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SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 3-6 February 2014

Chair: June Raine – Vice-Chair: Almath Spooner

### Explanatory notes

The notes give a brief explanation of relevant minutes items and should be read in conjunction with 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](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

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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/](http://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 3-6 February 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 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.

### ***1.2. Adoption of agenda of the meeting of 3-6 February 2014***

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

### ***1.3. Minutes of the previous PRAC meeting on 6-9 January 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 of 6-9 January 2014 [EMA/PRAC/96908/2014](http://www.ema.europa.eu/PRAC/96908/2014) were published on the EMA website on 17 January 2014.

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

None

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

### ***3.1. Newly triggered Procedures***

None

### ***3.2. Ongoing Procedures***

None

### **3.3. Procedures for finalisation**

None

### **3.4. Re-examination procedures**

#### **3.4.1. Diacerein (NAP)**

- Re-examination procedure of the PRAC recommendation following the review of the benefit-risk balance following notification by France 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)

#### **Administrative details:**

Procedure number: EMEA/H/A-31/1349

EPITT 15994 – Follow-up Nov 2013

MAH(s): Negma-Wockhardt, TRB Chemedica

Triggered by: FR

Following receipt of the grounds for the re-examinations from two MAHs of diacerein-containing medicinal products on 14 January 2014 the PRAC agreed on a timetable for the re-examination procedure (EMA/PRAC/747322/2012 Rev.4).

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

None

## **4. Signals assessment and prioritisation<sup>1</sup>**

### **4.1. New signals detected from EU spontaneous reporting systems**

#### **4.1.1. Enzalutamide - XTANDI (CAP)**

- Signal of myalgia

#### **Regulatory details:**

PRAC Rapporteur: Dolores Montero Corominas (ES)

#### **Administrative details:**

EPITT 17795 – New signal

MAH(s): Astellas Pharma Europe B.V.

Leading MS: ES

Enzalutamide is an androgen receptor signalling inhibitor used in the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

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<sup>1</sup> 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

The exposure for Xtandi, a centrally authorised medicine containing enzalutamide, is estimated to have been more than 7000 patient-years worldwide, from first authorisation in 2012 to 2013.

During routine signal detection activities, a signal of myalgia was identified by the EMA, based on 33 cases retrieved from EudraVigilance reported with related MedRA terms. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the information on the cases of myalgia reported and noted that some of them described a positive de-challenge and/or re-challenge. Therefore PRAC agreed to gather further information on other cases of myalgia reported during clinical trials and that a review of the published literature should be performed. It was emphasised that muscle spasms, muscle twitching and also muscle weakness could also be symptoms of neurological origin; therefore this aspect should also be taken into account in a further review of the signal.

### **Summary of recommendation(s)**

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

#### **4.1.2. Lansoprazole (NAP)**

- Signal of haemolytic anaemia

#### **Regulatory details:**

PRAC Rapporteur: *Kirsti Villikka (Finland)*

#### **Administrative details:**

EPITT 17805 – New signal

MAH(s): various

Leading MS: FI

### **Background**

Lansoprazole is a proton pump inhibitor used in the treatment of various clinical conditions including peptic ulcer, symptomatic gastro-oesophageal reflux disease and Zollinger-Ellison syndrome and in the treatment and prophylaxis of reflux oesophagitis, NSAID induced ulcers and eradication of *H. pylori* in combination with antibiotics.

The exposure for nationally authorised medicines containing lansoprazole is difficult to calculate accurately given the wide usage and the number of lansoprazole-containing medicines currently marketed in EU.

During routine signal detection activities, a signal of haemolytic anaemia was identified by the Finnish Medicines Agency, FIMEA, based on 36 cases of haemolytic anaemia including autoimmune haemolytic anaemia retrieved from EudraVigilance. FI, as the lead member state for signal detection activity for lansoprazole, confirmed that the signal needed initial analysis and prioritisation by the PRAC.

## **Discussion**

The PRAC discussed the information on the reported cases of suspected drug-induced haemolytic anaemia, which seemed to be a rare condition sometimes appearing after months of starting the therapy but sometimes soon after receiving the drug. In some of the cases the reaction was mild, but there were also more serious cases. Some of the cases were described in the scientific literature. The PRAC noted that some other adverse effects pertaining to blood and lymphatic system disorders had been previously reported in association with lansoprazole use. Therefore a further review of the signal was considered warranted.

The PRAC appointed Kirsti Villikka (FI) as Rapporteur for the signal.

## **Summary of recommendation(s)**

- The MAH for the nationally authorised originator lansoprazole product should submit to the PRAC Rapporteur, within 60 days, a cumulative review of all cases of haemolytic anaemia in association with lansoprazole.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### **4.1.3. Vildagliptin – JALRA (CAP), GALVUS (CAP), XILIARX (CAP) Vildagliptin, metformin – EUCREAS (CAP), ICANDRA (CAP), ZOMARIST (CAP)**

- Signal of interstitial lung disease

#### **Regulatory details:**

PRAC Rapporteur: Qun-Ying Yue (SE)

#### **Administrative details:**

EPITT 17793 – New signal  
MAH(s): Novartis Europharm Ltd  
Leading MS: SE

## **Background**

Vildagliptin is an anti-hyperglycaemic agent of the dipeptidyl-peptidase 4 (DPP-4) inhibitor class used in selected patients with type-2 diabetes mellitus, either as monotherapy or in combination with other agents.

The exposure for centrally authorised medicines containing vildagliptin is estimated to have been more than 1.1 million patient-years worldwide in the period from first authorisation in 2007 to 2012.

During routine signal detection activities, a signal of interstitial lung disease was identified by the EMA, based on 29 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 reported cases of interstitial lung disease and noted that the vast majority of them had occurred in Japan, where regulatory action had been taken to update the labelling of medicines containing vildagliptin to include this information. The PRAC recognised that for some of the cases there were confounding factors such as polymedication and a significant medical history of interstitial lung disease or chronic obstructive pulmonary disease (COPD), which could provide an alternative explanation for the development of the disease. However, as a temporal

relationship was apparent in some cases and the reaction is known to have been reported in association with other medicines of the same class, the PRAC agreed that the signal should be further investigated.

### **Summary of recommendation(s)**

- The MAH for centrally authorised vildagliptin-containing medicines should submit to the EMA, within 60 days, a cumulative review of the signal of interstitial lung disease including an analysis of reporting rate by country and discuss if and why there are geographic differences.
- 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. Cetuximab – ERBITUX (CAP); Panitumumab - VECTIBIX (CAP)**

- Signal of increased fatal adverse events in patients with advanced solid tumours – publication from clinical trials

#### **Regulatory details:**

PRAC Rapporteur: Ulla Wändel Liminga (SE)

PRAC Rapporteur: Julia Dunne (UK)

#### **Administrative details:**

Leading MS: UK

EPITT 17795 – New signal

MAH(s): Merck KgaA; Amgen Europe B.V.

### **Background**

Cetuximab and panitumumab are monoclonal antibodies directed towards the epidermal growth factor receptor (EGFR). Cetuximab is used in the treatment of selected patients with EGFR-expressing, wild-type receptor monoclonal antibody (RAS) metastatic colorectal cancer or for the treatment of squamous cell cancer of the head and neck. Panitumumab is indicated for the treatment of wild-type RAS metastatic colorectal cancer.

A signal of increased fatal adverse events in patients with advanced solid tumours was identified by the EMA following the publication of a meta-analysis of 21 randomized controlled trials (Li et al. 2013<sup>2</sup>) on risk of treatment-related mortality with anti-epidermal growth factor receptor monoclonal antibodies. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the meta-analysis and agreed that the study had some limitations and there were some questions about the statistical analyses conducted; in particular the use of odds ratios was not considered to be the best way of summarising data from oncology trials, since person-years of exposure were not taken into account. Among other aspects, it was also noted that the primary end point of 'treatment emergent, non-disease-related, fatal adverse events' did not consistently include fatal cases according to their original classification in the individual studies. There was also no

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<sup>2</sup> PLoS One. 2013 Nov 28;8(11):e81897. doi: 10.1371/journal.pone.0081897. eCollection 2013.

Incidence and risk of treatment-related mortality with anti-epidermal growth factor receptor monoclonal antibody in cancer patients: a meta-analysis of 21 randomized controlled trials.

Li X1, Shan BE, Wang J, Xing LP, Guo XJ, Zhang YH, Shi PH, Wang ZY.

consideration of the variety of tumour types studied and chemotherapy regimens used across the studies.

The PRAC acknowledged that study findings from trials conducted in the licensed indications - including a mortality imbalance noted with the addition of bevacizumab to panitumumab based regimens - were already included in the product information.

Furthermore the indications for both medicines had recently been updated to restrict their use to patients with wild-type RAS colorectal tumours, to reflect the fact that overall survival in patients with mutant RAS metastatic colorectal cancer is inferior.

Nevertheless, the PRAC agreed that this signal should be kept under review and further details on the signal including information on its biological plausibility should be gathered. The possible underlying aetiology of the reported increased risk of fatal adverse events as well as the latest evidence available on the use of cetuximab and panitumumab in combination with other therapies in the treatment of metastatic colorectal cancer should also be further investigated.

### **Summary of recommendation(s)**

- The MAH for Erbitux (cetuximab) should submit to the EMA further information on the signal, within the ongoing PSUR (DLP 30/09/2013) assessment procedure.
- The MAH for Vectibix (panitumumab) should submit to the EMA further information on the signal, within the ongoing PSUR (DLP 30/09/2013) assessment procedure.

#### **4.2.2. Mycophenolate mofetil - CELLCEPT (CAP)**

- Signal of bronchiectasis and hypogammaglobulinaemia - publication from *Boddana et al.*; Clinical Transplantation 2011

#### **Regulatory details:**

PRAC Rapporteur: Julia Dunne (UK)

#### **Administrative details:**

EPITT 17760 – New signal  
MAH(s): Roche Registration Ltd  
Leading MS: UK

#### **Background**

Mycophenolate mofetil (MMF) is an immunosuppressant used in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

Triggered by a case series published in the literature (Boddana P et al.; 2011)<sup>3</sup>, assessed in the framework of a variation for a nationally authorised product Poland, the Polish Medicines Agency, identified a signal of bronchiectasis and hypogammaglobulinaemia with MMF. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

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<sup>3</sup> Clin Transplant. 2011 May-Jun;25(3):417-9. doi: 10.1111/j.1399-0012.2010.01255.x. Epub 2010 Apr 21. Hypogammaglobulinemia and bronchiectasis in mycophenolate mofetil-treated renal transplant recipients: an emerging clinical phenomenon?  
Boddana P1, Webb LH, Unsworth J, Brealey M, Bingham C, Harper SJ.

## **Discussion**

The PRAC discussed the findings of the published article describing patients treated with mycophenolate for prevention of rejection of a renal transplant graft. The authors speculated that MMF was the cause of hypogammaglobulinaemia. All patients described developed hypogammaglobulinaemia and bronchiectasis. The PRAC noted that all patients had also been treated with other immunosuppressants, most commonly prednisolone and ciclosporin.

The PRAC agreed that, in relation to the extent of the population exposure to MMF, the evidence was extremely limited since the product was authorised almost 20 years ago. However, the occurrence of hypogammaglobulinaemia and also bronchiectasis was considered to be a biologically plausible consequence of treatment with MMF, possibly attributable to an antiproliferative effect on B-lymphocytes. Therefore, it was agreed that this signal should be further reviewed with a focus on possible risk minimisation.

### **Summary of recommendation(s)**

- The MAH for CellCept (mycophenolate mofetil) should submit to the EMA, within 60 days, a cumulative review of cases of both bronchiectasis and hypogammaglobulinaemia (occurring both individually and concurrently) in association with MMF. The MAH should include clinical data from all sources and evaluate the biological plausibility of a possible association. In particular the MAH should provide quantitative data on the effect of MMF on circulating gamma globulin concentrations in man.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### **4.2.3. Paracetamol (NAP)**

- Drug exposure in pregnancy – publication by *Brandlistuen et al.*; *Int. J. Epidemiol.*, 2013

#### **Regulatory details:**

PRAC Rapporteur: Veerle Verlinden (BE)

#### **Administrative details:**

EPITT 17796 – New signal

MAH(s): Bayer Pharma AG, various

Leading MS: BE

#### **Background**

Paracetamol is a widely used OTC medicine for the relief of mild to moderate pain and febrile conditions. Following a publication of a study on 'prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study'<sup>4</sup>, brought to the attention of the lead member state for signal detection activities for paracetamol by the Norwegian Medicines Agency, this was proposed as a signal for further analysis and prioritisation by the PRAC.

## **Discussion**

The PRAC noted several limitations of the study which did not make it possible to draw any conclusions on paracetamol use in pregnancy and its impact on children neurodevelopment. The PRAC agreed that

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<sup>4</sup> *Int J Epidemiol.* 2013 Dec;42(6):1702-13. doi: 10.1093/ije/dyt183. Epub 2013 Oct 24.  
Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study.  
Brandlistuen RE1, Ystrom E, Nulman I, Koren G, Nordeng H.

further clarification from the researchers would be required before any recommendation can be made on this and, in particular, a clarification around the methodology of the study and the analyses performed should be sought. Beside the article discussed, the PRAC also noted a recent pre-clinical study<sup>5</sup> in which the authors suggested that in mice neonatal paracetamol exposure could affect brain development.

The PRAC appointed Veerle Verlinden (BE) as Rapporteur for the signal.

### **Summary of recommendation(s)**

- The PRAC considered the article and noted the limitations of the study by Brandlistuen et al and agreed that further clarifications from the authors were necessary before making any recommendation. The PRAC Rapporteur should perform an assessment of the available data within 90 days.

