Regulatory details:
Lead member: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/001120/II/0036, EMEA/H/C/001120/II/0037, EMEA/H/C/001120/II/0027, EMEA/H/C/001120/II/0028
Procedure scope: see under 5.2.2. , 5.2.3. , 5.2.4. , 5.2.5.
MAH(s): Amgen Europe B.V.

Background

Prolia and Xgeva are centrally authorised products containing denosumab. Prolia is indicated for treatment of osteoporosis in postmenopausal women at increased risk of fractures and treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Prolia is given as a subcutaneous injection of 60 mg once every 6 months. Xgeva is indicated for prevention of skeletal related events (radiation to bone, pathological fracture, spinal cord compression, or surgery to bone) in adults with bone metastases from solid tumors. Xgeva is given as a single subcutaneous injection of 120 mg once every 4 weeks.

Variations had been submitted by the MAH, with the scope to update the product information, upon request of the PRAC following the assessment of the latest PSUR, to revise the warnings on osteonecrosis of the jaw (ONJ) and to refine the warnings on hypocalcaemia including a description of the clinical manifestations of severe symptomatic hypocalcaemia and increases in parathyroid hormone in sections 4.4 and 4.8, and to add musculoskeletal pain as an identified risk in section 4.8 further to post-marketing experience. The Package Leaflet and the RMP had been modified accordingly (see also under Section 5 of these minutes for the RMP related discussion submitted with these variations).

Summary of advice

PRAC proposed revisions of the proposed changes to the product information, and agreed that the MAH should issue a DHPC addressing both information on ONJ and new information related to hypocalcaemia.

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Cyproterone, ethinylestradiol (NAP)

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

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

Administrative details:
Procedure scope: Assessment of the MAH's responses relating to the assessment of RMP of all cyproterone, ethinylestradiol (2 mg/0.035 mg) containing products, authorised in Europe and belonging to MAH Bayer
MAH(s): Bayer

Background

For background information, see PRAC minutes 6-9 January 2014.

The European Commission Decision, following the Article 107i procedure for all cyproterone acetate/ethinylestradiol (2 mg/0.035 mg) (CPA/EE)-containing products, included the following conditions for marketing authorisation (Annex IV): that the MAH(s) should submit the core elements (including outline of DUS, PASS and educational materials) of a risk management plan in EU format, within 3 months after the EC decision.

A work-sharing procedure was started concerning the assessment of the RMPs of all cyproterone acetate/ethinylestradiol (2 mg/0.035 mg) containing products authorised in Europe and belonging to the MAH Bayer that have been submitted. All concerned products were authorised on a purely national basis. The Medicines Evaluation Board of the Netherlands (MEB) acts as Reference Authority. The MAH has submitted the response to the Preliminary Assessment Report, which has now been assessed by the Netherlands and presented for discussion at PRAC for advice.

Summary of advice

Based on the review of the available information the PRAC agreed that both a survey and database study are needed to fully understand CPA/EE use in daily clinical practice. The proposed databases from UK, NL and IT (with most complete data and information on indication) were considered to be sufficient to give a European picture.

The PRAC agree that it would be more informative if separate timelines for the survey DUS and the database DUS were provided. Regarding the proposed PASS planned the PRAC was reassured that the current design included some changes as previously requested.

11.1.2. Flucloxacillin (NAP)

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

Regulatory details:
Lead member: Sabine Straus (NL)

Administrative details:
Procedure scope: PRAC consultation on a variation proposing the addition of a warning in SmPC section 4.4 of Flucloxacillin and Floxapen to exercise special caution regarding drug induced liver injury in subjects with HLA-B*5701 haplotype
MAH(s): Actavis Group PTC

Background

For background see PRAC minutes 6-9 January 2014. The PgWP provided advice on the proposed wording to exercise special caution regarding drug induced liver injury in subjects with HLA-B*5701 haplotype in patients taking flucloxacillin, as previously requested by the PRAC.

Summary of advice

Based on the review of the available information the PRAC agreed that the information already available under liver injury should be complemented with pharmacogenomics information on the HL-B5701 in the more appropriate section[38]. A wording proposal was agreed.

11.1.3. Triptorelin (NAP)

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

Regulatory details:
Lead member: Martin Huber (DE)

Administrative details:
Procedure scope: PRAC consultation on a variation proposing the addition of a new warning associated with long-term androgen deprivation therapy which may prolong the QT interval
MAH(s): Laboratoires Pharmaceutiques Sodia, various

Background

Triptorelin, a decapeptide, is a gonadotropin-releasing hormone agonist (GnRH agonist). It is indicated for the treatment of locally advanced or metastatic, hormone-dependent prostate cancer and as concomitant to and following radiation therapy in locally advanced hormone-dependent prostate cancer.

The MAH submitted a variation proposing a new warning associated with the use of long-term androgen deprivation therapy which may prolong the QT interval. DE requested PRAC advice on the conclusions from this variation.

Summary of advice

The PRAC discussed the variation for triptorelin including the proposal for a labelling update to introduce a warning that long-term androgen deprivation therapy may prolong the QT interval. The studies presented by the MAH within the variation almost exclusively focused on other drugs from the same therapeutic class (i.e. used for long-term androgen deprivation therapy), as only scarce data was available specifically for triptorelin. The PRAC noted the limitations of the data submitted within this variation application in support of such an association. Furthermore, there were uncertainties regarding the clinical relevance of the effects seen in the available studies.

The PRAC noted that some other products from the same therapeutic class already contain information on QT prolongation in their product information and that a review of the evidence supporting possible warnings regarding an increased risk of cardiovascular diseases was performed in the past by the Pharmacovigilance Working Party (PhVWP) in January 2012.

Therefore the PRAC recommended that, before agreeing on the need for amendments to the product information for triptorelin, the issue should be further evaluated expanding the scope to also include other active substances from the same therapeutic class. This should take into account the findings of the review previously performed by the PhVWP on that topic. Furthermore, the PRAC advised that the final conclusion on the above mentioned variation application should await this further review.

