14 April 2016
EMA/PRAC/259752/2016
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the PRAC meeting on 14-17 March 2016

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

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

Of note, the minutes are a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 14-17 March 2016 meeting by welcoming all participants.

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

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

The PRAC also noted that the European Commission issued a Decision dated 11 March 2016 on appointing PRAC members and alternates to represent healthcare professionals and patient organisations for a term of three years as of 1 March 2016. Marco Greco was nominated as PRAC member to represent patients' organisations and Albert van der Zeijden as his alternate. John Raymond Anderson was nominated as PRAC member to represent healthcare professionals' organisations and Kirsten Myhr as his alternate. The PRAC thanked Filip Babylon for his contribution to the work of the PRAC in his role of PRAC member representing healthcare professionals' organisations over three years.

In addition, the PRAC chair announced that Jane Ahlqvist-Rastad was to step down as an independent scientific expert member nominated by the European Commission after the current PRAC plenary meeting. The PRAC thanked her for her important contribution to the work of the PRAC.

1.2. Agenda of the meeting of 14-17 March 2016

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

1.3. Minutes of the previous meeting of 08-11 February 2016

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

Post-meeting note: the PRAC minutes of the meeting held on 08-11 February 2016 were published on the EMA website on 9 April 2016 (EMA/PRAC/251925/2016).

2. EU referral procedures for safety reasons: urgent EU procedures

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

3. EU referral procedures for safety reasons: other EU referral procedures

3.1. Newly triggered procedures

3.1.1. Direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free): daclatasvir – DAKLINZA (CAP); dasabuvir – EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/A-20/1438

Applicant: Bristol-Myers Squibb Pharma EEIG (Daklinza); AbbVie Ltd (Exviera, Viekirax); Janssen-Cilag International N.V. (Olysio); Gilead Sciences International Ltd (Harvoni, Sovaldi)

PRAC Rapporteur: Margarida Guimarães; PRAC Co-rapporteur: Dolores Montero Corominas

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

Background

The European Commission sent a letter of notification dated 09/03/2016 of a referral under Article 20 of Regulation (EC) No 726/2004 for the review of direct-acting antivirals (DAAV) (daclatasvir (Daklinkza), dasabuvir (Exviera), ombitasvir/paritaprevir/ritonavir (Viekirax), simeprevir (Olysio), sofosbuvir (Sovaldi), sofosbuvir/ledipasvir (Harvoni)) indicated for the interferon-free treatment of chronic hepatitis C in adults under certain conditions.

In February 2016, the PRAC discussed the available evidence for a new signal based on cases of hepatitis B (HBV) re-activation reported in patients taking sofosbuvir. Considering the seriousness of the events, the biological plausibility of the reactivation and taking into account that additional cases were reported with other interferon-free DAAV therapies, the

PRAC recommended the conduct of a thorough evaluation within a formal review in order to assess the risk of hepatitis B reactivation in patients treated with a DAAV for the treatment of hepatitis C and whether any measures are necessary to minimise risk. For further background, see PRAC minutes February 2016.

Discussion

The PRAC noted the notification letter from the European Commission and discussed a list of questions to be addressed as well as a timetable for conducting the review.

The PRAC appointed Margarida Guimarães as Rapporteur and Dolores Montero Corominas as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/188631/2016) and a timetable for the procedure (EMA/PRAC/196120/2016).

3.1.2. Gadolinium-containing contrast agents (GdCA): gadobenic acid (NAP); gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid (NAP); gadoteric acid (NAP); gadoteridol (NAP); gadoxetic acid (NAP); gadoversetamide – OPTIMARK (CAP) - EMEA/H/A-31/1437

Applicant: Mallinckrodt Deutschland GmbH (Optimark); various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Doris Stenver

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

Background

The European Commission sent a letter of notification dated 09/03/2016 initiating a referral procedure under Article 31 of Directive 2001/83/EC for the review of gadolinium-containing medicines (GdCAs) (gadobenic acid; gadobutrol; gadodiamide; gadopentetic acid; gadoteric acid; gadoteridol; gadoxetic acid; gadoversetamide (Optimark)) used intravenously as an enhancement for magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA).