## **4.3. Signals follow-up and prioritisation**

### **4.3.1. Amiodarone (NAP)**

- Signal of carcinogenicity

#### **Regulatory details:**

PRAC Rapporteur: Menno van der Elst (NL)

#### **Administrative details:**

Procedure scope: Evaluation of the MAH's responses to PRAC recommendations as adopted at PRAC in October 2013

EPITT 17699 – Follow-up October 2013

MAH(s): Sanofi Aventis, various

#### **Background**

For background information, see [PRAC minutes of 7-10 October 2013](#).

The MAH replied to the request for information on the signal of carcinogenicity and the responses were assessed by the Rapporteur.

#### **Discussion**

The PRAC concluded that there were many important deficiencies in the design and analysis performed in the study by Su et al. The conclusion by the authors of an increased risk for malignancies and a dose dependent effect was therefore not considered to be adequately supported by the data and results from this study.

Assessment of post-marketing case reports concluded that a causal relationship between amiodarone and lung, thyroid, skin cancer and other malignancies could not be established. Additionally, the assessment of the data from clinical studies concluded that no evidence of an increased risk for malignancies in users of amiodarone could be identified. Therefore the PRAC agreed that the available data did not support a causal relationship between the use of amiodarone and the occurrence of malignant disease.

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<sup>5</sup> Viberg H, Eriksson P, Gordh T, Fredriksson A. Paracetamol (Acetaminophen) Administration During Neonatal Brain Development Affects Cognitive Function and Alters Its Analgesic and Anxiolytic Response in Adult Male Mice. *Toxicol Sci.* 2014 Jan 22. [Epub ahead of print].



However, it was noted that the product information was not fully updated regarding some preclinical data from carcinogenicity studies in rodents; therefore the PRAC agreed that the product information should be updated to reflect these findings.

### **Summary of recommendation(s)**

- Based on the data provided by the MAH, no causal association between the use of amiodarone and the occurrence of malignant disease (especially thyroid, lung and skin cancer) can be established. However, the MAHs for the nationally authorised amiodarone containing medicines<sup>6</sup> should be requested to submit to the NCAs of the MSs within 60 days a variation to update the product information to include updated information of results of pre-clinical studies in rodents<sup>7</sup>.
- The MAHs of generics 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 with that of the originator.

For the full PRAC recommendations, see [EMA/PRAC/65788/2014](#) published on the EMA website.

### **4.3.2. Basiliximab – SIMULECT (CAP)**

- Signal of cardiovascular instability resulting in fatal outcome following off-label use in heart transplantation

#### **Regulatory details:**

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000207/SDA/038

Procedure scope: Evaluation of the MAH's responses to PRAC recommendations as adopted at PRAC in February 2013

EPITT 17386 – Follow-up May 2013

MAH(s): Novartis Europharm Ltd

#### **Background**

For background information, see [PRAC minutes of 13-16 May 2013](#). The MAH replied to the request for information on the signal of cardiovascular instability resulting in fatal outcome following off-label use in heart transplantation and the responses were assessed by the Rapporteur.

#### **Discussion**

The PRAC noted data on efficacy and safety arising from six clinical trials (total of 1386 patients) in heart transplantation with basiliximab. A higher rate of cardiac adverse events in the Simulect group after 3 and 12 months compared to the 'other inductions' group and a similar level of cardiac events in the basiliximab group compared to the 'no-induction' group were noted. Although selection bias due to possible selective allocation of patients to the study treatment cannot be excluded, given that the majority of the trials were not randomized, a lack of benefit was noted.

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<sup>6</sup> 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

<sup>7</sup> Section 5.3 of the Summary of Product Characteristics

Analyses of adverse reaction reports from the clinical trials as well as spontaneous reports concerning cardiac arrest within 48 hours did not show a strong signal of increased cardiovascular risk. However, these cases were considered difficult to assess since they were heavily confounded by underlying diseases and/or concomitant treatments and because it remained unknown whether these adverse effects were anaphylaxis-related.

A publication from Massart A. et al. describing a case of acute respiratory distress syndrome leading to cardiac arrest in the context of living-related kidney transplantation, concluded in suggesting a role for basiliximab in the development of the reaction.

Having considered this evidence the PRAC agreed that the product information for Simulect (basiliximab) should be updated to reflect the available data from the clinical trials in cardiac transplantation on lack of benefit and on safety data. The PRAC also endorsed promoting awareness of these results among cardiac surgeons by appropriate communication.

### **Summary of recommendation(s)**

- The MAHs for the reference, centrally authorised basiliximab-containing medicine<sup>8</sup> should be requested to submit to the EMA within 60 days a variation to update the product information as regards to the findings reported above, including a proposal for active communication. The Risk Management Plan (RMP) should also be updated accordingly.
- Individual case safety reports of cardiac arrest/failure following close temporal relationship with Simulect (basiliximab) should be monitored and analysed in forthcoming PSURs

For the full PRAC recommendations, see [EMA/PRAC/65788/2014](https://www.ema.europa.eu/en/press-room/2014/04/W14-05001) published on the EMA website.

### **4.3.3. Etanercept – ENBREL (CAP)**

- Signal of glioblastoma and other brain neoplasms

#### **Regulatory details:**

PRAC Rapporteurs: Julia Dunne (UK)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000262/SDA 158

Procedure scope: Evaluation of the MAH's responses to PRAC recommendation as adopted at PRAC in October 2013

EPITT 17425 – Follow-up October 2013

MAH(s): Pfizer Limited

#### **Background**

For background information, see [PRAC minutes of 8-11 April 2013](#).

The MAH replied to the request for information on the signal of glioblastoma and other brain neoplasms and the responses were assessed by the Rapporteur.

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<sup>8</sup> 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

## **Discussion**

The PRAC noted that no additional cases were identified from the clinical trials, based on the new analysis that had been performed from the safety database of the MAH. The calculated reporting rate of primary malignant brain neoplasms was lower than the estimated incidence of these conditions in the general population. Four adult biologic registries in the EU were specifically analysed and the data presented did not appear to suggest an increased risk of brain malignancies in etanercept-treated patients. Furthermore, there were no relevant literature articles reporting brain malignancy in association with etanercept. Therefore the PRAC concluded that the current product information, which already reflects the risk of certain malignancies, was still adequate.

However, the PRAC acknowledged that the dataset from registries may not be large enough yet to fully assess a causal association at this time. Therefore this suspected ADR should be kept under monitoring.

## **Summary of recommendation(s)**

- The current product information was considered appropriate and no changes were considered necessary at this point in time. The suspected ADR should be reviewed in upcoming PSURs and specifically addressed in forthcoming registry reports.

For the full PRAC recommendations, see [EMA/PRAC/65788/2014](http://EMA/PRAC/65788/2014) published on the EMA website.

### **4.3.4. Interferon beta 1a – AVONEX (CAP), REBIF (CAP) Interferon beta 1b - BETAFERON (CAP), EXTAVIA (CAP)**

- Signal of thrombotic microangiopathy (TMA)

#### **Regulatory details:**

Lead PRAC Rapporteur: Julie Williams (UK)

Product-specific PRAC Rapporteurs: Dolores Montero Corominas (ES) (Avonex), Julie Williams (UK) (Betaferon, Extavia), Qun-Ying Yue (SE) (Rebif)

#### **Administrative details:**

Procedure number(s): EMEA/H/C000136/SDA 037, EMEA/H/C000933/SDA 017, EMEA/H/C000081/SDA 019 EMEA/H/C/000102/LEG 082.1

Procedure scope: Evaluation of the MAHs' responses to PRAC recommendation as adopted at PRAC in September 2013

EPITT 17653 – Follow-up September 2013

MAH(s): Bayer Pharma AG (Betaferon), Biogen Idec (Avonex), Merck Serono Europe Limited (Rebif), Novartis Europharm Ltd (Extavia)

## **Background**

For background information, see [PRAC minutes of 2-5 September 2013](#). The MAHs replied to the request for information on the signal of thrombotic microangiopathy (TMA) and the responses were assessed by the Rapporteurs.

## **Discussion**

The PRAC considered the MAHs' responses together with additional data, including published literature. An independent researcher (Dr D. Hunt University of Edinburgh) who had informed the Rapporteur of the upcoming submission for publication of an article related to the topic was invited to present to the meeting.

A number of plausible biological mechanisms have been investigated or proposed to explain a potential association of interferon beta with TMA. Overall, the PRAC considered that the evidence reviewed supported an association of TMA with interferon beta products as a class. Therefore the PRAC concluded that the product information for all interferon beta products should be updated to describe the possible risk of TMA, a serious and potentially fatal reaction, including the fact that it may develop from a few weeks to years after starting treatment, the need to monitor for it, and that the medicine should be stopped and the condition treated promptly should the condition occur. In addition, a letter should be sent to relevant healthcare professionals, warning them of the problem and making them aware of the early signs of TMA.

Furthermore, the PRAC recommended that TMA should be reflected in the RMPs for interferon beta products. TMA should also be kept under close monitoring in future PSURs for interferon beta products.

Additionally the PRAC agreed that the MAH for Rebif should provide further information and reply to a list of questions to evaluate a potential increase in risk of TMA with a new formulation of Rebif.

### **Summary of recommendation(s)**

- The MAHs for the reference centrally authorised<sup>9</sup> interferon beta containing medicines should be requested to submit to the EMA within 60 days a variation to update the product information to include "thrombotic microangiopathy"<sup>10</sup> as an undesirable effect and to introduce an appropriate warning; a proposal for a Direct Healthcare Professional Communication (DHPC) should also be included. In the framework of the requested variation, the MAH for Rebif (interferon beta 1a) should provide further specific information.
- The MAHs should update the RMPs, where these exist, to categorise TMA as an important identified risk. TMA should also be kept under close monitoring in future PSURs for interferon beta products.

For the full PRAC recommendations, see [EMA/PRAC/65788/2014](http://EMA/PRAC/65788/2014) published on the EMA website.

#### **4.3.5. Mefloquine (NAP)**

- Signal of possibly permanent neurologic (vestibular) side effects

#### **Regulatory details:**

PRAC Rapporteur: Martin Huber (DE)

#### **Administrative details:**

Procedure scope: Evaluation of the MAH's responses to PRAC recommendations as adopted at PRAC in October 2013

EPITT 10279 – Follow-up October 2013

MAH(s): Roche, various

#### **Background**

For background information, see [PRAC minutes of 7-10 October 2013](#). The MAH replied to the request for information on the signal and the responses were assessed by the Rapporteur.

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<sup>9</sup> 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

<sup>10</sup> Section 4.4 and 4.8 of the Summary of Product Characteristics

## **Discussion**

The PRAC discussed the evidence received and agreed that the data available could be interpreted as the occurrence of very rare cases of long lasting and/or persistent neuropsychiatric adverse reactions, that are already known to be associated with mefloquine. Therefore the PRAC agreed to update the existing wording in the product information to better reflect this aspect.

### **Summary of recommendation(s)**

- The MAH for the reference, nationally authorised<sup>11</sup> mefloquine-containing products should be requested to submit to the NCAs of the MSs within 60 days a variation to the product information to update warnings and undesirable effects sections, regarding the very rare cases of prolonged duration of neuropsychiatric adverse reactions<sup>12</sup>.
- The MAHs of generic products should then be requested to submit 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/65788/2014](#) published on the EMA website.

#### **4.3.6. Paracetamol (NAP)**

- Signal of drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP)

#### **Regulatory details:**

PRAC Rapporteur: Veerle Verlinden (BE)

#### **Administrative details:**

Procedure scope: Assessment of available studies, scientific literature and data from RegiSCAR further to PRAC recommendations as adopted at PRAC in November 2013

EPITT 17744 – Follow-up November 2013

MAH(s): Bayer Pharma AG, various

#### **Background**

For background information, see [PRAC minutes of 4-7 November 2013](#).

The Rapporteur assessed the data from the scientific literature and published epidemiological studies. Furthermore input was provided on the matter by the RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples) consortium.

## **Discussion**

The potential association between paracetamol use and SJS/TEN has been analysed in five case-control studies; one case-control study evaluated the risk of AGEP. Overall, the results of epidemiological case-control studies showed a relatively weak but significant association between use of paracetamol and SJS/TEN. No significant association could be detected for paracetamol and AGEP. The PRAC concurred that the potential for protopathic bias (the drug is administered because of prodromal signs

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<sup>11</sup> 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

<sup>12</sup> Section 4.8 of the Summary of Product Characteristics

of the reaction of interest) and confounding by indication should be considered as important limitations. On the other hand the PRAC noted that some cases of positive rechallenge were reported in the medical literature, and there were cases of SJS, TEN, and AGEP in which the only drug administered prior to the suspected reaction was paracetamol. In few cases paracetamol hypersensitivity was demonstrated by skin testing or other means and all cases resolved with discontinuation of the drug.

On the regulatory side the PRAC noted that, currently, information on serious cutaneous reactions is not consistently reflected in, or is even absent, from the product information for paracetamol containing medicines marketed in the EU.

The PRAC agreed, overall, on the limited strength of the evidence on a possible causal association, particularly in light of the extremely high population exposure to paracetamol. Nevertheless the PRAC recognised that it would be appropriate for all formulations and combinations of paracetamol containing medicines to reflect consistently the information that very rare cases of serious skin reactions had been reported.

### **Summary of recommendation(s)**

- The MAHs for the nationally authorised <sup>13</sup> paracetamol containing medicines should submit to the NCAs of the MSs, at the next routine opportunity, an update of the product information to include "very rare cases of serious skin reactions"<sup>14</sup> as an undesirable effect.

For the full PRAC recommendations, see [EMA/PRAC/65788/2014](https://www.ema.europa.eu/en/press-room/2014/04/W14-04001) published on the EMA website.