[38] Section 5.1 'There is evidence that the risk of flucloxacillin induced liver injury is increased in subjects carrying the HLA-B*5701 allele. Despite this association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA-B*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended'

11.2. Renewals of the Marketing Authorisation

None

11.3. Other requests

11.3.1. Cefepime (NAP)

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

Regulatory details:
Lead member: Margarida Guimarães (PT)

Administrative details:
Procedure number(s): PT/H/PSUR/0008/001
Procedure scope: PRAC consultation on an ongoing PSUR worksharing procedure and request for PRAC advice regarding association of Cefepime with increased all-cause mortality compared to other β–lactam antibacterials
MAH(s): Bayer, various

Background

For background see PRAC minutes 6-9 January 2014.

The Infectious Disease Working Party (IDWP) provided input on the use of monotherapy cefepime in febrile neutropenic patients as requested by the PRAC.

Summary of advice

Based on the review of the available information the PRAC agreed that there was no evidence supporting the existence of a higher risk of all-cause mortality for cefepime vs. other antibiotics in febrile neutropenic patients; the product information for products marketed in the EU already contains advice to consult official guidance on appropriate use and the physicians who manage the types of patients who are at risk of febrile neutropenia are considered to be fully aware of national and international guidance. Prescribers are also very likely to be acutely aware of problematic resistant organisms circulating in their institution and catchment areas, and to have a hierarchical approach to drug selection along the lines discussed by the EU guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance. Haematologica 2013; 98 (12).

Therefore the assessment of the PSUR for cefepime could be concluded, and the outcome of this review should be considered in the revision of the related core safety profile for cefepime.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Work Programme

- Draft PRAC Work Programme 2014-2015

At the organisational matters teleconference held on 24 April 2014, the EMA secretariat presented to PRAC the consolidated draft list of topics for the PRAC Work Programme, including names of the delegates who volunteered to participate in their fulfilment. Prioritisation, deliverables and identification of topic leaders will be discussed in May 2014.

12.2. Pharmacovigilance audits and inspections

12.2.1. Pharmacovigilance Systems and their Quality Systems

None

12.2.2. Pharmacovigilance Inspections

None

12.2.3. Pharmacovigilance Audits

Pharmacovigilance Audit Facilitation Group (PAFG)

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

At the organisational matters teleconference held on 24 April 2014, Julia Pallos (HU) updated the PRAC following consultation of the members on the risk rating of procedures for the audit strategy. PAFG will review the proposals and feedback will be provided accordingly.

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

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

- Handling of submissions of PSURs part of a PSUSA

Following the January 2014 discussion, the EMA Secretariat presented an update on the handling of submissions of PSURs part of a PSUSA in order to ensure the PSURs part of the procedures are submitted in line with the EU legislation and the EURD list as well as the EMA rules for submission currently under revision. The current EMA Post-Authorisation procedural advice on PSURs is being updated and will be shared with the PRAC before finalisation.

12.3.2. Periodic Safety Update Reports

None

12.3.3. PSURs Repository

None

12.3.4. Union Reference Date List

- Consultation on the draft List, version April 2014

The EMA Secretariat provided feedback to PRAC on the EMA Management Board discussion in March 2014 on the handling of PSURs for substances contained in Nationally Approved Products (NAPs). The Management Board agreed that such assessment should start in line with the EURD list, without any modification.

The PRAC endorsed the draft revised EURD list version April 2014 reflecting the PRAC comments impacting 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 April 2014, the updated EURD list was adopted by the CHMP at its April 2014 meeting and published on the EMA website on 02/05/2014 (see: Home >Regulatory>Human medicines >Pharmacovigilance >EU reference date and PSUR submission).

12.4. Signal Management

12.4.1. Signal Management

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

At the organisational matters teleconference held on 24 April 2014, the PRAC was given the monthly update on the work of the SMART Working Group.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

12.5.2. Individual Case Safety Report (ICSR) standard

- Draft EU ICSR Implementation Guide

Following consultation on the Draft EU ICSR Implementation Guide in March 2014, the PRAC was informed at the organisational matters teleconference held on 24 April 2014, that the comments received had been implemented. The next steps include a consultation with the CHMP and CMDh followed by a public consultation.

12.5.3. Additional Monitoring

None

12.5.4. List of Product under Additional Monitoring

- Consultation on the draft List, version April 2014

The PRAC was informed of the products newly added to the additional monitoring list and the updated list.

Post-meeting note: The updated additional monitoring list was published on 30/04/2014 on the EMA website (see: Home >Human Regulatory>Human medicines >Pharmacovigilance >Signal management>List of medicines under additional monitoring).

12.6. EudraVigilance Database

12.6.1. Activities related to the confirmation of full functionality

None

12.6.2. Changes to EudraVigilance Database and functional specifications

None

12.7. Risk Management Plans and Effectiveness of Risk Minimisations

12.7.1. Risk Management Systems

- Principles for RMP revised process

The PRAC was updated on the principles for a revised RMP process outlining the PRAC and CHMP responsibilities for the RMP development for initial MAAs. Further discussion will take place in May 2014.

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

- Qualitative and quantitative review of studies aimed to evaluate the effectiveness of additional risk minimisation measures

At the organisational matters teleconference held on 24 April 2014, the EMA Secretariat presented to PRAC some outline proposal for conducting a qualitative and quantitative review of studies aimed to evaluate the effectiveness of additional risk minimisation measures. EMA Secretariat agreed to prepare an overview paper to provide more details to PRAC.

12.8. Post-authorisation Safety Studies

None

12.9. Community Procedures

None

12.10. Risk communication and Transparency

None

12.11. Continuous pharmacovigilance

None

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Committees

12.12.1.1. Paediatric Committee (PDCO)

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

The PRAC endorsed the final draft concept paper on revising the guideline on conduct of pharmacovigilance for medicines used by the paediatric population. The draft revised guideline will be presented to PRAC after the summer 2014 for agreement before its release for public consultation.