Following the recent evaluation by the PRAC of the available literature and data related to the issue of accumulation of gadolinium in the brain as part of PSUSA procedures for individual gadolinium-related substances, the PRAC considered that this issue and its clinical consequences needed further investigation. For further background, see PRAC minutes January 2016. Taking into account the evidence of accumulation of gadolinium in different body tissues, the European Commission considered that such a review will enable an assessment of the overall safety profile and benefit-risk of GdCAs, which is of public health importance in view of their use in MRI and MRA investigations.

Discussion

The PRAC noted the notification letter from the European Commission and discussed a list of questions to be addressed during the procedure as well as a timetable for conducting the review. The PRAC agreed on the need for an expert meeting to be organised in the course of the review.

The PRAC appointed Rafe Suvarna as Rapporteur and Doris Stenver as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/188631/2016) and a timetable for the procedure (EMA/PRAC/195601/2016).

3.1.3. Idelalisib – ZYDELIG (CAP) - EMEA/H/A-20/1439

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Ulla Wändel Liminga

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

The European Commission sent a letter of notification dated 11/03/2016 triggering a procedure under Article 20 of Regulation (EC) No 726/2004 for the review of idelalisib (Zydelig) indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or *TP53* mutation in patients unsuitable for chemo-immunotherapy. Idelalisib is also indicated in monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment. In addition, an extension of indication in combination with ofatumumab in CLL treatment received a positive opinion at the CHMP in February 2016.

The review was initiated following an increased rate of serious adverse events (SAE) including deaths, mostly due to opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus (CMV) among subjects receiving idelalisib compared to control groups, observed in the interim results of three clinical trials[1]. These clinical trials were investigating the medicine in a treatment combination that is currently not authorised for Zydelig, and/or in a population with earlier disease characteristics than the currently approved indications. Nevertheless, in light of the emerging safety data, the European Commission considered that the findings from the clinical trials and all available safety data related to idelalisib should be reviewed by the EMA in order to assess the potential impact on the benefit-risk balance of Zydelig in the approved indications and relevant ongoing variations. In addition, the European Commission requested the EMA to consider whether provisional measures were necessary to protect public health.

Discussion

The PRAC noted the notification letter from the European Commission. The PRAC appointed Rafe Suvarna as Rapporteur and Ulla Wändel Liminga as Co-Rapporteur for the procedure.

[1] GS-US-312-0123: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously untreated chronic lymphocytic leukaemia
GS-US-313-0124: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated indolent non-Hodgkin lymphomas
GS-US-313-0125: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS 1101) in combination with bendamustine and rituximab for previously treated indolent non-Hodgkin lymphomas

Following an oral explanation with the MAH during the meeting, the PRAC discussed the need for provisional measures to protect public health as well as a list of questions to be addressed during the procedure together with a timetable for conducting the review.

With regard to provisional measures, the PRAC reviewed the very limited and preliminary data provided by the MAH on the three clinical trials in question as well as available safety data from clinical trials submitted in support of the initial Marketing Authorisation, the recent extension of indication as well as EudraVigilance data in relation to the overall risk of treatment with idelalisib. The PRAC noted that the use of idelalisib in these three clinical trials was not in line with the currently approved Marketing Authorisation. Although the potential impact of these new safety findings in the current authorised indications is presently uncertain, the PRAC recommended provisional amendments of the indication of idelalisib and considered that as a precautionary measure, idelalisib should not be initiated as a first line treatment in CLL patients with 17p deletion or *TP53* mutation. Nevertheless, the PRAC recommended that idelalisib could be used for continuing treatment in those patients who had already initiated the medicine as first line treatment based on individual benefit-risk balance assessment, and with the addition of new risk minimisation measures (described below).

The PRAC noted that most of the SAE reported in studies 0123, -0124 and -0125 were related to infections. Whilst the matter is being further reviewed, the PRAC recommended as a provisional measure an update of the posology and warnings that treatment should not be initiated in patients with systemic infections, patients should be monitored for respiratory symptoms and should be administered PJP prophylaxis. Regular clinical and laboratory screening for CMV should also be performed. In addition, given the higher risk of infection, advice on dose reduction or treatment interruption in the event of severe neutropenia was also proposed. In view of the risk minimisation measures above, the PRAC considered that the benefit-risk balance of Zydelig remains favourable subject to the agreed provisional amendments to the product information and other risk minimisation measures.