### **4.3.7. Ustekinumab – STELARA (CAP)**

- Signal of exfoliative dermatitis

#### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000958/SDA 040

Procedure scope: Evaluation of MAH's response to PRAC recommendation as adopted by PRAC in September 2013

EPITT 17661 – Signal follow-up September 2013

MAH(s): Janssen-Cilag International N.V.

### **Background**

For background information, see [PRAC minutes of 2-5 September 2013](https://www.ema.europa.eu/en/press-room/2013/09/W13-09001). The MAH replied to the request for information on the signal of exfoliative dermatitis and the responses were assessed by the Rapporteur.

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<sup>13</sup> 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

<sup>14</sup> Section 4.8 of the Summary of Product Characteristics

## **Discussion**

The PRAC discussed the assessment of the new information from the clinical and post-marketing data provided. The PRAC agreed that the available data, given a plausible temporal relationship, a positive rechallenge reported with some cases and the lack of possible confounding factors, provided good evidence of a causal relationship between ustekinumab and exfoliative dermatitis or erythrodermic psoriasis.

The data showed that the reactions occurred most commonly within the first week of treatment. With regards to possible predisposing factors, the available data did not suggest an obvious link between the events and the doses used and the numbers of reported cases did not suggest a particular pattern with regards to distribution of patient sex and age.

The PRAC concluded that this information needed to be appropriately reflected in the product information and that patients and healthcare professionals should be made aware of these changes with appropriate communication. Furthermore, the Risk Management Plan for ustekinumab should also be updated and ways of retrieving further data on these conditions should be considered in the next PSUR.

### **Summary of recommendation(s)**

- The MAHs for the reference centrally authorised <sup>15</sup> ustekinumab-containing medicine should be requested to submit to the EMA within 60 days a variation to update the product information to include new warnings for “exfoliative dermatitis and skin exfoliation”<sup>16</sup> as an undesirable effect. Targeted communication to inform dermatologists of the risk of exfoliative dermatitis and skin exfoliation in the form of a Direct Health Care Professional Communication (DHPC) should also be submitted.
- The Risk Management Plan for ustekinumab should be updated by the MAH to reflect accordingly the changes of the product information regarding the risk of erythrodermic psoriasis which should be classified as an important identified risk.
- In the next PSUR the MAH should discuss the feasibility of using data from a new or existing epidemiological study to further investigate skin exfoliation, exfoliative dermatitis and erythrodermic psoriasis.

For the full PRAC recommendations, see [EMA/PRAC/65788/2014](https://www.ema.europa.eu/en/press-room/news/2014/04/ema-prac-recommends-changes-ustekinumab) published on the EMA website.

## **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.

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<sup>15</sup> 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

<sup>16</sup> Section 4.4 and 4.8 of the Summary of Product Characteristics

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

#### **5.1.1. Bupropion, naltrexone**

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

##### **Administrative details:**

Product number(s): EMEA/H/C/003687

Intended indication: Management of obesity

#### **5.1.2. Canagliflozin, metformin**

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

##### **Administrative details:**

Product number(s): EMEA/H/C/002656

Intended indication: Treatment of type 2 diabetes mellitus

#### **5.1.3. Dulaglutide**

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

##### **Administrative details:**

Product number(s): EMEA/H/C/002825

Intended indication: Treatment of adults with type 2 diabetes mellitus

#### **5.1.4. Propranolol**

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

##### **Administrative details:**

Product number(s): EMEA/H/C/002621

Intended indication: Treatment of proliferating infantile haemangioma

## **5.2. Medicines already authorised**

### **RMP in the context of a variation<sup>17</sup> – PRAC-led procedure**

#### **5.2.1. Aclidinium bromide – BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (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/002706/II/0012, EMEA/H/C/002211/II/0012

Procedure scope: update of the RMP to version 4.0

MAH(s): Almirall S.A

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<sup>17</sup> In line with the revised variation regulation for any submission as of 4 August 2013



## **Background**

Aclidinium bromide is a selective muscarinic receptor antagonist indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The CHMP is evaluating a type II variation procedure for Bretaris Genuair and Eklira Genuair, centrally authorised products containing acclidinium bromide, to introduce some revisions to the RMP. The PRAC is responsible for providing advice to the CHMP to support this variation.

## **Summary of advice**

- The RMP version 4 for Bretaris Genuair and Eklira Genuair in the context of the variation under evaluation by the CHMP was considered acceptable provided that the distribution of Genuair demonstration kits is captured as an additional risk minimisation measure to address the 'risk of medication/use of device error'. Proposals to measure the effectiveness of this additional risk minimisation measure should be captured in the updated RMP before finalisation of the variation procedure by the CHMP.

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

### **5.2.2. Aflibercept – EYLEA (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/002392/II/0009

Procedure scope: Extension of indication

MAH(s): Bayer Pharma AG

## **Background**

Aflibercept is a recombinant fusion protein (portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1), used for the treatment of neovascular (wet) age-related macular degeneration (AMD) in adults and visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).

The CHMP is evaluating an extension of the therapeutic indication for Eylea to include treatment of adult patients with diabetic macular oedema. 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 13 for Eylea (aflibercept) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable.
- The PRAC noted that the Annex II should reflect the new indication of diabetic macular oedema. Since a PASS protocol is currently under preparation to measure physicians' and patients' knowledge and understanding of the key messages of the educational material, the PRAC confirmed the continued need of educational materials in support also of this new indication.

### 5.2.3. Crizotinib – XALKORI (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/C/002489/II/0004

Procedure scope: Update of SmPC sections 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 to reflect the efficacy and safety data from study 1007 and the updated data from studies 1001 and 1005

MAH(s): Pfizer Limited

#### **Background**

Crizotinib is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (RTK) and its oncogenic variants used in the treatment of adults with previously treated ALK-positive advanced non-small cell lung cancer (NSCLC).

The CHMP is evaluating a type II variation procedure for Xalkori to update various sections of the product information and the RMP to fulfil the Specific Obligations/Obligation related to the conditional marketing authorisation. The PRAC is responsible for providing advice to the CHMP on the updates to the RMP accompanying this variation.

#### **Summary of advice**

- The RMP version 4.2 for Xalkori (crizotinib) in the context of the variation under evaluation by the CHMP was considered acceptable provided that an updated RMP is submitted after taking into account remaining changes to the SmPC as requested in the variation before finalisation of the variation procedure by the CHMP.

### 5.2.4. Infliximab – REMICADE (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/000240/II/0179

Procedure scope: Update of SmPC section 4.8 to add intestinal obstruction based on the data available from clinical trials, post-marketing experience and from registries in adult Crohn's Disease

MAH(s): Janssen Biologics B.V.

#### **Background**

Infliximab is a monoclonal antibody directed towards tumour necrosis factor (TNF) alpha used in the treatment of rheumatoid arthritis, adult Crohn's disease, paediatric Crohn's disease, ulcerative colitis and paediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis.

The CHMP is evaluating a type II variation procedure for Remicade, a centrally authorised product containing infliximab to update the product information and to include in the RMP information arising from the final report from European National Crohn's Observational Registry (ENCORE) initiated in 2003 to collect long-term safety data on patients with active or fistulising Crohn's disease; the update includes the outcome of the review of the signal of glioblastoma and brain neoplasm as previously

discussed by PRAC. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP submitted in this variation.

### **Summary of advice**

- The RMP version 9 for Remicade (infliximab) in the context of the variation under evaluation by the CHMP was considered acceptable provided that an updated version taking into account some points raised by the PRAC is submitted before finalisation of the variation procedure by the CHMP.
- The PRAC considered that bowel stenosis, stricture and obstruction should be retained in the RMP until additional analyses of the ENCORE study have been fully evaluated, pending evaluation of whether intestinal stenosis and intestinal obstruction should be listed in the product information. The PRAC also considered that further updates to the RMP may be required depending on the findings from the additional analyses from the ENCORE study.

### **RMP evaluated in the context of a PSUR procedure**

See Corifollitropin alfa (ELONVA); Fampridine (FAMPYRA); Gefitinib (IRESSA); Human rotavirus, live attenuated (ROTARIX); Hydroxycarbamide (SIKLOS) ; Mirabegron (BETMIGA); Perampanel (FYCOMPA); Rufinamide (INOVELON) – under 6 or 15 as applicable.

### **RMP evaluated in the context of PASS results**

See Epoetin zeta (RETACRIT); Epoetin zeta (SILAPO).

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

See Alipogene tiparvovec (GLYBERA), Efavirenz – (STOCRIN, SUSTIVA)17.1.4. , Fentanyl (INSTANYL), Liraglutide (VICTOZA).

## **6. Periodic Safety Update Reports (PSURs)**

### **6.1. Evaluation of PSUR procedures<sup>18</sup>**

#### **6.1.1. Acridinium bromide – BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP)**

- Evaluation of a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/002706/PSU 007, EMEA/H/C/002211/PSU 007 (without RMP)  
MAH(s): Almirall S.A

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<sup>18</sup> 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

## **Background**

Acidinium bromide is a selective muscarinic receptor antagonist 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 Bretaris Genuair and Eklira Genuair, centrally authorised medicines containing acilidium bromide, and issued a recommendation on their marketing authorisations.

## **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bretaris Genuair and Eklira Genuair (acilidium bromide) in the approved indication(s) remains favourable.
- The product information should be updated to include hypersensitivity reactions and angioedema as undesirable effects with a rare and unknown frequency respectively, as well as rash and pruritus with an uncommon frequency. Therefore the current terms of the marketing authorisations should be varied<sup>19</sup>.
- In the next PSUR, the MAH should closely monitor cases of eye disorders, blurred vision and medication/device errors. In addition, the MAH should provide further information particularly details on potential concomitant use of anticholinergic medicines and of reported cases suggestive of anticholinergic-related effects. The MAH should also assess the potential anticholinergic effects related to reported cases of dizziness and palpitations and propose to update the product information as warranted.
- The MAH should update the RMP in the context of an ongoing variation to include medication/use of device errors as an important potential risk and the distribution of Genuair demo kits as an additional risk minimisation measure. Proposals to measure the effectiveness of this additional risk minimisation measure should also be provided.

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. Fampridine – FAMPYRA (CAP)**

- Evaluation of a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Sabine Straus (NL)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/002097/PSU 005 (with RMP version 8.0)

MAH(s): Biogen Idec Ltd.

## **Background**

Fampridine is a potassium channel blocker indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fampyra, a

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<sup>19</sup> 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

centrally authorised medicine containing fampridine, 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 Fampyra (fampridine) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the context of the ongoing assessment of the annual renewal of the conditional marketing authorisation(s), the MAH should submit a proposal to update the warning section of the product information to better reflect the timing and occurrence of falls as well as information on falls that do not only affect patients who use walking aids.
- In the next PSUR, the MAH should provide a full cumulative overview of trigeminal neuralgia and discuss whether the treatment duration pattern in the US is compatible with the discontinuation rate estimated by the MAH for the EU and worldwide.
- The MAH should update the RMP within the next regulatory procedure affecting the RMP to include interaction with organic cation transporter 2 (OCT2) substrates as an identified risk.

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

### **6.1.3. Hydroxycarbamide – SIKLOS (CAP)**

- Evaluation of a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Jean-Michel Dogné (BE)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000689/PSU 031 (with RMP version 14)

MAH(s): Addmedica

#### **Background**

Hydroxycarbamide is an antineoplastic agent indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic sickle-cell syndrome.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Siklos, a centrally authorised medicine containing hydroxycarbamide, 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 Siklos (hydroxycarbamide) in the approved indication(s) remains favourable.
- The product information should be updated to refine the information under the fertility section relating to oligo- and azoospermia and to reflect these as undesirable effects with a very

common frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>20</sup>.

- In the next PSUR, the MAH should provide a review of cases of hyperkalaemia and hyponatraemia and propose to update the product information as warranted. The MAH should also provide a thorough review of cases of medication error and consider whether additional risk minimisation measures are needed. In addition, the MAH should measure the effectiveness of risk minimisation measures, particularly, those relating to educational guides given to prescribers and patients, mainly about blood test surveillance and adverse events. The RMP should be updated accordingly.

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. Idursulfase – ELAPRASE (CAP)**

- Evaluation of a PSUR procedure

##### **Regulatory details:**

PRAC Rapporteur: Julia Dunne (UK)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/000700/PSU 034 (without RMP)

MAH(s): Shire Human Genetic Therapies AB

##### **Background**

Idursulfase is a purified form of the lysosomal enzyme iduronate-2-sulfatase indicated for the long-term treatment of patients with Hunter syndrome (mucopolysaccharidosis II, MPS II).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Elaprase, a centrally authorised medicine containing idursulfase, 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 Elaprase (idursulfase) in the approved indication(s) remains favourable.
- The product information should be updated to revise the warning regarding patients with the complete deletion/large rearrangement genotype to reflect the fact that patients with this genotype have a higher risk of developing infusion-related adverse events. This reaction should also be added as an undesirable effect with an appropriate frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>21</sup>.
- In the upcoming annual reassessment procedure, the MAH should discuss the update of the current pharmacovigilance activities to include the relationship amongst antibody status, genotype and longer-term clinical outcome via the Hunter Outcome Survey moving forwards. This should include reports of anaphylactic reactions and anti-idursulfase IgE positivity.

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<sup>20</sup> Update of SmPC sections 4.6 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.

<sup>21</sup> 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.

- The MAH should update the RMP to reflect the additional pharmacovigilance activities requested by the FDA following the recent accelerated approval of the supplemental biologics licence application (sBLA) 125151/184 providing safety and efficacy information in patients 5 years of age and younger.

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. Mirabegron – BETMIGA (CAP)**

- Evaluation of a PSUR procedure

##### ***Regulatory details:***

PRAC Rapporteur: Miguel-Angel Macia (ES)

##### ***Administrative details:***

Procedure number(s): EMEA/H/C/002388/PSU 004 (with RMP version 2.0)

MAH(s): Astellas Pharma Europe B.V.