12.12.2. Working Parties

12.12.2.1. Patients and Consumers Working Party (PCWP) Healthcare Professionals Working Party (HCPWP)

- Feedback from joint meeting Workshop on regulatory and methodological standards to improve benefit/risk evaluation of medicines

The PRAC received feedback from the PCWP/HCPWP workshop held on 25-26 February 2014 on regulatory and methodological standards to improve benefit/risk evaluation of medicines. The outcome will be taken into consideration in refining the draft list of topics for the PRAC Work Programme.

Post-meeting note: The full workshop report was published on 28/04/2014 on the EMA website (Home >Committees >Working parties and other groups>CHMP Patients' and Consumers' Working Party>Meetings).

12.12.2.2. Vaccine Working Party (VWP)

- Draft interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU

Following consolidation of comments, the PRAC endorsed the interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.

Post-meeting note: The interim guidance was published on 10/04/2014 on the EMA website (Home >Human regulatory>Scientific guidelines>Multidisciplinary>Vaccines)

12.12.3. Working Groups

12.12.3.1. EudraVigilance Working Group (EV-EWG)

The EMA secretariat circulated the draft EV-EWG Work Programme 2014. The EMA circulated a call for volunteer to participate in the EV-EWG as PRAC representative and provided details of the tasks involved.

Post-meeting note: At its May 2014 meeting, the PRAC endorsed Hervé Le Louet as PRAC representative at EV EWG.

12.13. Interaction within the EU regulatory network

12.13.1. European Commission: Directorate General for Health & Consumers (DG SANCO)

- Commission Delegated Regulation on Post-Authorisation Efficacy Studies (PAES)

The EC presented an overview of the Commission Delegated Regulation (EU) No 357/2014 regarding situations where a PAES may be requested. PAES are considered an exceptional instrument at the time of granting a marketing authorisation when concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. PAES can also be necessary after granting a marketing authorisation, for example, when a better understanding of the disease, the clinical methodology or if the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct a PAES should address certain well-reasoned scientific concerns which could have a direct impact on the maintenance of the marketing authorisation.

EMA outlined the principles for the development of a scientific guidance. A drafting group with expert consultation is being set up jointly with CHMP. PRAC endorsed S Evans (independent expert nominated by the EC) and Almath Spooner (IE, Vice-Chair) as PRAC Rapporteurs to contribute to the development of such a guidance document. The scientific guidance will be shared with the PRAC for agreement before public consultation.

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

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

None

12.14.2. Others

None

13. Any other business

13.1. EMA move in 2014 to new building

The PRAC received a status update from the EMA secretariat on the preparation of the EMA's move to a new building in July 2014. The first PRAC meeting in the new building will be in September 2014.

13.2. EMA reorganisation

- New organisational model

At the organisational matters teleconference held on 24 April 2014, the implementation of the EMA reorganisation was presented to the PRAC to provide details on the new operating model to manage medicinal products through their lifecycle, introducing new functions, including the 'EMA Product Lead' responsible for the overall product oversight, the 'Procedure Manager' and 'Risk Management Specialist'. The new operations are gradually implemented starting with variations (type I and type II), PSURs, PASS protocol assessments, administrative procedures (transfers, 61(3) notifications, corrigenda) as of April 2014.

PRAC requested the EMA Secretariat the possibility to create a Q&A or similar explanatory document for use by delegates and assessors at NCAs' level.

13.3. Marketing Authorisation Applications planned for the remainder of 2014

The EMA Secretariat presented to the PRAC a report on marketing authorisation applications planned for submission before the end of 2014 for information.

13.4. EMA policy on declaration of interest

- Principles of the revised EMA policy

EMA secretariat outlined the core principles of the revised EMA policy on declaration of interests aiming at streamlining the process of identification of potential conflict of interest and evaluation of declaration of interest that is due for implementation mid-2014.

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(s).

14.1.1. Allogenic human heterologous liver cells

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

Administrative details:
Product number(s): EMEA/H/C/003750, *Orphan, ATMP*
Intended indication: Treatment of urea cycle disorders (UCD)

14.1.2. Apremilast

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

Administrative details:
Product number(s): EMEA/H/C/003746
Intended indication: Treatment of psoriatic arthritis and psoriasis

14.1.3. Brinzolamide

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

Administrative details:
Product number(s): EMEA/H/C/003698
Intended indication: Treatment of open-angle glaucoma or ocular hypertension

14.1.4. Ciclosporin

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

Administrative details:
Product number(s): EMEA/H/C/002066
Intended indication: Treatment of dry eye disease in adult patients with severe keratitis that does not improve despite treatment with tear substitutes

14.1.5. Clopidogrel, acetylsalicylic acid

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

Administrative details:
Product number(s): EMEA/H/C/002272
Intended indication: Prevention of atherothrombotic events

14.1.6. Daklatasavir

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

Administrative details:
Product number(s): EMEA/H/C/003768
Intended indication: Treatment of chronic hepatitis C virus (HCV)

14.1.7. Dalbavancin

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

Administrative details:
Product number(s): EMEA/H/C/002840
Intended indication: Treatment of complicated skin and soft tissue infections (cSSTI)

14.1.8. Dasiprotimut-t

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

Administrative details:
Product number(s): EMEA/H/C/002772, *Orphan*
Intended indication: Treatment of non-Hodgkin's lymphoma (FL)

14.1.9. 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: Treatment of high-risk neuroblastoma

14.1.10. Human alfa-1 proteinase inhibitor

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

Administrative details:
Product number(s): EMEA/H/C/002739
Intended indication: maintenance treatment to slow the underlying destruction of lung tissue leading to emphysema in adults with alpha$_1$-proteinase inhibitor deficiency (also called alpha$_1$-antitrypsin deficiency) with clinically evident lung disease