Summary of recommendation(s)/conclusions

The Committee recommended, by consensus, the variation to the terms of the marketing authorisations for Zydelig (idelalisib) as a provisional measure, without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004. See EMA press release (EMA/201814/2016) entitled 'EMA recommends new safety measures for Zydelig'. The PRAC also agreed the distribution of a Direct Healthcare Professional Communication (DHPC) together with a communication plan.

In addition, the PRAC agreed on the need for a Scientific Advisory Group in Oncology (SAG-O) meeting to be organised in the course of the review.

Finally, the Committee adopted a list of questions (EMA/PRAC/197574/2016) and a timetable for the ongoing procedure (EMA/PRAC/196144/2016).

Post-meeting note: The PRAC assessment report on provisional measures (EMA/215033/2016) was published on the EMA website on 23 March 2016. On 23 March 2016, the European Commission also granted a Commission Decision on the temporary measures.

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

3.3.1. Inhaled corticosteroids (ICS)-containing medicinal products indicated in the treatment of chronic obstructive pulmonary disease: beclomethasone (NAP); beclomethasone, formoterol (NAP); budesonide (NAP); budesonide, formoterol – BIRESP SPIROMAX (CAP); BUDESONIDE FORMOTEROL TEVA (CAP); DUORESP SPIROMAX (CAP); VYALER SPIROMAX (CAP), NAP; flunisolide, salbutamol (NAP); fluticasone (NAP); fluticasone, salmeterol (NAP); fluticasone, vilanterol – RELVAR ELLIPTA (CAP); REVINTY ELLIPTA (CAP) – EMEA/H/A-31/1415

Applicant: Glaxo Group Ltd, Teva Pharma B.V., Teva Pharmaceuticals Europe, various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Jan Neuhauser

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for inhaled corticosteroids (ICS)-containing products (beclomethasone-, budesonide-, flunisolide-, fluticasone propionate- and fluticasone furoate-containing products) reviewing the risk of pneumonia in patients with chronic obstructive pulmonary disease (COPD) is to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For background information, see PRAC minutes May 2015, PRAC minutes June 2015 and PRAC minutes November 2015.

Discussion

The PRAC reviewed the data submitted by the MAHs in relation to the risk of pneumonia in patients with COPD associated with ICS-containing medicinal products and discussed the conclusions reached by the Rapporteurs. The PRAC considered that the evidence provided supports a causal association between the use of ICS-containing products and an increased risk of pneumonia in COPD patients. In addition, the PRAC concurred that there is no conclusive clinical evidence for intra-class differences in the magnitude of the risk among ICS-containing products. The PRAC also considered that some evidence exists of an increased risk of pneumonia with increasing steroid dose, although this has not been demonstrated conclusively across all studies. Therefore, the PRAC considered that the increased risk of pneumonia should be included in the product information of all ICS-containing products indicated in the treatment of COPD, with a warning for healthcare professionals and patients to remain vigilant for the possible development of pneumonia in patients with COPD, taking into consideration the overlap of the symptoms of pneumonia with those of exacerbation of COPD.

Overall, the PRAC considered that the benefit-risk balance of ICS-containing products remains favourable in the treatment of COPD subject to the agreed amendments to the product information.

Summary of recommendation(s)/conclusions

The PRAC adopted, by consensus, the variation of the marketing authorisations for ICS-containing products indicated in the treatment of COPD and adopted a recommendation to be considered by the CHMP for an opinion. See EMA press release (EMA/197713/2016)

entitled 'PRAC reviews known risk of pneumonia with inhaled corticosteroids for chronic obstructive pulmonary disease'.

Post-meeting note: the press release entitled 'EMA completes review of inhaled corticosteroids for chronic obstructive pulmonary disease' (EMA/285392/2016) representing the opinion adopted by the CHMP was published on the EMA website on 29 April 2016.

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

None

3.5. Others

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Ferrous sulfate (NAP)

Applicant: various

PRAC Rapporteur: Leonor Chambel

Scope: Signal of mouth ulceration
EPITT 18623 – New signal
Lead Member State: PT

Background

Ferrous sulfate contains iron and is indicated in the treatment of iron-deficiency anaemia.

During routine signal detection activities, a signal of mouth ulceration was identified by Portugal, based on 16 cases retrieved from EudraVigilance and one additional case retrieved from the literature. Portugal confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from case reports in EudraVigilance and in the literature. Taking into account that oral iron-therapy is known to cause direct gastro-intestinal mucosal injury and that persistence of ferrous sulfate in contact with the oral mucosa may cause local irritation, the PRAC considered that the MAHs of ferrous sulfate-containing medicines products should provide a cumulative review of cases of mouth ulceration and related terms in association with ferrous sulfate oral solid forms.