##### ***Background***

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

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

##### ***Summary of recommendation(s) and conclusions***

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Betmiga (mirabegron) in the approved indication(s) remains favourable.
- The product information should be updated to add a warning on urinary retention for patients with bladder outlet obstruction (BOO) and patients taking antimuscarinic medications for OAB. Therefore the current terms of the marketing authorisation(s) should be varied<sup>22</sup>.
- In the next PSUR, the MAH should provide a cumulative review of cerebrovascular events and detailed analyses of cases of nausea, vomiting and chest pain/chest discomfort and a detailed analysis of cases of urinary retention when mirabegron is used concomitantly with solifenacin. In addition, the MAH should closely monitor cases of lack of efficacy. Finally, the missing information section relating to pre-existing cardiovascular diseases should be further revised, detailing cases with a concurrent or underlying cardiovascular disease condition and from hypertension cases.

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. Palonosetron – ALOXI (CAP)**

- Evaluation of a PSUR procedure

<sup>22</sup> 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.

**Regulatory details:**

PRAC Rapporteur: Almath Spooner (IE)

**Administrative details:**

Procedure number(s): EMEA/H/C/000563/PSU 021 (without RMP)

MAH(s): Helsinn Birex Pharmaceuticals Ltd.

**Background**

Palonosetron is a serotonin (5HT<sub>3</sub>) antagonist indicated in adults for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy, and for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aloxi, a centrally authorised medicine containing palonosetron 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 Aloxi (palonosetron) in the approved indication(s) remains favourable.
- The product information should be updated to add a warning on serotonin syndrome in accordance with the mechanistic plausibility of this occurring when 5-HT<sub>3</sub> antagonist antiemetics are administered in combination with other serotonergic agents. Therefore the current terms of the marketing authorisation(s) should be varied<sup>23</sup>.
- In the next PSUR, the MAH should provide detailed analyses of cases of serotonin syndrome, extrapyramidal symptoms, QTc prolongation and seizure/convulsions.

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

**6.1.7. Peginterferon alfa-2a – PEGASYS (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Qun-Ying Yue (SE)

**Administrative details:**

Procedure number(s): EMEA/H/C/000395/PSU 050 (without RMP)

MAH(s): Roche Registration Ltd

**Background**

Peginterferon alfa-2a is a pegylated interferon indicated for the treatment of hepatitis B envelope antigen (HBeAg)-positive or HBeAg-negative chronic hepatitis B (CHB) and for the treatment of chronic hepatitis C (CHC) under certain conditions.

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<sup>23</sup> 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 Pegasys, a centrally authorised medicine containing peginterferon alfa-2a, 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 Pegasys (peginterferon alfa-2a) in the approved indication(s) remains favourable.
- The product information should be updated to refine the warning on laboratory tests prior to and during therapy to advise specifically that glucose monitoring should be performed periodically during therapy. In addition, tongue pigmentation should be added to the product information as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>24</sup>.

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

### **6.1.8. Ribavirin – REBETOL (CAP), RIBAVIRIN MYLAN (CAP), RIBAVIRIN TEVA (CAP), RIBAVIRIN TEVA PHARMA BV (CAP), COPEGUS (CAP), NAPs**

- Evaluation of a PSUSA<sup>25</sup> procedure

#### **Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/PSUSA/00010007/201307

MAH(s): CT Arzneimittel GmbH (Ribavirin CT), Generics (UK) Limited (Ribavirin Mylan), JSC Olainfarm (Ribavirin 200mg capsules), Laboratorios Normon S.A. (Ribavirin Normon), Merck Sharp & Dohme Limited (Rebetol), Roche registration Limited (Copegus), Teva Pharma B.V. (Ribavirin Teva, Ribavirin Teva Pharma B.V.), Valeant (Ribavirin NL/H/2303/001/DC), Zentiva (Ribavirin Zentiva)

#### **Background**

Ribavirin is a synthetic nucleoside analogue indicated in combination therapy for the treatment of chronic hepatitis C (CHC) under certain conditions.

Based on the assessment of the individual PSURs part of the PSUR Single assessment procedure<sup>26</sup>, the PRAC reviewed the benefit-risk balance of oral formulations of ribavirin-containing products<sup>27</sup> and issued a recommendation on their marketing authorisations.

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of oral formulations of ribavirin-containing products in the approved indication(s) remains favourable.
- The product information should be updated to include tinnitus and hypotension as undesirable effects with a common frequency, vasculitis with a rare frequency, cerebrovascular ischaemia

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<sup>24</sup> 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.

<sup>25</sup> PSUR single assessment, referring to CAP, NAP

<sup>26</sup> Abbreviated PSUSA, assessing PSURs for CAPs and NAPs

<sup>27</sup> Including products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended, as requested by Competent Authorities [DIR Article 107b (3b)] and reflected in the EURD list for the current PSUSA procedure

with a very rare frequency and tongue pigmentation with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied<sup>28</sup>.

- Moreover, the MAHs for Rebetol and Copegus should submit to the relevant competent authorities within 90 days a variation to update the product information to refine the indication section by removing reference to peginterferon, to update the posology section according to the relevant regimens, to revise the current recommendations on the use of ribavirin in patients with moderate to severe renal impairment including dialysis to better adjust the dose of ribavirin as warranted. The MAHs should also revise the contraindication in patients with hepatic impairment or decompensation which is based on the safety profile of peginterferon used in combined therapy with ribavirin. In addition, the MAHs should consider revising their product information to distinguish safety concerns related to ribavirin from those related to the combination with peginterferon. Finally, the MAH for Copegus should provide the rationale behind the inclusion of malignant hepatic neoplasm as an undesirable effect.
- In the next PSUR, the MAH for Rebetol and Copegus should provide a comprehensive safety analysis for several specific adverse reactions.

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 for the following PSUR should be revised from yearly to three-yearly and the EURD list will need to be updated accordingly.

#### **6.1.9. Saxagliptin – ONGLYZA (CAP)**

- Evaluation of a PSUR procedure

##### **Regulatory details:**

PRAC Rapporteur: Menno van der Elst (NL)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/001039/PSU 030 (without RMP)

MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

##### **Background**

Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as add-on combination therapy in adult patients with type 2 diabetes mellitus to improve glycaemic control under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Onglyza, a centrally authorised medicine containing saxagliptin, 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 Onglyza (saxagliptin) in the approved indication(s) remains favourable.
- The product information should be updated to add diarrhoea as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>29</sup>.

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<sup>28</sup> 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

- Moreover, the MAH should submit to EMA within 60 days a variation to update the product information and RMP with the findings of the SAVOR<sup>30</sup> study. In this study, an imbalance in hospitalisation for heart failure was observed, with an increased incidence in saxagliptin-treated subjects. This variation should include a detailed analysis of the possible association between saxagliptin and hospitalisations for heart failure and a discussion whether additional risk minimisation measures are warranted.
- In the next PSUR, the MAH should provide a detailed analysis of cases of constipation in terms of de-challenge and/or re-challenge, time to onset and medical history and propose to update the product information 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.

#### **6.1.10. Telithromycin – KETEK (CAP)**

- Evaluation of a PSUR procedure

##### **Regulatory details:**

PRAC Rapporteur: Qun-Ying Yue (SE)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/000354/PSU 047 (without RMP)

MAH(s): Aventis Pharma S.A.

##### **Background**

Telithromycin is a semisynthetic derivative of erythromycin A belonging to the ketolides related to macrolides and is indicated in adults for the treatment of community-acquired pneumonia, infections caused by known or suspected beta-lactam- and/or macrolide-resistant strains covered by the antibacterial spectrum of telithromycin, as well as for acute exacerbation of chronic bronchitis and acute sinusitis under certain conditions. In patients aged 12 years and older, telithromycin is indicated for tonsillitis/pharyngitis caused by *Streptococcus pyogenes* under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ketek, a centrally authorised medicine containing telithromycin, 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 Ketek (telithromycin) in the approved indication(s) remains favourable.
- The product information should be updated to reinforce the warning on visual disturbances and reflect the occurrence of severe and/or sudden visual reactions as undesirable effects with an uncommon frequency. The information on the drug-drug interaction between telithromycin and sotalol should be also amended to further describe the decreased absorption of sotalol. Finally, increased gamma-glutamyl transferase should be added to the product information as an

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<sup>29</sup> 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.

<sup>30</sup> Scirica BM et al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. The New England Journal of Medicine Sept 2013

undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>31</sup>.

- The MAH should submit to EMA within 90 days cumulative reviews on tremor and convulsions.
- In the next PSUR, the MAH should provide additional data, including detailed reviews on cases of ventricular arrhythmias, dyspnoea, hyperhidrosis and chromaturia. The MAH should submit an updated RMP to include ventricular arrhythmias as an important potential risk.

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

## **6.2. Follow-up to PSUR procedures<sup>32</sup>**

### **6.2.1. Clofarabine – EVOLTRA (CAP)**

- Evaluation of a follow-up to a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000613/LEG 037.1

Procedure scope: MAH's response to PSU-037 (PSUR#9) as adopted in May 2013

MAH(s): Genzyme Europe BV

#### **Background**

Following the evaluation of the last PSUR for the above mentioned medicine under the pharmaceutical legislation preceding the entry into force of the revised legislation on pharmacovigilance in July 2012, the CHMP requested the MAH to submit further data. The responses were assessed by the Rapporteur for PRAC advice.

#### **Summary of recommendation(s)/conclusions**

- The MAH should submit to EMA within 60 days a variation to update the product information to add the risk of haemorrhage as a warning and a wording regrouping the adverse drug reactions relating to bleeding, including bleeding caused by respiratory and nervous system disorders.

### **6.2.2. Pregabalin – LYRICA (CAP)**

- Evaluation of a follow-up to a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Sabine Straus (NL)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000546/LEG 040.1

Procedure scope: MAH's response to PSUR#14 as adopted at PRAC in September 2013

MAH(s): Pfizer Limited

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<sup>31</sup> Update of SmPC sections 4.4, 4.5 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

<sup>32</sup> Follow up as per the conclusions of the previous PSUR procedure, assessed outside the following PSUR procedure

## **Background**

Following the evaluation of the last PSUR for the above mentioned medicine, the PRAC requested the MAH to submit further data (see [PRAC Minutes September 2013](#)). The responses were assessed by the Rapporteur for further PRAC advice.

### **Summary of recommendation(s)/conclusions**

- The MAH should submit to EMA within 60 days a variation to update the product information to add the risk of dependence to the warnings on misuse and potential abuse and on withdrawal symptoms.

## **7. Post-authorisation Safety Studies (PASS)**

### **7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>33</sup>**

#### **7.1.1. 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/041.2

Procedure scope: Evaluation of a revised protocol for a retrospective drug utilisation study (CC-5013-MDS-012): a post-authorisation, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)

MAH(s): Celgene Europe Limited

## **Background**

For background information, see [PRAC Minutes 6-9 January 2014](#). A synopsis for a drug utilisation study (DUS) was submitted and assessed by the Rapporteur.

### **Endorsement/Refusal of the protocol**

The PRAC considers that the study is non-interventional and the DUS protocol for Revlimid could be endorsed provided that the answers to some questions and comments on study design are taken into account, and modalities of data collection are addressed.

The PRAC therefore recommended that:

- An updated revised DUS protocol taking into account the above comments should be submitted within one month. Later, once data sources become available, an updated protocol should be provided.

#### **7.1.2. Solutions for parenteral nutrition, combination - NUMETA G16%E EMULSION FOR INFUSION and associated names (NAP)**

- Evaluation of an imposed PASS protocol

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<sup>33</sup> In accordance with Article 107n of Directive 2001/83/EC

**Regulatory details:**

PRAC Rapporteur: Ulla Wändel Liminga (SE)

**Administrative details:**

Scope: adoption of timetable and appointment of Rapporteur for the evaluation of a PASS protocol (following conclusion of 107i Referral) on a multicentre, non-interventional, uncontrolled, open-label, observational study in children to evaluate serum magnesium levels associated with the intake of Numeta G 16% E  
MAH(s): Baxter

**Background**

Numeta G16%E emulsion for infusion is a nationally authorised product that was subject to a referral procedure under Article 107i of Directive 2001/83/EC, which concluded in September 2013 (see [EMA/564255/2013](#)). The conclusion of the referral requested (see [Annex V](#)) a prospective non-interventional post-authorisation safety study to further evaluate magnesium levels observed in term newborn infants and children up to two years of age treated with Numeta G16%E in routine clinical practice. A protocol to perform this study was submitted by the MAH for assessment by the PRAC.

**Endorsement/Refusal of the protocol**

The PRAC agreed on a timetable for the review and appointed Ulla Wändel Liminga (SE) as Rapporteur.

**7.1.3. Trimetazidine (NAP)**

- Evaluation of an imposed PASS protocol

**Regulatory details:**

PRAC Rapporteur: Dolores Montero Corominas (ES)

**Administrative details:**

Scope: Evaluation of a protocol for a drug utilisation study to verify the compliance of prescribers regarding the restriction of indications after marketing authorisation changes.  
MAH(s): Lupin Europe (on behalf of Actavis Group PTC ehf., Alvogen IPCo S.a.r.l., Apotex Europe B.V., Chemical Works of Gedeon Richter Plc., Generis Farmacêutica, S. A., Glenmark Pharmaceuticals s.r.o., Hexal AG (Sandoz / Novartis), Labesfal – Laboratorios Almiro S.A., Laboratorios Cinfa, S.A., Lupin (Europe) Limited, Mylan S.A.S., Pensa Pharma, S.A., Terapia S.A. (Ranbaxy group), Teva Pharmaceuticals Europe B.V.)