14.1.11. Levofloxacin

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

Administrative details:
Product number(s): EMEA/H/C/002789, *Orphan*
Intended indication: Treatment of chronic pulmonary infections

14.1.12. Recombinant L-asparaginase

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

Administrative details:
Product number(s): EMEA/H/C/002661, *Orphan*
Intended indication: Combination therapy for B/T cell lymphoblastic leukaemia (ALL) or B/T cell lymphoblastic lymphoma (LBL)

14.1.13. Trametinib

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

Administrative details:
Product number(s): EMEA/H/C/002643
Intended indication: Treatment of unresectable or metastatic melanoma with a BRAF V600 mutation

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 – PRAC led procedure

14.2.1. Panitumumab – VECTIBIX (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/000741/II/0056
Procedure scope: Update to the RMP (version 12) to amend important identified and potential risks, address PRAC recommendations, enhance the Physicians education brochure (PEB), provide an update on the European Society of Pathologists (ESP) external Quality Assurance (EQA) programme and revise the timelines for category 1 and category 3 clinical studies
MAH(s): Amgen Europe B.V.

14.2.2. Dabigatran – PRADAXA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/II/0062
Procedure scope: Update to the RMP (version 28.4) following modification to study 1160 - 144 (post-authorisation non-interventional study aiming to evaluate potential off-label use of dabigatran etexilate in Europe)
MAH(s): Boehringer Ingelheim International GmbH

RMP in the context of a variation – CHMP led procedure

14.2.3. Alogliptin – VIPIDIA (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002182/II/0005
Procedure scope: Update of SmPC section 4.4 of to implement the recommendations of Art 5(3) procedure on GLP-1-based therapies and pancreatic safety
MAH(s): Takeda Pharma A/S

14.2.4. Alogliptin, metformin – VIPDOMET (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002654/II/0006
Procedure scope: Update of SmPC section 4.1 to implement the recommendations of Art 5(3) procedure on GLP-1-based therapies and pancreatic safety
MAH(s): Takeda Pharma A/S

14.2.5. Alogliptin, pioglitazone – INCRESYNC (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002178/II/0006
Procedure scope: Update of SmPC section 4.1 to implement the recommendations of Art 5(3) procedure on GLP-1-based therapies and pancreatic safety
MAH(s): Takeda Pharma A/S

14.2.6. Belimumab – BENLYSTA (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/002015/II/0023
Procedure scope: Update of SmPC section 4.4 to add a warning regarding progressive multifocal leukoencephalopathy (PML)
MAH(s): Glaxo Group Ltd

14.2.7. Canagliflozin – INVOKANA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002649/II/0005
Procedure scope: Update of the SmPC with new clinical data collected from the CANVAS (DIA3008) study, to reclassify bone fracture as an adverse drug reaction (ADR)
MAH(s): Janssen-Cilag International N.V.

14.2.8. Darunavir – PREZISTA (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/000707/II/0063

Procedure scope: Update of SmPC section 4.1 for the 100mg/ml oral suspension and the 400mg, 800mg film-coated tablets with information on the use of darunavir with cobicistat as pharmacokinetic enhancer
MAH(s): Janssen-Cilag International N.V.

14.2.9. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002574/II/0022
Procedure scope: Update of SmPC sections 4.2, 4.4 and 4.8 to revise recommendations to initiate/discontinue treatment based on creatinine levels and to update safety data as a result of the interim 48 weeks data from the GS-US-236-0118 study. Consequently Annex II.D 'Conditions or Restrictions with regard to the Safe and Effective Use of the Medicinal Product' is updated. The MAH included additional analyses using the pooled Week 144 safety analysis set from the GS-US-236-0102 and GS-US-236-0103 studies to support this variation. The Management Plan (RMP) has been updated accordingly
MAH(s): Gilead Sciences International Ltd

14.2.10. Exenatide – BYDUREON (CAP), BYETTA (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/002020/II/0019, EMEA/H/C/000698/II/0043
Procedure scope: Update of SmPC section 4.4 of to implement the recommendations of Art 5(3) procedure on GLP-1-based therapies and pancreatic safety
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

14.2.11. Filgrastim – GRASTOFIL (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/002150/II/0003/G
Procedure scope: Inclusion of the paediatric population in the currently approved indication for use in adults, as per the reference product SmPC, and to introduce graduations on the syringe barrel enabling use of the Grastofil in accordance with the paediatric posology. Sections 4.1, 4.2, 4.8 of the SmPC and Section 3.0 of the Package Leaflet are proposed to be updated to include the paediatric population. In addition, Sections 5.1 and 6.6 of the SmPC have been updated in alignment with the Neupogen PI
MAH(s): Apotex Europe BV

14.2.12. Ivacaftor – KALYDECO (CAP)

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

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:
Procedure number(s): EMEA/H/C/002494/II/0009, *Orphan*
Procedure scope: Update of SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 to extend the indication in the treatment of cystic fibrosis to patients aged 6 years and older who have other gating (class III) mutation in the CFTR gene than G551D
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

14.2.13. Linagliptin, metformin – JENTADUETO (CAP), **TRAJENTA** (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002279/WS0524/0017, EMEA/H/C/002110/WS0524/0014
Procedure scope: Update of the product information with regard to pancreatic events, following the CHMP conclusions on the Art 5(3) procedure
MAH(s): Boehringer Ingelheim International GmbH

14.2.14. Liraglutide – VICTOZA (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/001026/II/0027
Procedure scope: Update of SmPC section 4.4 to implement the conclusions of Art 5(3) referral procedure on GLP-1 based products and pancreatic safety
MAH(s): Novo Nordisk A/S

14.2.15. Lixisenatide – LYXUMIA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002445/II/0003
Procedure scope: Update of SmPC section 4.4 to implement the recommendations of Art 5(3) procedure on GLP-1-based therapies and pancreatic safety
MAH(s): Sanofi-Aventis Groupe

14.2.16. Lopinavir, ritonavir – ALUVIA (Art 58), **KALETRA** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/W/000764/II/0084, EMEA/H/C/000368/II/0143
Procedure scope: Update of SmPC sections 4.2, 4.6 and 5.2 for 200 mg/50 mg film-coated tablets and 100 mg/25 mg film-coated tablets to include a dosing recommendation for HIV-1-infected women during pregnancy and postpartum as well to include additional information relevant to the use of Lopinavir/ritonavir (LPV/r). In addition, the MAH proposes to update SmPC section 4.6 of the oral

solution and film-coated tablets with the results from the most recent interim report from the Antiretroviral Pregnancy Registry (APR)
MAH(s): AbbVie Ltd.