The PRAC appointed Leonor Chambel as Rapporteur for the signal.

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

Summary of recommendation(s)

- The MAH of ferrous sulfate-containing medicines products (Wörwag Pharma GmBH & Co. KG, Teva GmBH, Teofarma S.R.L., Pierre Fabre, Meda Pharma, Egis Pharmaceuticals PLC, Novartis, and Aco Hud Nordic AB) should submit to the EMA, within 60 days, a cumulative review of cases of mouth ulceration and related terms in association with ferrous sulfate oral solid forms. The review should focus on vulnerable populations with conditions such as dysphagia, dementia or impaired cognition, as well as concomitant medication or other comorbidities. The MAHs should discuss how the risk of this event may be minimised by proposing any appropriate amendment to the product information.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Intravenous fluids containing electrolytes and/or carbohydrates (NAP)

Applicant: various

PRAC Rapporteur: Not applicable

Scope: Signal of risk of hyponatremia
EPITT 18631 – New signal
Lead Member States: DK, UK, SE

Background

Intravenous (IV) fluids containing electrolytes and/or carbohydrates are indicated for hospitalised patients to maintain the circulating volume and maintain electrolyte and/or glucose concentrations.

During routine signal detection activities, a signal of risk of hyponatremia was identified by Denmark, based on 6 cases retrieved from the Danish Medicines Agency (DKMA) database. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the case reports in the DKMA database and in the literature. Overall, the PRAC was of the opinion that the administration of physiologically hypotonic IV fluids to (hospitalised) patients is associated with the risk of hyponatremia, and that this risk may not be consistently reflected in the product information of the various IV fluids authorized across the EU. However, the PRAC considered there is no need to further assess this risk within a signal procedure at this point, given that this constitutes an already known risk, which can be managed by appropriate use of the product and adequate monitoring of patients supported by clinical guidelines.

The PRAC therefore considered that this safety concern may best be managed by strengthening clinical guidance, and raising further awareness through e.g. educational programs, rather than by updating the product information of the various IV fluids authorized across Europe. A two-step approach is therefore proposed. First, non-urgent information (NUI) request could be used to learn from the experiences and best practices within the different Member States for raising awareness among healthcare professionals regarding the risk of hyponatremia with physiologically hypotonic IV fluids, and strategies to minimize the risk. As a second step, the Paediatric Committee (PDCO) and Coordination

Group (CMDh) could be consulted on how to further manage the risk of hyponatremia associated with physiologically hypotonic IV fluids.

Summary of recommendation(s)

- The PRAC agreed that the signal for hyponatremia with physiologically hypotonic IV fluids may be closed.

4.1.3. Propofol (NAP)

Applicant: various

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Signal of diabetes insipidus
EPITT 18622 – New signal
Lead Member State: NO

Background

Propofol is a short-acting general anaesthetic agent with a rapid onset of action indicated for induction and maintenance of general anaesthesia, for sedation for diagnostic and surgical procedures and for sedation of ventilated patients (> 16 years) in the intensive care unit (ICU).

Following a variation for a propofol generic medicinal product submitted based on two cases published in the literature (*Soo et al.*[3], *Kassebaum et al.*[4]) to add diabetes insipidus as a new undesirable effect, Norway raised a signal of diabetes insipidus based on seven supportive cases retrieved from EudraVigilance, including 4 cases also published, and one from the literature. Norway confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance. Taking into account that a plausible mechanism has been proposed based on animal data and that a positive dechallenge was reported in two cases, the PRAC agreed to request the MAH for Diprivan to provide a cumulative review of all cases of diabetes insipidus, nephrogenic diabetes insipidus and related preferred terms associated with propofol.

The PRAC appointed Kristin Thorseng Kvande as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Diprivan (propofol) should submit to the EMA, within 60 days, a cumulative review of all cases of diabetes insipidus, nephrogenic diabetes insipidus and related preferred terms associated with propofol. The cumulative review should include a review of published literature, post-marketing experience and clinical trials. The possible mechanism of action should also be discussed. The MAH should also discuss the need for any potential amendment to the product information and/or the RMP and include a proposal to update the relevant sections within this discussion.