**Background**

Nationally authorised medicines containing trimetazidine - a metabolic agent indicated as add-on therapy for the symptomatic treatment of adults with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies- were subject to a referral Article 31 procedure for which an opinion was reached in June 2012 (see Q&A [EMA/H/A-31/1305](#)).

The conclusion of the referral procedure included the requirement (see [Annex IV](#)) for the MAHs to conduct a drug utilisation study to verify the compliance of prescribers with respect to the restricted indication following the referral. A protocol for a joint study was presented by some of the MAHs and assessed by the Rapporteur.

**Endorsement/Refusal of the protocol**

The PRAC, having assessed the draft protocol version 1.0 submitted on 22 November 2013, endorsed the protocol, subject to minor amendments and some clarifications on the impact of the limitations of

the design and the representativeness of the sample on the ability of the study to address the proposed objectives.

The MAH should submit an updated protocol to the EMA and to the PRAC rapporteur, within 30 days.

#### **7.1.4. Trimetazidine (NAP)**

- Evaluation of an imposed PASS protocol

##### ***Regulatory details:***

PRAC Rapporteur: Dolores Montero Corominas (ES)

##### ***Administrative details:***

Procedure scope: Evaluation of a protocol for a drug utilisation study to verify the compliance of prescribers regarding the restriction of indications after marketing authorisation changes  
MAH(s): Servier

##### ***Background***

Nationally authorised medicines containing trimetazidine - a metabolic agent indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies – were subject to a referral Article 31 procedure which an opinion was reached in June 2012 (see Q&A [EMA/H/A-31/1305](#)).

The conclusion of the referral included the requirement that (see [Annex IV](#)) the MAH should conduct a drug utilisation study to verify the compliance of prescribers regarding the restricted indication after marketing authorisation changes. A protocol for such study was presented by one of the MAH and was assessed by the Rapporteur.

##### ***Endorsement/Refusal of the protocol***

The PRAC, having assessed the draft protocol version 1.0 submitted the 20 December 2013, endorsed the protocol, subject to minor amendments and some clarifications on the impact of the limitations of the proposed data sources and the statistical analysis plan on the ability of the study to address the proposed objectives.

The MAH should submit an updated protocol to the EMA and to the PRAC rapporteur, within 30 days.

#### **7.1.5. Trimetazidine (NAP)**

- Evaluation of an imposed PASS protocol

##### ***Regulatory details:***

PRAC Rapporteur: Dolores Montero Corominas (ES)

##### ***Administrative details:***

Procedure scope: Evaluation of a protocol for a case-control study to assess and estimate the relationship between trimetazidine use and Parkinsonism  
MAH(s): Servier

##### ***Background***

Nationally authorised medicines containing trimetazidine - a metabolic agent indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies – were subject to a referral Article 31 procedure which an opinion was reached in June 2012 (see Q&A [EMA/H/A-31/1305](#)).

The conclusion of the referral included the requirement (see [Annex IV](#)) for MAHs to conduct a study to address all important, potential and identified risks, particularly Parkinsonism. A full study protocol should be submitted for a nested case-control study within the European Society of Cardiology cohort to investigate the potential association between extrapyramidal symptoms (EPS) and trimetazidine. A protocol for such study was presented by one of the MAH and was assessed by the Rapporteur.

### ***Endorsement/Refusal of the protocol***

The PRAC, having assessed the draft protocol sent on 20 December 2013, objected to the draft protocol, as the Committee considered that that the design of the study did not fulfil the study objectives. Concerns were expressed on the feasibility of the proposed study considering that the proposed case-control study solely conducted within the European Society of Cardiology cohort would not deliver the expected research questions within the specified timeframe in the light of information on enrolment in the cohort due to limited statistical power.

The PRAC therefore recommended the MAH to provide a new study protocol for the safety evaluation, which should include:

1. A thorough overview of all EU data sources potentially able to detect eligible patients exposed to Trimetazidine-containing products as well as patients with ACS and patients with extrapyramidal symptoms;
2. A study proposal for the safety evaluation that is informed by the above overview of potential data sources to be used as well as the preliminary results of the drug utilisation study. It is considered a teleconference or pre-submission meeting between the PRAC Rapporteur, EMA and the MAH may help ensure submission of a mature protocol to avoid multiple assessment rounds where possible.

The proposal should be submitted to the EMA and the PRAC within three months.

### ***7.2. Protocols of PASS non-imposed in the marketing authorisation(s)***<sup>34</sup>

See Annex I

### ***7.3. Results of PASS imposed in the marketing authorisation(s)***<sup>35</sup>

None

### ***7.4. Results of PASS non-imposed in the marketing authorisation(s)***<sup>36</sup>

See Annex I

### ***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***<sup>37</sup>

See Annex I

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<sup>34</sup> 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

<sup>35</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>36</sup> 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

<sup>37</sup> In line with the revised variations regulation for any submission before 4 August 2013



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

### 8.1.1. Anagrelide – XAGRID (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

#### **Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000480/S/0057 (without RMP)

MAH(s): Shire Pharmaceutical Contracts Ltd.

#### **Background**

Anagrelide is a cyclic AMP phosphodiesterase III inhibitor indicated for the reduction of elevated platelet counts in patients with essential thrombocythaemia (ET) who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

Xagrid was authorised in 2004 under exceptional circumstances. The benefit-risk balance of Xagrid is reviewed on a yearly basis by the CHMP based on the submission and assessment of additional post-authorisation data (i.e. specific obligations). The PRAC is responsible for providing advice to the CHMP on this annual re-assessment with regard to safety and risk management aspects.

#### **Summary of advice**

Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, the PRAC considered that the annual re-assessment procedure for Xagrid could be finalised provided that the MAH undertakes to fulfil the conditions and obligations. In particular, the MAH should further investigate the excess non-haematological malignancies observed in the SPD422-401 study.

### 8.1.2. Fentanyl – INSTANYL (CAP)

- PRAC consultation on a renewal of the marketing authorisation

#### **Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000959/R/0022 (with RMP version 14)

MAH(s): Takeda Pharma A/S

#### **Background**

Fentanyl is an opioid analgesic indicated as a nasal spray for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain. Instanyl was authorised in 2009.

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

## **Summary of advice**

Based on the review of the available pharmacovigilance data for Instanyl (fentanyl) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal is warranted given the remaining safety concerns relating to off label use, dependence, misuse and abuse.

## **9. Product related pharmacovigilance inspections**

None

## **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. Interferon beta 1a – AVONEX (CAP), REBIF (CAP) Interferon beta 1b - BETAFERON (CAP), EXTAVIA (CAP)**

- PRAC consultation on variation procedures, on CHMP's request

#### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK) (lead), Dolores Montero Corominas (Avonex), Qun-Ying Yue (Rebif)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000102/II/0141, EMEA/H/C/000136/II/0104, EMEA/H/C/000081/II/0091, EMEA/H/C/000933/II/0061

Procedure scope: Update of SmPC sections 4.4 and 4.8 to add safety information with regard to focal segmental glomerulosclerosis

MAH(s): Bayer Pharma AG, Biogen Idec, Merck Serono Europe Limited, Novartis Europharm Ltd

#### **Background**

For background, see PRAC minutes 13-16 May and 2-5 September 2013. The MAHs for all interferon beta-1a and interferon beta-1b products submitted variations to include collapsing focal segmental glomerulosclerosis (FSGS) during interferon-beta treatment in the product information. In the context of these types II variations the MAHs submitted additional cumulative reviews of all cases of nephrotic syndrome associated with these products. These variations are under evaluation at CHMP and PRAC was asked to provide advice.

#### **Summary of advice**

Overall, the PRAC agreed that the available data support a possible causal association between interferon beta-1a and interferon beta-1b and the risk of nephrotic syndrome and agreed that the product information should be updated to include warnings about not only FGSG but also nephrotic syndrome. The PRAC endorsed the proposal that common wording on these risks should be introduced for all interferon beta-1a and interferon beta-1b products.

### **10.2. Other requests**

#### **10.2.1. Fluticasone furorate, vilanterol – RELVAR ELLIPTA (CAP)**

- PRAC consultation on the evaluation of an interventional PASS protocol on CHMP's request

**Regulatory details:**

PRAC Rapporteur: Miguel Angel-Macia (ES)

**Administrative details:**

Procedure number(s): EMEA/H/C/002673/ANX 002

Procedure scope: CHMP request for PRAC advice on clinical trial protocol for study HZC115151: interventional post-authorisation safety study to further investigate the risk of pneumonia with Relvar Ellipta compared with other inhaled corticosteroid (ICS)/ long-acting beta2 agonists (LABA) FDC in the treatment of chronic obstructive pulmonary disease (COPD)

MAH(s): Glaxo Group Ltd

**Background**

Relvar Ellipta inhalation powder is a pre-dispensed multi dose dry powder for oral inhalation. The active ingredients are fluticasone furoate (FF) and vilanterol (VI). FF is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity, while VI is a selective long-acting, beta2-adrenergic agonist (LABA) indicated for the treatment of asthma and chronic obstructive pulmonary disease (COPD) in selected patients.

During the PRAC meeting held on 2-5 September 2013, the PRAC also advised that the two (interventional) post-authorisation safety studies to investigate the risk of pneumonia should be a condition of the Marketing Authorisation: the Amended Salford Study (COPD) (HZC115151) and the Amended Salford Study (Asthma) (HZA115150) should be conditions of the Marketing Authorisation. The full protocols have been submitted for assessment and the CHMP asked for PRAC advice on their assessment.

**Summary of advice**

The PRAC discussed the revised PASS protocols for studies HZA115150 and HZC115151 and concurred that the study design cannot yet be considered acceptable. The PRAC agreed on some amendments and clarifications required on the description of the secondary endpoint. Aspects related to the analysis plan as well as validation of possible pneumonia cases beyond the capture of diagnostic codes should be revised by the MAH for both studies. Updated protocols for both studies should be requested.

**10.2.2. Fluticasone furoate, vilanterol – RELVAR ELLIPTA (CAP)**

- PRAC consultation on the evaluation of an interventional PASS protocol on CHMP's request

**Regulatory details:**

PRAC Rapporteur: Miguel Angel-Macia (ES)

**Administrative details:**

Procedure number(s): EMEA/H/C/002673/ANX 004

Procedure scope: CHMP request for PRAC advice on clinical trial protocol for study HZA115150: interventional post-authorisation safety study to further investigate the risk of pneumonia with Relvar Ellipta compared with other inhaled corticosteroid (ICS)/ long-acting beta2 agonists (LABA) FDC in the treatment of asthma

MAH(s): Glaxo Group Ltd

See above 10.2.1.

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

### **11.1. Safety related variations of the marketing authorisation**

#### **11.1.1. Flucloxacillin (NAP)**

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

##### **Regulatory details:**

Lead PRAC member: Sabine Straus (NL)

##### **Administrative details:**

Procedure scope: PRAC consultation on a variation to add 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**

In the Netherlands Actavis Group PTC ehf/Iceland submitted a proposal to include a warning in the product information for nationally authorised flucloxacillin medicines regarding special caution in relation to drug induced liver injury in subjects harbouring the HLA-B\*5701 haplotype, as liver injury is being seen in a growing number of subjects with HIV-infection who may also be more likely to be exposed to flucloxacillin.

##### **Summary of advice**

HLA-B\*5701 carriers have an increased risk of developing flucloxacillin-induced liver injury (DILI), however the absolute risk of flucloxacillin DILI \* is small, both for HLA-B\*5701 carriers as well as non-carriers. The positive predictive value of HLA-B\*5701 carriage for flucloxacillin DILI (0.12%) is low and it was acknowledged that HLA status is unknown for majority (HIV infected) patients. The PRAC agreed that the clinical value of testing should be further clarified since HLA-B\*5701 is unsuitable for use as a screening test. How the proposed warning for flucloxacillin will contribute to the prevention of DILI or recognition of the warning signals of DILI in clinical practice has to be further established. Therefore the PRAC supported consultation with the Pharmacogenomics Working Party (PgWP) on the matter.

### **11.2. Renewals of the Marketing Authorisation**

None

### **11.3. Other requests**

#### **11.3.1. Gadolinium containing contrast agents (NAP, CAP)**

- PRAC consultation on harmonised traceability of gadolinium-containing contrast agents (GdCAs), on a Member State's request

##### **Regulatory details:**

Lead PRAC member: Qun-Ying Yue (SE)

##### **Administrative details:**

Procedure scope: PRAC consultation on EU harmonised traceability method for effective monitoring of the use of Gadolinium containing contrast agents (GdCAs)  
MAH(s): Mallinckrodt Deutschland GmbH (Optimark), various

## **Background**

Following the conclusion of the CHMP referral procedures on GdCAs and risk of nephrogenic systemic fibrosis (NSF) in 2010 (Article 31, Article 20) to have a harmonised traceability method across the EU for the effective monitoring of the use of GdCAs, the implementation of detachable (“sticky”) labels on the vials and syringes of the GdCAs was an outcome of the referral and has been implemented.

Sweden highlighted that as patient records in many MSs have been transferred from paper to electronic systems, sticky labels are no longer suitable and Sweden put forward a proposal for an EU level approach to ensure the continuity of a harmonised traceability system (several products involved, CAP, NAPs, and MRP/DCP products).

## **Summary advice**

The PRAC stressed the importance of the traceability method being in place whenever a gadolinium contrast agent is used, allowing the individual tracking of the contrast agent used, dose and batch via the patient’s records regardless of whether this is kept electronically or in paper.

The PRAC supported a proposed updated core Product Information wording with regards to the electronic record explaining that if electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

The MAHs should be requested to discuss the agreed core wording via the variation. The same advice will be transmitted to CHMP to consider parallel action for the centrally authorised product Optimark (gadoversetamide).