14.2.17. Meningococcal group a, c, w 135 and y conjugate vaccine – MENVEO (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/001095/II/0040
Procedure scope: Update of SmPC section 4.5 with information on co-administration with hepatitis A and B vaccines
MAH(s): Novartis Vaccines and Diagnostics S.r.l.

14.2.18. Olanzapine – ZYPREXA (CAP), ZYPREXA VELOTAB (CAP)

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

Regulatory details:
PRAC Rapporteur: Terhi Lehtinen (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000115/WS0485/0110, EMEA/H/C/000287/WS0485/0085
Procedure scope: Update of the SmPC to reflect the results of study HGMX, long-term, open-label, Safety Study of Oral Olanzapine in Adolescents with bipolar I Disorder (Manic or Mixed Episodes) or Schizophrenia. Updates are proposed to the SmPC in order to reflect the level of data now available in this patient population
MAH(s): Eli Lilly Nederland B.V.

14.2.19. Pneumococcal polysaccharide conjugate vaccine (adsorbed) – SYNFLORIX (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/000973/II/0075
Procedure scope: Update of SmPC section 4.8 to include Kawasaki's disease following the assessments of EMEA/H/C/973/PSU045 and EMEA/H/C/973/LEG045.1, in which an association between Synflorix and Kawasaki's disease could not be ruled out
MAH(s): GlaxoSmithKline Biologicals

14.2.20. Rituximab – MABTHERA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000165/II/0089
Procedure scope: Update of SmPC sections 4.2 and 4.8 to reflect change in infusion rate for RA patients and add infusion reactions as undesirable effect. Submission of RMP version 9.4
MAH(s): Roche Registration Ltd

14.2.21. Saxagliptin, metformin – KOMBOGLYZE (CAP), **ONGLYZA** (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/002059/WS0528/0015, EMEA/H/C/001039/WS0528/0025
Procedure scope: Update of SmPC section 4.4 to implement the recommendations of Art 5(3) procedure on GLP-1-based therapies and pancreatic safety
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

14.2.22. Sitagliptin – JANUVIA (CAP), **RISTABEN** (CAP), **TESAVEL** (CAP), **XELEVIA** (CAP)
sitagliptin, metformin - **EFFICIB** (CAP), **JANUMET** (CAP), **RISTFOR** (CAP), **VELMETIA** (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/000722/WS0534/0039, EMEA/H/C/001234/WS0534/0029, EMEA/H/C/000910/WS0534/0039, EMEA/H/C/000762/WS0534/0043
EMEA/H/C/000896/WS0535/0058, EMEA/H/C/000861/WS0535/0057,
EMEA/H/C/001235/WS0535/0043, EMEA/H/C/000862/WS0535/0061
Procedure scope: Update to SmPC section 4.4 and updated RMP to implement the CHMP recommendation of Art 5(3) referral procedure on GLP-1-based therapies and pancreatic safety. The RMP is also updated to include rhabdomyolysis as a potential risk as outcome of post-authorisation measure LEG 006.2
MAH(s): Merck Sharp & Dohme Limited

14.2.23. Tocilizumab – ROACTEMRA (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/000955/II/0032
Procedure scope: Extension of indication to the treatment in combination with methotrexate (MTX) of severe, active and progressive RA in adults not previously treated with MTX
MAH(s): Roche Registration Ltd
For adoption: PRAC RMP AR, PRAC RMP Assessment overview and Advice

14.2.24. Vildagliptin – GALVUS (CAP), **JALRA** (CAP), **XILIARX** (CAP)
vildagliptin, metformin – EUCREAS (CAP), **ICANDRA** (CAP), **ZOMARIST** (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

Procedure number(s): EMEA/H/C/000771/WS0518/0035, EMEA/H/C/001048/WS0518/0034, EMEA/H/C/001051/WS0518/0033
EMEA/H/C/000807/WS0518/0039, EMEA/H/C/001050/WS0518/0039,
EMEA/H/C/001049/WS0518/0039

Procedure scope: Update of the SmPC and PL to implement the recommendations of Art 5(3) procedure on GLP-1-based therapies and pancreatic safety
MAH(s): Novartis Europharm Ltd

14.2.25. Vinflunine – JAVLOR (CAP)

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s EMEA/H/C/000983/II/0011
Procedure scope: Extension of indication to include: in combination with capecitabine for the treatment of adult patients with locally advanced or metastatic breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant
MAH(s): Pierre Fabre Médicament

14.2.26. Voriconazole – VFEND (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/000387/II/0097
Procedure scope: Update of SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 to include information pertaining to the proposed new indication in prophylaxis of invasive fungal infections in high risk hematopoietic stem cell transplant recipients
MAH(s): Pfizer Limited

RMP in the context of a PSUR procedure

Not applicable

RMP evaluated in the context of PASS results

Not applicable

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

14.2.27. Alendronic acid, colecalciferol – VANTAVO (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): MEA/H/C/001180/R/0019
MAH(s): Merck Sharp & Dohme Limited

14.2.28. Bivalirudin – ANGIOX (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000562/R/005
MAH(s): The Medicines Company UK Ltd.