## **12. Organisational, regulatory and methodological matters**

### **12.1. Mandate and organisation of the PRAC**

None

### **12.2. Pharmacovigilance audits and inspections**

#### **12.2.1. Pharmacovigilance Inspections**

##### **12.2.1.1. Union Procedure on Follow-up to Pharmacovigilance Inspections**

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

Following discussion at the 2-5 December 2013 meeting, EMA secretariat presented a revised version of the document to the PRAC. The revised version was endorsed with minor changes as an ANNEX to the GVP Module III in the coming months.

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

#### **12.3.1. Union Reference Date List**

##### **12.3.1.1. Consultation on the draft List, version February 2014**

The EMA Secretariat presented to PRAC a draft revised EURD list version February 2014 that the PRAC endorsed. The EMA Secretariat also presented a proposal to streamline the preparatory phase for the

handling of upcoming PSUR single assessment (PSUSA)<sup>38</sup> procedures, including a monthly review of upcoming procedures at least 6 months ahead of their DLP to review the appropriateness of these PSUSAs and to confirm the appointment of Rapporteurs for newly identified procedures in line with the principles previously endorsed by the PRAC (see [PRAC Minutes April 2013](#)).

The PRAC also had a preliminary discussion on the start of single assessment procedures of PSURs for substances contained in nationally approved products only and authorised in more than one Member State. Further discussion will take place in due course.

Post-meeting note: following the PRAC meeting in February 2014, the updated EURD list was adopted by the CHMP at its February 2014 meeting and was published on the EMA website on 4 March 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

The PRAC received an update on the work of the SMART group. Points discussed included awareness and implementation of recommendations for signals by MAHs for generic medicines and periodicity of the frequency for signal monitoring for some nationally authorised medicines. Discussion on these points will progress at the coming PRAC meetings.

## **12.5. Adverse Drug Reactions reporting and additional reporting**

### **12.5.1. List of Product under Additional Monitoring**

- Consultation on the draft List, version February 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 XX/XX/2014 on the EMA website (see: [Home>Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#)).

## **12.6. EudraVigilance Database**

None

### **12.6.1. EudraVigilance annual report**

- 2013 EudraVigilance (human) annual report

EMA secretariat provided the highlights of the 2013 EudraVigilance Annual Report. The report is intended for the European Parliament, the Council and the Commission and is required by the pharmacovigilance legislation<sup>39</sup>. The report will be published on the Agency's website in due course. The Committee welcomed the highlights and suggested areas for further exploitation of methodologies applied impacting on regulatory decisions, based on the experience gained so far.

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<sup>38</sup> Referring to procedures with CAP, NAP

<sup>39</sup> Regulation (EC) No 726/2004 Article 24(2), paragraph 2

## **12.7. Risk Management Plans and Effectiveness of risk Minimisations**

None

## **12.8. Post-authorisation Safety Studies**

None

## **12.9. Community Procedures**

### **12.9.1. Practical implementation of Article 20 pharmacovigilance referral procedures**

- Questions and answers documents on practical implementation

At the organisational matters teleconference held on 20 February 2014, the EMA Secretariat presented the Questions & answers on practical implementation of Article 20 Pharmacovigilance Procedure (EMA/796802/2013) due for publication on the EMA website.

## **12.10. Renewals, conditional renewals, annual reassessments**

### **12.10.1. 5-year renewal procedures**

- Proposal for refining the handling of 5-year renewal PRAC advice

At the organisational matters teleconference held on 20 February 2014, the EMA Secretariat presented a proposal to streamline the PRAC involvement in the handling of 5-year renewal procedures. Taking into account the comments from PRAC delegates, EMA will further develop a simplified and integrated process for PRAC input into the procedure.

## **12.11. Risk communication and Transparency**

None

## **12.12. Continuous pharmacovigilance**

None

## **12.13. Interaction with EMA Committees and Working Parties**

### **12.13.1. Biologics Working Party (BWP), Blood Products Working Party (BPWP)**

- Review of intravenous and subcutaneous immunoglobulins for thromboembolic events, pro-coagulant activity

At the Organisational matters teleconference on 20 February 2014, B K Stanislawski presented a progress report on the implementation of additional steps in the manufacturing process for intravenous immunoglobulin (IVIg) to reduce pro-coagulant impurities. The specific steps for removing pro-coagulant activity have been determined for each IVIg product. The tests used by individual companies differ in methods and settings (e.g. normal vs deficient plasma). However, it can be concluded that, for the intravenous route, the procoagulant activity is now reduced for all products and under reasonable control. Discussion will progress with experts and within BWP to discuss what is still needed to move towards a common assay and limits. The PRAC was informed that a joint workshop is being planned and organised for March 2014 by EDQM on the establishment of a common test for pro-coagulant activity of immunoglobulins.

### **12.13.2. Paediatric committee (PDCO)**

- Strengthening interaction between PDCO and PRAC

At the organisational matters teleconference held on 20 February 2014, the PDCO Chair and EMA secretariat presented an overview of current processes to ensure exchange of information between the PRAC and PDCO on commonly discussed topics in particular focusing on RMPs. The PRAC supported a strengthened interaction with PDCO. EMA will present a proposal for a framework of interaction at the coming meetings.

### **12.13.3. Vaccine Working Party (VWP)**

- Enhanced safety surveillance of seasonal influenza vaccines

At the organisational matters teleconference held on 20 February 2014, the PRAC endorsed a draft document prepared by PRAC delegates/experts in vaccine surveillance to be published as an interim stand-alone document for public consultation, concerning principles of yearly enhanced safety surveillance for seasonal influenza vaccines. Further discussion will take place at the March 2014 meeting for finalisation.

## **13. Any other business**

### **13.1.1. Cutaneous severe adverse drug reactions**

H Le Louet presented a review of serious drug related adverse skin reactions and the most recent scientific debate on them, including maculopapular exanthema, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP). The PRAC thanked H Le Louet for the comprehensive overview presented which provided valuable insight into the ascertainment and evaluation of the cases in the future risk assessments.

### **13.1.2. EMA move in 2014 to new building**

At the organisational matters teleconference held on 20 February 2014, EMA secretariat gave an update to the PRAC regarding the relocation of the Agency. Further updates will be provided to the Committee periodically.

### **13.1.3. EMA reorganisation**

- Member States' consultation on the implementation

EMA secretariat informed the PRAC of planned modalities for wider consultation of NCAs on aspects of the EMA's current reorganisation.

### **13.1.4. EMA's proposal for a framework to incorporate patients' views during evaluation of benefit-risk by the EMA Scientific Committees**

EMA secretariat outlined some principles based on the legal framework provided by Article 78 of Regulation (EC) no 726/2004 to incorporate patients' views during evaluation of benefit-risk by the EMA Scientific Committees. The PRAC welcomed the proposals and commented on aspects relating to the additional perspectives and value which patients' representatives can bring into the evaluation of benefit-risk balance, based on the positive experience of patient representatives as members of PRAC. The PRAC also noted proposed modalities to ensure the independence of patient experts.



EMA will provide further updates on the proposal for a framework to incorporate patients' views during evaluation of benefit risk as this evolves following input and consultation with other EMA Committees and PCWP.

## 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. Budesonide, formoterol

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

**Administrative details:**

Product number(s): EMEA/H/C/003890, EMEA/H/C/002348

Intended indication: Treatment of asthma and chronic obstructive pulmonary disease (COPD)

#### 14.1.2. Darunavir, cobicistat

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

**Administrative details:**

Product number(s): EMEA/H/C/002819

Intended indication: Treatment of patients with human immunodeficiency virus (HIV-1)

#### 14.1.3. Eliglustat

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

**Administrative details:**

Product number(s): EMEA/H/C/003724

Intended indication: Treatment of Gaucher disease type 1

#### 14.1.4. Nintedanib

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

**Administrative details:**

Product number(s): EMEA/H/C/002569

Intended indication: Treatment of non-small cell lung cancer (NSCLC)

#### 14.1.5. Oseltamivir

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

**Administrative details:**

Product number(s): EMEA/H/C/003717, *Generic*

Intended indication: Treatment and prevention of influenza

#### 14.1.6. Recombinant human n-acetylgalactosamine-6-sulfatase (rhgalns) – VIMIZIM (CAP MAA)

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

**Administrative details:**

Product number(s): EMEA/H/C/002779, *Orphan*

Intended indication: Treatment of mucopolysaccharidosis  
Applicant: BioMarin Europe Ltd

#### **14.1.7. Umeclidinium bromide**

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

##### **Administrative details:**

Product number(s): EMEA/H/C/002809

Intended indication: Treatment of symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

#### **14.1.8. Vedolizumab**

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

##### **Administrative details:**

Product number(s): EMEA/H/C/002782

Intended indication: Treatment of ulcerative colitis and Crohn's disease

#### **14.1.9. Vintafolide**

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

##### **Administrative details:**

Product number(s): EMEA/H/C/002571

Intended indication: Treatment of platinum resistant ovarian cancer (PROC)

### **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. Agomelatine – THYMANAX (CAP), VALDOXAN (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/000916/II/0018, EMEA/H/C/000915/II/0020

Procedure scope: Update of the RMP version 16.0

MAH(s): Servier (Ireland) Industries Ltd. (Thymanax), Les Laboratoires Servier (Valdoxan)

##### **14.2.2. Aliskiren – RASILAMLO (CAP), RASILEZ (CAP)**

##### **Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP)**

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

##### **Regulatory details:**

PRAC Rapporteur: Carmela Macchiarulo (IT)

**Administrative details:**

Procedure number(s): EMEA/H/C/002073/WS0500/0089, EMEA/H/C/000780/WS0500/0089, EMEA/H/C/000964/WS0500/0059

Procedure scope: Update of the RMP to 1) reflect important pharmacovigilance milestones that were reached and to update accordingly timelines for completed and ongoing studies, 2) remove rash/SCARS, hypotension, cough, dizziness, peripheral oedema and hypokalaemia as identified risks  
MAH(s): Novartis Europharm Ltd

**14.2.3. Bosutinib – BOSULIF (CAP)**

- Evaluation of an RMP in the context of a variation

**Regulatory details:**

PRAC Rapporteur: Martin Huber (DE)

**Administrative details:**

Procedure number(s): EMEA/H/C/002373/II/0001

Procedure scope: Update of SmPC sections 4.2, 4.4 and 5.2 further to the results of a study in patients with renal impairment conducted as a post-authorisation measure

MAH(s): Pfizer Limited

**14.2.4. Colistimethate sodium – COLOBREATHE (CAP)**

- Evaluation of an RMP in the context of a variation

**Regulatory details:**

PRAC Rapporteur: Julia Dunne (UK)

**Administrative details:**

Procedure number(s): EMEA/H/C/001225/II/0010

Procedure scope: Evaluation of the updated RMP version 4.0 in line with the revised variation regulation for any submission as of 4 August 2013

MAH(s): Forest Laboratories UK Limited

**14.2.5. Eltrombopag – REVOLADE (CAP)**

- Evaluation of an RMP in the context of a variation

**Regulatory details:**

PRAC Rapporteur: Dolores Montero Corominas (ES)

**Administrative details:**

Procedure number(s): EMEA/H/C/001110/II/0014/G

Procedure scope: Evaluation of 4 final study reports for the fulfilment of RMP commitments and a proposal for changes in the RMP (replacement of a study and date extensions for RMP commitments listed in section III 4.3)

MAH(s): GlaxoSmithKline Trading Services

**14.2.6. Everolimus – VOTUBIA (CAP)**

- Evaluation of an RMP in the context of a variation

**Regulatory details:**

PRAC Rapporteur: Martin Huber (DE)

**Administrative details:**

Procedure number(s): EMEA/H/C/002311/II/0021

Procedure scope: Evaluation of the updated RMP version 8

MAH(s): Novartis Europharm Ltd

#### **14.2.7. Imatinib – IMATINIB ACTAVIS (CAP)**

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

##### **Regulatory details:**

PRAC Rapporteur: Dolores Montero Corominas (ES)

##### **Administrative details:**

Product number(s): EMEA/H/C/002594/X/0003

Intended scope: Line extension to add a new strength 400mg hard capsule

MAH(S): Actavis Group PTC ehf

#### **14.2.8. Levetiracetam – KEPPRA (CAP)**

- Evaluation of an RMP in the context of a variation

##### **Regulatory details:**

PRAC Rapporteur: Jean-Michel Dogné (BE)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/000277/II/0147

Procedure scope: Evaluation of the updated RMP to add information on the risks and related pharmacovigilance activities and risk minimisation measures for patients aged four years and older

MAH(s): UCB Pharma SA

#### **14.2.9. Panitumumab – VECTIBIX (CAP)**

- Evaluation of an RMP in the context of a variation

**Status:** for discussion and adoption of PRAC Assessment Report

##### **Regulatory details:**

PRAC Rapporteur: Julia Dunne (UK)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/000741/II/0056

Procedure scope: Evaluation of the updated 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.

#### **14.2.10. Vemurafenib – ZELBORAF (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/002409/II/0013

Procedure scope: Evaluation of the updated RMP version 7 with proposal for revised study design to address MEA011, MEA012, MEA013

MAH(s): Roche Registration Ltd

#### **14.2.11. Zoledronic acid – ACLASTA (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/000595/II/0044

Procedure scope: Evaluation of the updated RMP version 9.0

MAH(s): Novartis Europharm Ltd

**RMP in the context of a variation – CHMP led procedure****14.2.12. Apixaban – ELIQUIS (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/002148/II/014/G

Procedure scope: Grouping of 2 variations including an extension of indication to add the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults and a type IA variation to add a new pack size of 28 film coated tablets for Eliquis 5mg strength

MAH(s): Bristol-Myers Squibb / Pfizer EEIG

**14.2.13. Dabrafenib – TAFINLAR (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/002604/II/0002/G

Procedure scope: Update of SmPC section 5.3 to add data from a 26-week toxicology study, G12071.

The MAH has also revised the submission date for the final report for a drug-drug interaction study (MEA 006) and updated the RMP accordingly

MAH(s): GlaxoSmithKline Trading Services

**14.2.14. Dexamethasone – OZURDEX (CAP)**

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

**Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

**Administrative details:**

Procedure number(s): EMEA/H/C/001140/II/0015

Procedure scope: Extension of indication to include treatment of adult patients with diabetic macular oedema

MAH(s): Allergan Pharmaceuticals Ireland

**14.2.15. Entecavir – BARACLUDE (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/000623/II/0041

Procedure scope: Extension of indication to include treatment of chronic hepatitis B virus (HBV) infection in paediatric patients from 2 to <18 years of age with compensated liver disease and evidence of active viral replication and persistently elevated serum ALT levels

MAH(s): Bristol-Myers Squibb Pharma EEIG

**14.2.16. Icatibant – FIRAZYR (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/000899/II/0024/G

Procedure scope: Extension of indication to include treatment of ACE-inhibitor induced angioedema: update to SmPC sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8 and 5.1 and update of section 5.1 to include the results of the open-label extension phase of study FAST-3 (HGT-FIR-054)

MAH(s): Shire Orphan Therapies GmbH

**14.2.17. Palivizumab – SYNAGIS (CAP)**

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

**Regulatory details:**

PRAC Rapporteur: Line Michan (DK)

**Administrative details:**

Procedure number(s): EMEA/H/C/000257/X/0095

Procedure scope: Introduction of a new pharmaceutical form: 100 mg/ml solution for injection presented in vials containing 0.5 ml and 1 ml

MAH(s): AbbVie Ltd.

**14.2.18. Peginterferon alfa-2a – PEGASYS (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/000395/II/0073

Procedure scope: Extension of indication to include the use of hepatitis C virus (HCV) NS3/4A protease inhibitors for the treatment of HCV genotype 1

MAH(s): Roche Registration Ltd

**14.2.19. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) – PREVENAR 13 (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/001104/II/0098

Procedure scope: Update of SmPC sections 4.2, 4.4, 4.8 and 5.1 to add information on the use of Prevenar 13 in populations associated with high risk of pneumococcal infection

MAH(s): Pfizer Limited

#### **14.2.20. Telaprevir – INCIVO (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/002313/II/0023

Procedure scope: Update of sections 4.5 and 5.1 of the SmPC with study results of VX-950-HPC3008 darunavir substudy

MAH(s): Janssen-Cilag International N.V.

#### **14.2.21. Vismodegib – ERIVEDGE (CAP)**

- Evaluation of an RMP in the context of a variation

##### **Regulatory details:**

PRAC Rapporteur: Ulla Wändel Liminga (SE)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/002602/II/0005

Procedure scope: Evaluation of a non-clinical study (MEA) and revised version of the RMP (as a consequence of MEA fulfilment)

MAH(s): Roche Registration Ltd

##### **RMP in the context of a stand-alone RMP procedure**

#### **14.2.22. Atosiban – TRACTOCILE (CAP)**

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

##### **Regulatory details:**

PRAC Rapporteur: Carmela Macchiarulo (IT)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/000253/RMP 015.1

MAH(s): Ferring Pharmaceuticals A/S

#### **14.2.23. Bromfenac – YELLOX (CAP)**

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

##### **Regulatory details:**

PRAC Rapporteur: Line Michan (DK)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/001198/RMP 009

MAH(s): Croma-Pharma GmbH

#### **14.2.24. Imiglucerase – CEREZYME (CAP)**

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

##### **Regulatory details:**

PRAC Rapporteur: Sabine Straus (NL)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/000157/RMP 046.1



MAH(s): Genzyme Europe BV

#### **14.2.25. Oseltamivir – TAMIFLU (CAP)**

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

##### ***Regulatory details:***

PRAC Rapporteur: Kirsti Villikka (FR)

##### ***Administrative details:***

Procedure number(s): EMEA/H/C/000402/RMP 096.1

MAH(s): Roche Registration Ltd

##### ***RMP in the context of a PSUR procedure***

Not applicable

##### ***RMP evaluated in the context of PASS results***

#### **14.2.26. Filgrastim – BIOGRASTIM (CAP), RATIOGRASTIM (CAP), TEVAGRASTIM (CAP)**

- Evaluation of the RMP

##### ***Regulatory details:***

PRAC Rapporteur: Kirsti Villikka (FI)

##### ***Administrative details:***

Procedure number(s): EMEA/H/C/000826/MEA 019 (Biograstim), EMEA/H/C/000825/MEA 019 (Ratiograstim), EMEA/H/C/000827/MEA 019 (Tevagrastim)

Procedure scope: Evaluation of first annual report on safety data concerning suspect cases of immunogenicity

MAH(s): AbZ Pharma GmbH (Biograstim), Ratiopharm GmbH (Ratiograstim), Teva GmbH (Tevagrastim)

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

Not applicable

## **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<sup>40</sup>**

### **15.1.1. Agalsidase alfa – REPLAGAL (CAP)**

- Evaluation of a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Sabine Straus (NL)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000369/PSU 080 (without RMP)

MAH(s): Shire Human Genetic Therapies AB

### **15.1.2. Aripiprazole – ABILIFY (CAP)**

- Evaluation of a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Margarida Guimarães (PT)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000471/PSU 069 (without RMP)

MAH(s): Otsuka Pharmaceutical Europe Ltd

### **15.1.3. Corifollitropin alfa – ELONVA (CAP)**

- Evaluation of a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Menno van der Elst (NL)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/001106/PSU 011 (with RMP version 6.0)

MAH(s): Merck Sharp & Dohme Limited

### **15.1.4. Dasatinib – SPRYCEL (CAP)**

- Evaluation of a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Doris Stenver (DK)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000709/PSU 039 (without RMP)

MAH(s): Bristol-Myers Squibb Pharma EEIG

### **15.1.5. Gefitinib – IRESSA (CAP)**

- Evaluation of a PSUR procedure

#### **Regulatory details:**

PRAC Rapporteur: Ulla Wändel Liminga (SE)

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<sup>40</sup> 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/001016/PSU 011 (with RMP version 8.0)  
MAH(s): AstraZeneca AB

**15.1.6. Human rotavirus, live attenuated – ROTARIX (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Jean-Michel Dogné (BE)

**Administrative details:**

Procedure number(s): EMEA/H/C/000639/PSU 078 (with RMP version 9.0)  
MAH(s): GlaxoSmithKline Biologicals S.A.

**15.1.7. Ingenol mebutate – PICATO (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

**Administrative details:**

Procedure number(s): EMEA/H/C/002275/PSU 005 (without RMP)  
MAH(s): Leo Pharma A/S

**15.1.8. Ivacaftor – KALYDECO (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Miguel-Angel Macia (ES)

**Administrative details:**

Procedure number(s): EMEA/H/C/002494/PSU 013 (without RMP)  
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

**15.1.9. Linagliptin, metformin – JENTADUETO (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Menno van der Elst (NL)

**Administrative details:**

Procedure number(s): EMEA/H/C/002279/PSU 006 (without RMP)  
MAH(s): Boehringer Ingelheim International GmbH

**15.1.10. Lixisenatide – LYXUMIA (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Qun-Ying Yue (SE)

**Administrative details:**

Procedure number(s): EMEA/H/C/002445/PSU 010 (without RMP)  
MAH(s): Sanofi-Aventis Groupe

**15.1.11. Meningococcal group b vaccine (rDNA, component, adsorbed) – BEXSERO (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Qun-Ying Yue (SE)

**Administrative details:**

Procedure number(s): EMEA/H/C/002333/PSU 009 (without RMP)  
MAH(s): Novartis Vaccines and Diagnostics S.r.l.

**15.1.12. Methoxy polyethylene glycol-epoetin beta – MIRCERA (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Dolores Montero Corominas (ES)

**Administrative details:**

Procedure number(s): EMEA/H/C/000739/PSU 018 (without RMP)  
MAH(s): Roche Registration Ltd

**15.1.13. Pegloticase – KRYSTEXXA (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Martin Huber (DE)

**Administrative details:**

Procedure number(s): EMEA/H/C/002208/PSU 011 (without RMP)  
MAH(s): Savient Pharma Ireland Ltd.  
For adoption: PRAC recommendation

**15.1.14. Perampanel – FYCOMPA (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

**Administrative details:**

Procedure number(s): EMEA/H/C/002434/PSU 008 (with RMP version 1.6)  
MAH(s): Eisai Europe Ltd.

**15.1.15. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) – PREVENAR 13 (CAP)**

- Evaluation of a PSUR procedure

**Regulatory details:**

PRAC Rapporteur: Qun-Ying Yue (SE)

**Administrative details:**

Procedure number(s): EMEA/H/C/001104/PSU 053 (without RMP)  
MAH(s): Pfizer Limited

#### **15.1.16. Rufinamide – INOVELON (CAP)**

- Evaluation of a PSUR procedure

##### **Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/000660/PSU 027 (with RMP version 8.0)

MAH(s): Eisai Ltd

#### **15.2. Follow-up to PSUR procedures<sup>41</sup>**

##### **15.2.1. Oseltamivir – TAMIFLU (CAP)**

- Evaluation of a follow-up to a PSUR procedure

##### **Regulatory details:**

PRAC Rapporteur: Kirsti Villikka (FI)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/000402/LEG 087.1

Procedure scope: MAH's response to PSUR#12 as adopted at PRAC in April 2013

MAH(s): Roche Registration Ltd

See also Interferon beta-1a (AVONEX) under **Error! Reference source not found.**4.3.4.

## **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)<sup>42</sup>**

None

#### **16.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>43</sup>**

##### **16.2.1. Aliskiren – RASILEZ (CAP)**

- Evaluation of a PASS protocol

##### **Regulatory details:**

PRAC Rapporteur: Carmela Macchiarulo (IT)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/000780/MEA 034.1

Procedure scope: Evaluation of a revised PASS protocol (CSPP100A2418): cohort study exploring the incidence of colorectal hyperplasia and gastrointestinal cancer in treated adult hypertensive patients in the United States

MAH(s): Novartis Europharm Ltd

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<sup>41</sup> Follow up as per the conclusions of the previous PSUR procedure, assessed outside next PSUR procedure

<sup>42</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>43</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

### **16.2.2. Canakinumab – ILARIS (CAP)**

- Evaluation of a PASS protocol

#### **Regulatory details:**

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/001109/MEA 037

Procedure scope: Evaluation of a PASS protocol (Study CACZ885G2401): non-interventional study collecting safety and efficacy data from systemic juvenile idiopathic arthritis (SJIA) patients enrolled in the Pharmachild registry and who are initiated on treatment with canakinumab

MAH(s): Novartis Europharm Ltd

### **16.2.3. Dapagliflozin – FORXIGA (CAP)**

- Evaluation of a PASS protocol

#### **Regulatory details:**

PRAC Rapporteur: Qun-Ying Yue (SE)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/002322/MEA 008.2

Procedure scope: MAH's response to MEA 008.1 [Updated Drug Utilisation SR protocol] as adopted at PRAC/CHMP in October 2013 and a revised study protocol for MB102134

MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

### **16.2.4. Fenofibrate, simvastatin – CHOLIB (CAP)**

- Evaluation of a PASS protocol

#### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/002559/MEA 002

Procedure scope: Evaluation of PASS protocol ABT285.E.001: drug utilisation research (DUR) study on the use of Cholib (fenofibrate and simvastatin fixed combination): a European multinational study using secondary health records databases

MAH(s): Abbott Healthcare Products Ltd.

### **16.2.5. Hydrocortisone – PLENADREN (CAP)**

- Evaluation of a PASS protocol

#### **Regulatory details:**

PRAC Rapporteur: Qun-Ying Yue (SE)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/002185/MEA 005

Procedure scope: Evaluation of a PASS protocol for study SWE-DUS: a Swedish, retrospective, study progress reports to be provided on a yearly basis evaluating the pattern of Plenadren use from as part of the PSURs Swedish quality registries

MAH(s): ViroPharma SPRL

### **16.2.6. Indacaterol, glycopyrronium bromide – ULTIBRO BREEZHALER (CAP), XOTERNA BREEZHALER (CAP)**

- Evaluation of a PASS protocol

**Regulatory details:**

PRAC Rapporteur: Line Michan (DK)

**Administrative details:**

Procedure number(s): EMEA/H/C/002679/MEA 003, EMEA/H/C/003755/MEA 003

Procedure scope: Evaluation of a drug utilisation study protocol (QVA 149A2401): multinational, multi-database drug utilisation study of indacterol/glycopyrronium bromide in Europe

MAH(s): Novartis Europharm Ltd

**16.2.7. Lixisenatide – LYXUMIA (CAP)**

- Evaluation of a PASS protocol

**Regulatory details:**

PRAC Rapporteur: Qun-Ying Yue (SE)

**Administrative details:**

Procedure number(s): EMEA/H/C/002445/MEA 007.1, EMEA/H/C/002445/MEA 008.1

Procedure scope: Evaluation of updated PASS protocols for retrospective database study and patient registry on GLP-1 receptor agonists and risk of acute pancreatitis, pancreatic cancer and thyroid cancer, in Particular medullary thyroid cancer. Also including response to MEA 007 and MEA 008 as adopted at PRAC/CHMP in July 2013

MAH(s): Sanofi-Aventis Groupe

**16.2.8. Moroctocog alfa – REFACTO AF (CAP)**

- Evaluation of a PASS protocol

**Regulatory details:**

PRAC Rapporteur: Doris Stenver (DK)

**Administrative details:**

Procedure number(s): EMEA/H/C/000232/MEA 115

Procedure scope: Evaluation of clinical study report for a post-authorisation safety surveillance registry or ReFacto AF in previously untreated patients (PUPs) in usual care settings - Study 443

MAH(s): Pfizer Limited

**16.2.9. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – FOCLIVIA (CAP)**

**Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – AFLUNOV (CAP), PREPANDEMIC INFLUENZA VACCINE (H5N1) (SURFACE ANTIGEN, INACTIVATED, ADJUVANTED) NOVARTIS VACCINES AND DIAGNOSTIC (CAP)**

- Evaluation of a PASS protocol

**Regulatory details:**

PRAC Rapporteur: Carmela Macchiarulo (IT)

**Administrative details:**

Procedure number(s): EMEA/H/C/002094/MEA 020, EMEA/H/C/001208/MEA 024,

EMEA/H/C/002269/MEA 019

Procedure scope: Evaluation of a PASS protocol synopsis V87\_27 OB: post-marketing observational cohort safety study of the Novartis Vaccines and Diagnostics pandemic influenza A (H5N1) vaccine Foclivia in pregnant women in Great Britain using data from the clinical practice research datalink (CPRD)

MAH(s): Novartis Vaccines and Diagnostics S.r.l.