14.2.29. Mannitol – BRONCHITOL (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001252/RM 011.1
MAH(s): Pharmaxis Pharmaceuticals Limited

14.2.30. Pegfilgrastim – NEULASTA (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000420/RM 055.1
MAH(s): Amgen Europe B.V.

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

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

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

15.1. Evaluation of PSUR procedures[39]

15.1.1. Belimumab – BENLYSTA (CAP)

- Evaluation of a PSUR procedure

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

[39] 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

Administrative details:
Procedure number(s): EMEA/H/C/002015/PSU 018
MAH(s): Glaxo Group Ltd

15.1.2. Bosutinib – BOSULIF (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002373/PSU 009
MAH(s): Pfizer Limited

15.1.3. Brinzolamide – AZOPT (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000267/PSU 014
MAH(s): Alcon Laboratories (UK) Ltd

15.1.4. Cetuximab – ERBITUX (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000558/PSU 051
MAH(s): Merck KGaA

15.1.5. Colestilan – BINDREN (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002377/PSU 004
MAH(s): Mitsubishi Pharma Europe Ltd

15.1.6. Collagenase clostridium histolyticum – XIAPEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002048/PSU 021
MAH(s): Auxilium UK Limited

15.1.7. Dabigatran – PRADAXA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/PSU 039
MAH(s): Boehringer Ingelheim International GmbH

15.1.8. Daptomycin – CUBICIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000637/PSU 029
MAH(s): Novartis Europharm Ltd

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001120/PSU 037, EMEA/H/C/002173/PSU 015
MAH(s): Amgen Europe B.V.

15.1.10. Dexmedetomidine – DEXDOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002268/PSU 004
MAH(s): Orion Corporation

15.1.11. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002574/PSU 009 (with RMP version 1.0)
MAH(s): Gilead Sciences International Ltd

15.1.12. Etravirine – INTELENCE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000900/PSU 046 (with RMP version 9.0)
MAH(s): Janssen-Cilag International N.V.

15.1.13. Hepatitis A (inactivated) and hepatitis B (rDNA) (HAB) vaccine (adsorbed) – AMBIRIX (CAP), **TWINRIX ADULT** (CAP), **TWINRIX PAEDIATRIC** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000426/PSU 030, EMEA/H/C/000112/PSU 053, EMEA/H/C/000129/PSU 051
MAH(s): GlaxoSmithKline Biologicals

15.1.14. Influenza vaccine (split virion, inactivated) – IDFLU (CAP), **INTANZA** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000966/PSU 029, EMEA/H/C/000957/PSU 029
MAH(s): Sanofi Pasteur, Sanofi Pasteur MSD, SNC

15.1.15. Lapatinib – TYVERB (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000795/PSU 035
MAH(s): Glaxo Group Ltd

15.1.16. Measles, mumps, rubella and varicella vaccine (live) – PROQUAD (CAP), NAP

- Evaluation of a PSUSA[40] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001936/201309
MAH(s): Sanofi Pasteur MSD, SNC (Proquad)

15.1.17. Mecasermin – INCRELEX (CAP)

- Evaluation of a PSUR procedure

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

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000704/PSU 052
MAH(s): Ipsen Pharma

15.1.18. Memantine – AXURA (CAP), **EBIXA** (CAP), **MEMANTINE MERZ** (CAP), NAP

- Evaluation of a PSUSA[41] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001967/201309
MAH(s): Merz Pharmaceuticals GmbH (Axura, Memantine Merz), H. Lundbeck A/S (Ebixa), Aristo Pharma GmbH (Memantin NeuroPharma), Neuraxpharm Arzneimittel GmbH (Memantinhydrochlorid-neuraxpharm)

15.1.19. Midazolam – BUCCOLAM (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002267/PSU 008
MAH(s): ViroPharma SPRL

15.1.20. Pirfenidone – ESBRIET (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002154/PSU 007
MAH(s): InterMune UK Ltd.

15.1.21. Pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture) – PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP),
Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)-VEPACEL (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001200/PSU 024, EMEA/H/C/002089/PSU 003
MAH(s): Baxter AG, Baxter Innovations GmbH

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

15.1.22. Retigabine – TROBALT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001245/PSU 007
MAH(s): Glaxo Group Ltd

15.1.23. Ritonavir – NORVIR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000127/PSU 047 (with RMP version 5.0)
MAH(s): AbbVie Ltd.

15.1.24. Sulfur hexafluoride – SONOVUE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000303/PSU 028
MAH(s): Bracco International B.V.

15.1.25. Teduglutide – REVESTIVE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002345/PSU 005
MAH(s): NPS Pharma Holdings Limited

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001242/PSU 008
MAH(s): Nordic Group B.V.

15.1.27. Telavancin – VIBATIV (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001240/PSU 013
MAH(s): Clinigen Healthcare Ltd

15.1.28. Teriparatide – FORSTEO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000425/PSU 047
MAH(s): Eli Lilly Nederland B.V.

15.1.29. Trastuzumab – HERCEPTIN (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000278/PSU 093 (with RMP version 12.0)
MAH(s): Roche Registration Ltd

15.1.30. Vandetanib – CAPRELSA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002315/PSU 015
MAH(s): AstraZeneca AB

15.2. Follow-up to PSUR procedures[42]

15.2.1. Filgrastim – FILGRASTIM HEXAL (CAP), **ZARZIO** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000918/LEG 013.1, EMEA/H/C/000917/LEG 013.1
Procedure scope: MAH's response to PSUR#6 (PSU 013) RSI adopted in September 2013
MAH(s): Hexal AG

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

15.2.2. Pegfilgrastim – NEULASTA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000420/LEG 056
Procedure scope: MAH's response to PSUV-0071 (PSU-053 and RMP-055) RSI adopted at PRAC in September 2013
MAH(s): Amgen Europe B.V.

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

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

16.1. Protocols of PASS imposed in the marketing authorisation(s)[43]

16.1.1. Deferasirox – EXJADE (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000670/ANX/038.3
Procedure scope: Evaluation of MAH's response to ANX 038.2 as adopted by PRAC on 15 January 2014 via written procedure 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. Lenalidomide – REVLIMID (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000717/ANX 041.3, EMEA/H/C/000717/ANX 041.4
Procedure scope: MAH's responses to ANX-041.1 and ANX-041.2 [PASS Protocol CC-5013-MDS-012 / Drug Utilisation Study] as adopted at PRAC in January 2014
MAH(s): Celgene Europe Limited

16.1.3. Levonorgestrel (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
Lead member: Ulla Wändel Liminga (SE)

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

Administrative details:
Procedure scope: Evaluation of an updated PASS protocol entitled EURAS-LCS12: European Active Surveillance Study of LCS-12 for non-CAP: Jaydess and Luadei (levonorgestrel). The objective of the study is to assess among new users the risks of certain events associated with the use of LCS12 compared with established IUDs (Mirena, copper IUDs) during standard clinical practice. In addition, drug utilisation patterns are described
MAH(s): Bayer Pharma AG

16.1.4. Modified vaccinia Ankara virus – IMVANEX (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002596/SOB 002
Procedure scope: PASS protocol of studies POX-MVA-038 (observational, non-interventional post-authorisation safety study for the prophylactic vaccination with Imvanex in adults) and POX-MVA-039: (observational, non-interventional post-authorisation safety and efficacy study for the prophylactic vaccination with Imvanex following re-emergence of circulating smallpox infections)
MAH(s): Bavarian Nordic A/S

16.1.5. Teicoplanin (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: *to be appointed*

Administrative details:
Procedure scope: Evaluation of an imposed PASS protocol to evaluate the safety of higher loading dose of 12mg/kg bid
MAH(s): Sanofi Aventis

16.1.6. Trastuzumab – HERCEPTIN (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/000278/MEA 095
Procedure scope: PASS protocol BO29159: interventional phase IV safety clinical trial with prospective cardiac monitoring in patients with metastatic breast cancer (MBC)
MAH(s): Roche Registration Ltd

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[44]

16.2.1. Aripiprazole – ABILIFY MAINTENA (CAP)

- Evaluation of a PASS protocol

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

[44] 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

Administrative details:
Procedure number(s): EMEA/H/C/002755/MEA 002
Procedure scope: PASS protocol for a non-interventional, non-imposed study (Study No. 15893N) related to Extrapyramidal symptoms in patients treated with Abilify Maintena: cohort study with a 2-year follow-up using European automated healthcare databases
MAH(s): Otsuka Pharmaceutical Europe Ltd

16.2.2. Certolizumab pegol – CIMZIA (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/001037/MEA 004.1
Procedure scope: MAH's response to MEA-004 RSI (reports CDP870-028 and CDP870-051) as adopted in September 2013
MAH(s): UCB Pharma SA

16.2.3. Dabigatran – PRADAXA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/MEA 041
Procedure scope: Revised PASS protocol for study 1160.149 to evaluate the effectiveness of the risk minimisation activities in the treatment of stroke prevention in atrial fibrillation (SPAF)
MAH(s): Boehringer Ingelheim International GmbH

16.2.4. Golimumab – SIMPONI (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/000992/MEA 026
Procedure scope: PASS protocol MK-8259 (non-interventional observational PASS in treatment of ulcerative colitis using Nordic national health registries
MAH(s): Janssen Biologics B.V.

16.2.5. Lipegfilgrastim – LONQUEX (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002556/MEA 004
Procedure scope: PASS protocol Study XM22-ONC-50002: Prescribing patterns of lipegfilgrastim (Lonquex) in the EU
MAH(s): Teva Pharma B.V.

16.2.6. Radium Ra223 – XOFIGO (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002653/MEA 10
Procedure scope: Final draft protocol for a non-interventional post-authorisation safety study (NIS PASS) with RMP version 1.0
MAH(s): Bayer Pharma AG

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

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000169/MEA 034.1, EMEA/H/C/000255/MEA 035
Procedure scope: Updated PASS protocol – MHA's response to RSI as adopted at PRAC in October 2013
MAH(s): Novartis Europharm Ltd

16.2.8. Ustekinumab – STELARA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000958/MEA 022.8
Procedure scope: PASS protocol of a PSOLAR (PSOriasis Longitudinal Assessment and Registry), an international prospective cohort study/registry program designed to collect data on Psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics
MAH(s): Janssen-Cilag International N.V.

16.2.9. Vernakalant – BRINAVESS (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/001215/MEA 003.3
Procedure scope: Revised PASS protocol of a study SPECTRUM - change to target enrolment
MAH(s): Cardiome UK Limited

16.3. Results of PASS imposed in the marketing authorisation(s)[45]

None

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

16.4. Results of PASS non-imposed in the marketing authorisation(s)[46]

16.4.1. Dolutegravir – TIVICAY (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002753/II/0001 (with RMP)
Procedure scope: Submission of data from a physiologically-based pharmacokinetic model in fulfilment of the MEA 4 regarding the potential for a drug-drug interaction with midazolam
MAH(s): ViiV Healthcare

16.4.2. Ivacaftor – KALYDECO (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002494/II/0015/G (with RMP)
Procedure scope: Submission of final study reports for studies VX08-770-102 and VX08-770-104 covering results from the post-treatment, 2-year, observational long-term follow up
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd

16.4.3. Retigabine – TROBALT (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001245/II/0025 (with RMP)
Procedure scope: Submission of the final study report for a non-interventional PASS (WEUKBRE5744)
MAH(s): Glaxo Group Ltd

16.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS submitted before the entry into force of the revised variations regulation[47]

16.5.1. Cobicistat – TYBOST (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002572/MEA 013
Procedure scope: Interim report of the Antiretroviral Pregnancy Registry (APR)