**16.2.10. Radium-223 – XOFIGO (CAP)**

- Evaluation of a PASS protocol

**Regulatory details:**

PRAC Rapporteur: Julia Dunne (UK)

**Administrative details:**

Procedure number(s): EMEA/H/C/002653/MEA 004

Procedure scope: Evaluation of a PASS protocol (REASSURE study 16913): observational study to assess the long term safety profile and risks of developing second primary malignancies and their potential relationship to radium-223 in the routine clinical practice setting

MAH(s): Bayer Pharma AG

**16.3. Results of PASS imposed in the marketing authorisation(s)<sup>44</sup>**

None

**16.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>45</sup>****16.4.1. Epoetin zeta – RETACRIT (CAP)**

- Evaluation of non-imposed PASS results

**Regulatory details:**

PRAC Rapporteur: Valerie Strassmann (DE)

**Administrative details:**

Procedure number(s): EMEA/H/C/000872/II/0053/G (with RMP)

Procedure scope: Evaluation of 1) MEA 44: clinical PASCO (PMS-830-07-0043) post-authorisation safety cohort observation of Silapo (epoetin zeta) administered for the treatment of renal anaemia; 2) MEA 45: clinical REG-830-10-0098 and REG-830-10-0097 (pilot study): epidemiological study based on healthcare insurance data to determine the risk of venous thromboembolism and all-cause mortality in cancer patients treated with epoetins either with or without transfusions versus cancer patients treated with transfusions alone

MAH(s): Hospira UK Limited

**16.4.2. Epoetin zeta – SILAPO (CAP)**

- Evaluation of non-imposed PASS results

**Regulatory details:**

PRAC Rapporteur: Valerie Strassmann (DE)

**Administrative details:**

Procedure number(s): EMEA/H/C/000760/II/0031/G (with RMP)

Procedure scope: Submission of the final reports for the following two studies in order to fulfil the post-authorisation measures MEA 036 and LEG 038: 1) MEA 036: post-authorisation safety cohort observation of Silapo (epoetin zeta) administered intravenously for the treatment of renal anaemia (PASCO); 2) LEG 038: risk of venous thromboembolism and all-cause mortality in cancer patients treated with epoetins either with or without transfusions versus cancer patients treated with transfusions alone. This submission includes an updated RMP to reflect the outcome of the two studies

MAH(s): Stada Arzneimittel AG

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<sup>44</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>45</sup> 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



## **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<sup>46</sup>**

### **16.5.1. Bazedoxifene – CONBRIZA (CAP)**

- Evaluation of interim PASS results

#### **Regulatory details:**

PRAC Rapporteur: Martin Huber (DE)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/000913/MEA 012.5

Procedure scope: Evaluation of second progress report on PASS study B1781044: cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe

MAH(s): Pfizer Limited

### **16.5.2. Boceprevir – VICTRELIS (CAP)**

- Evaluation of interim PASS results

#### **Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/002332/MEA 017.5

Procedure scope: Evaluation of second interim status report of postmarketing drug utilisation study: an observational PASS of Victrelis (boceprevir) among chronic hepatitis C patients (P08518)

MAH(s): Merck Sharp & Dohme Limited

### **16.5.3. Caffeine – PEYONA (CAP)**

- Evaluation of interim PASS results

#### **Regulatory details:**

PRAC Rapporteur: Harald Herkner (AT)

#### **Administrative details:**

Procedure number(s): EMEA/H/C/001014/MEA 001.8

Procedure scope: Evaluation of fourth interim report on Peyona PASS study to assess drug utilisation and safety of caffeine citrate (Nymusa) in treatment of premature infants

MAH(s): Chiesi Farmaceutici S.p.A.

### **16.5.4. Glycopyrronium bromide – ENUREV BREEZHALER (CAP), SEEBRI 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/MEA 002.2, EMEA/H/C/002430/MEA 002.2, EMEA/H/C/002690/MEA 002.2

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<sup>46</sup> In line with the revised variations regulation for any submission before 4 August 2013

Procedure scope: Evaluation of first interim results of a drug utilisation study: multinational, multi-database drug utilisation study of inhaled glycopyrronium in Europe  
MAH(s): Novartis Europharm Ltd

#### **16.5.5. Mannitol – BRONCHITOL (CAP)**

- Evaluation of interim PASS results

##### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/001252/ANX 002.2

Procedure scope: Evaluation of second interim analysis of the cystic fibrosis (CF) study

MAH(s): Pharmaxis Pharmaceuticals Limited

#### **16.5.6. Ticagrelor – BRILIQUE (CAP)**

- Evaluation of interim PASS results

##### **Regulatory details:**

PRAC Rapporteur: Menno van der Elst (NL)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/001241/MEA 008.3

Procedure scope: Evaluation of the third annual progress report on drug utilisation study D5130N00010: pharmacoepidemiological study to examine patient characteristics, drug utilisation pattern and crude incidence rates of selected outcomes in new users of ticagrelor, clopidogrel and prasugrel in national Swedish registries

MAH(s): AstraZeneca AB

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

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

#### **17.1.1. Alipogene tiparvovec – GLYBERA (CAP)**

- PRAC consultation on an annual reassessment of the marketing authorisation

##### **Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

##### **Administrative details:**

Procedure number(s): EMEA/H/C/002145/S/0027 (with RMP version 5.1)

MAH(s): uniQure biopharma B.V.

#### **17.1.2. Clopidogrel – GREPID (CAP)**

- PRAC consultation on a renewal of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Margarida Guimarães (PT)

**Administrative details:**

Procedure number(s): EMEA/H/C/001059/R/0029 (without RMP)  
MAH(s): Pharmathen S.A.

**17.1.3. Clofarabine – EVOLTRA (CAP)**

- PRAC consultation on an annual reassessment of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

**Administrative details:**

Procedure number(s): EMEA/H/C/000613/S/0041 (without RMP)  
MAH(s): Genzyme Europe BV

**17.1.4. Efavirenz – STOCRIN (CAP), SUSTIVA (CAP)**

- PRAC consultation on a renewal of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Margarida Guimarães (PT)

**Administrative details:**

Procedure number(s): EMEA/H/C/000250/R/0096 (with RMP), EMEA/H/C/000249/R/0120 (with RMP)  
MAH(s): Merck Sharp & Dohme (Stocrin), Bristol-Myers Squibb Pharma EEIG (Sustiva)

**17.1.5. Histamine dihydrochloride – CEPLENE (CAP)**

- PRAC consultation on an annual reassessment of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Almath Spooner (IE)

**Administrative details:**

Procedure number(s): EMEA/H/C/000796/S/0020 (without RMP)  
MAH(s): Meda AB

**17.1.6. Lamivudine – ZEFFIX (CAP)**

- PRAC consultation on a renewal of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

**Administrative details:**

Procedure number(s): EMEA/H/C/000242/R/0062 (without RMP)  
MAH(s): Glaxo Group Ltd

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

- PRAC consultation on a renewal of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Menno van der Elst (NL)

**Administrative details:**

Procedure number(s): EMEA/H/C/001026/R/0025 (with RMP)  
MAH(s): Novo Nordisk A/S

**17.1.8. Pixantrone – PIXUVRI (CAP)**

- PRAC consultation on a conditional renewal of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Julia Dunne (UK)

**Administrative details:**

Procedure number(s): EMEA/H/C/002055/R/0014 (without RMP)  
MAH(s): CTI Life Sciences Limited

**17.1.9. Plerixafor – MOZOBIL (CAP)**

- PRAC consultation on a renewal of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Sabine Straus (NL)

**Administrative details:**

Procedure number(s): EMEA/H/C/001030/R/0019 (without RMP)  
MAH(s): Genzyme Europe BV

**17.1.10. Tafamidis – VYNDAQEL (CAP)**

- PRAC consultation on an annual reassessment of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Isabelle Robine (FR)

**Administrative details:**

Procedure number(s): EMEA/H/C/002294/S/0012 (without RMP)  
MAH(s): Pfizer Limited

**17.1.11. Tocofersolan – VEDROP (CAP)**

- PRAC consultation on a renewal of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

**Administrative details:**

Procedure number(s): EMEA/H/C/000920/R/0007 (with RMP)  
MAH(s): Orphan Europe S.A.R.L.

**17.1.12. Tolvaptan – SAMSCA (CAP)**

- PRAC consultation on a renewal of the marketing authorisation

**Regulatory details:**

PRAC Rapporteur: Julie Williams (UK)

**Administrative details:**

Procedure number(s): EMEA/H/C/000980/R/0016 (without RMP)  
MAH(s): Otsuka Pharmaceutical Europe Ltd

### **17.1.13. Trabectedin – YONDELIS (CAP)**

- PRAC consultation on an annual reassessment of the marketing authorisation

#### ***Regulatory details:***

PRAC Rapporteur: Line Michan (DK)

#### ***Administrative details:***

Procedure number(s): EMEA/H/C/000773/S/0037 (without RMP)

## ANNEX II – List of participants:

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 3-6 February 2014 meeting.

<i>PRAC member PRAC alternate</i>	<i>Country</i>	<i>Outcome restriction following evaluation of e-DoI for the meeting</i>	<i>Topics on the current Committee Agenda for which restriction applies</i>  <i>Product/ substance</i>
Aleksandra Martinovic	Austria	Cannot act as Rapporteur or Peer reviewer for:	linagliptin, metformin
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer-reviewer for:	paracetamol, interferon beta 1a, interferon beta 1b, aflibercept, radium-223
Veerle Verlinden	Belgium	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Marin Banovac	Croatia	Full involvement	
Nectaroula Cooper	Cyprus	Full involvement	
Eva Jirsova	Czech Republic	Full involvement	
Line Michan	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Katrin Kiisk	Estonia	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	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer-reviewer for:	etanercept , apixaban, bosutinib, crizotinib, pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed), pregabalin, moroctocog alfa, bazedoxifene, tafamidis
Melinda Palfi	Hungary	Full involvement	
Julia Pallos	Hungary	Full involvement	
Gudrun Kristin Steingrimsdottir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Jelena Ivanovic	Italy	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Inguna Adoviča	Latvia	Full involvement	
Andis Lacis	Latvia	Cannot act as Rapporteur or Peer reviewer for:	fenofibrate, simvastatin
Jolanta Gulbinovic	Lithuania	Full involvement	
Nadine Petitpain	Luxembourg	Full involvement	

<b>PRAC member PRAC alternate</b>	<b>Country</b>	<b>Outcome restriction following evaluation of e-DoI for the meeting</b>	<b>Topics on the current Committee Agenda for which restriction applies</b>	<b>Product/ substance</b>
Amy Tanti	Malta	Full involvement		
Sabine Straus	Netherlands	Full involvement		
Menno van der Elst	Netherlands	Full involvement		
Ingebjorg Buajordet	Norway	Full involvement		
Adam Przybylkowski	Poland	Full involvement		
Margarida Guimaraes	Portugal	Full involvement		
Roxana Stroe	Romania	Full involvement		
Tatiana Magalova	Slovakia	Full involvement		
Milena Radoha- Bergoč	Slovenia	Full involvement		
Miguel-Angel Maciá	Spain	Full involvement		
Dolores Montero	Spain	Full involvement		
Ulla Wändel Liminga	Sweden	Full involvement		
Qun-Ying Yue	Sweden	Full involvement		
June Munro Raine		Full involvement		
Julie Williams	UK	Full involvement		
Julia Dunne	UK	Full involvement		

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

**Additional European  
experts participating at  
the meeting for specific  
Agenda items**

Sawchik Javier	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Defays Laurence	Belgium	
Céline Druet	France	
Vincent Gazin	France	
Björn Arvidson	Sweden	
Charlotte Backman	Sweden	
Rolf Gedeborg	Sweden	
Philip Bryan	United Kingdom	
Cecilia Chisholm	United Kingdom	
Katherine Donegan	United Kingdom	
Saira Mahmood	United Kingdom	
Jose Miyar	United Kingdom	
Jane Woolley	United Kingdom	
David Hunt	United Kingdom	

<b>Health care professionals and patients members</b>	<b>Country</b>	<b>Outcome restriction following evaluation of e-DoI for the meeting:</b>	<b>Topics on the current Committee Agenda for which restriction applies</b>	<b>Product/substance</b>
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) <a href="http://www.ema.europa.eu/docs/en_GB/document_library/contacts/avanderzeijden_DI.pdf">http://www.ema.europa.eu/docs/en_GB/document_library/contacts/avanderzeijden_DI.pdf</a>		

## 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](http://www.ema.europa.eu)

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