[46] 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
[47] In line with the revised variations regulation for any submission before 4 August 2013

MAH(s): Gilead Sciences International Ltd

16.5.2. Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP)

- Evaluation of interim PASS results

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000797/MEA 038
Procedure scope: Interim report of the Antiretroviral Pregnancy Registry (APR)
MAH(s): Bristol-Myers Squibb and Gilead Sciences Ltd

16.5.3. Elvitegravir – VITEKTA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002577/MEA 009
Procedure scope: Interim report of the Antiretroviral Pregnancy Registry (APR)
MAH(s): Gilead Sciences International Ltd

16.5.4. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil– STRIBILD (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002574/MEA 013
Procedure scope: Interim report of the Antiretroviral Pregnancy Registry (APR)
MAH(s): Gilead Sciences International Ltd

16.5.5. Emtricitabine – EMTRIVA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000533/MEA 047
Procedure scope: Interim report of the Antiretroviral Pregnancy Registry (APR)
MAH(s): Gilead Sciences International Ltd

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

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002312/MEA 028
Procedure scope: Interim report of the Antiretroviral Pregnancy Registry (APR)
MAH(s): Gilead Sciences International Ltd

16.5.7. Emtricitabine, tenofovir disoproxil – TRUVADA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000594/MEA 040
Procedure scope: Interim report of the Antiretroviral Pregnancy Registry (APR)
MAH(s): Gilead Sciences International Ltd

16.5.8. 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 089.11
Procedure scope: Interim study reports of the remaining EU rheumatoid arthritis registries: ARTIS and RABBIT cohort 2
MAH(s): Janssen Biologics B.V.

16.5.9. Glycopyrronium bromide – ENUREV BREEZHALER (CAP), **SEEBRRI BREEZHALER** (CAP), **TOVANOR BREEZHALER** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Line Michan (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002691/ANX 001.3, EMEA/H/C/002430/ANX 001.3, EMEA/H/C/002690/ANX 001.3
Procedure scope: First interim result of an imposed non interventional PASS study (CNVA237A2402T): multinational database cohort study to assess adverse cardiovascular outcomes and mortality in association with inhaled NVA237
MAH(s): Novartis Europharm Ltd

16.5.10. Ivacaftor – KALYDECO (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002494/ANX 001.1
Procedure scope: First interim results of a 5-year long-term observational study (PASS study ENCEPP/SDPP/4270) with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations)
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

16.5.11. Tenofovir disoproxil – VIREAD (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000419/MEA 267
Procedure scope: Interim report of the Antiretroviral Pregnancy Registry (APR)
MAH(s): Gilead Sciences International 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 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. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

17.1.1. Everolimus – VOTUBIA (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002311/R/0024 (without RMP)
MAH(s): Novartis Europharm Ltd

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 7-10 April 2014 meeting.

PRAC member PRAC alternate	*Country*	*Outcome restriction following evaluation of e-DoI for the meeting*	*Topics on the current Committee Agenda for which restriction applies* *Product / substance*
Aleksandra Martinovic	Austria	Cannot act as Rapporteur or Peer reviewer for:	ambroxol; bromhexine, agents acting on the renin-angiotensin system: angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEi), direct renin inhibitors (aliskiren), dabigatran, liraglutide
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer reviewer for:	agents acting on the renin-angiotensin system: angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEi), direct renin inhibitors (aliskiren), levonorgestrel-releasing

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
			intrauterine device (IUD), simvastatin, iloprost, rivaroxaban, levonorgestrel, radium Ra223, cyproterone, ethinylestradiol, cefepime
Veerle Verlinden	Belgium	Full involvement	
Yuliyan Eftimov	Bulgaria	Full involvement	
Marin Banovac	Croatia	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Nectaroula Cooper	Cyprus	Full involvement	
Jana Mladá	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
George Aislaitner	Greece	Full involvement	
Julia Pallos	Hungary	Full involvement	
Hrefna Guðmundsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Jelena Ivanovic	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Amy Tanti	Malta	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*
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Karen Pernille Harg	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Roxana Stroe	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Milena Radoha-Bergoč	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
June Munro Raine	Chair	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:	human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed), trametinib, belimumab,

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***
			pneumococcal polysaccharide conjugate vaccine (adsorbed), hepatitis A (inactivated) and hepatitis B (rDNA) (HAB) vaccine (adsorbed), lapatinib, orlistat, retigabine
Birgitte Keller-Stanislawski		Full involvement	
Hervé Le Louet		Cannot act as Rapporteur or Peer reviewer for:	lenalidomide
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		Full involvement	
Marco Greco		Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (2013-05-30) http://www.ema.europa.eu/docs/en_GB/document_library/contacts/avanderzeijden_DI.pdf	

Additional European experts participating at the meeting for specific Agenda items	**Country**	
Torbjörn Callreus	Denmark	No restrictions were identified for the participation of

Additional European experts participating at the meeting for specific Agenda items	Country	
Samir Bekkai	France	European experts attending the PRAC meeting for discussion on specific agenda items
Corinne Kiger	France	
Patrick Maison	France	
Cyndie Picot	France	
Anne Marie Coleman	Ireland	
Giuseppe Rosano	Italy	
Ineke Crijns	Netherlands	
Cristel Loeb	Netherlands	
Rob van Ojen	Netherlands	
Tamar Wohlfarth	Netherlands	
Zuzana Murgašová	Slovakia	
Eva Segovia	Spain	
Charlotte Backman	Sweden	
Rebecca Chandler	Sweden	
Karin Franck-Larsson	Sweden	
Helena Möllby	Sweden	
Elina Rönnemaa	Sweden	
Julie Beynon	United Kingdom	
Philip Bryan	United Kingdom	
Claire Doe	United Kingdom	
Dervla Mahoney	United Kingdom	
Sarah Mee	United Kingdom	
Janet Nooney	United Kingdom	

ANNEX III – List of abbreviations

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

www.ema.europa.eu

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