[3] Soo J, Gray J, Manecke G. Propofol and diabetes insipidus. J Clin Anesth. 2014; 26(8):679-83
[4] Kassebaum N, Hairr J, Goldsmith W, Barwise J, Pandharipande P. Diabetes insipidus associated with propofol anesthesia. J Clin Anesth 2008; 20: 466-8.

- 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. Proton pump inhibitors (PPIs): esomeprazole – NEXIUM CONTROL (CAP), NAP; lansoprazole (NAP); omeprazole (NAP); pantoprazole – CONTROLOC CONTROL (CAP), PANTECTA CONTROL (CAP), PANTOLOC CONTROL (CAP), PANTOZOL CONTROL (CAP), SOMAC CONTROL (CAP), NAP; rabeprazole (NAP)

Applicant: various

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of elevated circulating levels of chromogranin A
EPITT 18614 – New signal
Lead Member States: AT, FI, LT, NL, SE, UK

Background

Proton pump inhibitors (PPIs) are indicated for the treatment of gastroesophageal reflux disease, gastric and duodenal ulcer, Zollinger-Ellison syndrome, and in combination with antibiotics for the eradication of Helicobacter pylori.

Following a case report showing increased levels of chromogranin A in a patient treated with omeprazole and lansoprazole published by *Igaz P et al.*[5], in 2011 the MAH for Losec (omeprazole) updated the product information. Consequently a review of the literature was conducted and a signal of elevated circulating levels of chromogranin A was identified by Italy. The United Kingdom confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the case reports in EudraVigilance. Taking into account the common mechanism of action for all PPIs and the biological plausibility, it is plausible to consider that these drugs, as a class, might be causally associated to the elevation of circulating chromogranin A (CgA) levels even after short-term intake (weeks). The PRAC therefore agreed to request the MAHs of pantoprazole, rabeprazole, lansoprazole and dexlansoprazole-containing medicinal products to submit a cumulative review of cases of increased level of chromogranin A in association with these PPIs. The MAH for esomeprazole- and omeprazole-containing products (for which there are already references to effects on chromogranin A levels in the product information) should submit a review of literature and non-serious cases of increased level of chromogranin A in association with these PPIs.

The PRAC appointed Rafe Suvarna as Rapporteur for the signal.

Summary of recommendation(s)

[5] Igaz P, et al. Marked chromogranin A elevation in a patient with bilateral adrenal incidentalomas, and its rapid normalization after discontinuation of proton pump inhibitor therapy. Clin Endocrinol 2007 Nov;67(5):805-6. Epub 2007 Jul 3.

- The MAHs for pantoprazole-, rabeprazole-, lansoprazole- and dexlansoprazole-containing medicinal products (Takeda and Janssen-Cilag) should submit to the EMA, within 60 days, a cumulative review of cases of increased levels of chromogranin A in association with proton pump inhibitors (PPIs). The MedDRA[6] preferred terms 'blood chromogranin A' and 'blood chromogranin A increased' should be included in the search. The review should include evidence from spontaneous reports, cases from studies and the literature and should discuss the possible biological mechanism. In consideration of the likely class effect, the MAHs should discuss the need for any potential amendment to the product information and/ or the RMP. More specifically, they should discuss the proposal to harmonize the SmPC and Package Leaflet in line with the existing relevant recommendations for omeprazole/esomeprazole.
- Additionally, the MAH for esomeprazole- and omeprazole-containing medicinal products (AstraZeneca) should submit to the EMA, within 60 days, a review of literature and non-serious cases of increased level of chromogranin A in association with esomeprazole and omeprazole. The MAH should discuss whether the systemic clearing period between discontinuation of PPIs and chromogranin A testing (5 days and retesting after 14 days as suggested in the omeprazole SmPC) is supported in the literature and case report data. A revised proposal should be made if appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Tramadol, paracetamol (NAP)

Applicant: various

PRAC Rapporteur: Julie Williams

Scope: Signal of hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH)
EPITT 18471 – New signal
Lead Member States: UK, FR

Background

Tramadol is an opioid agent which acts on the central nervous system. Paracetamol is a para-aminophenol derivative with analgesic and antipyretic properties. The combination is indicated for the symptomatic treatment of moderate to severe pain in adults and children above 12 years of age.

During routine signal detection activities, MAH Actavis identified in its Pharmacovigilance database 26 cases of hyponatraemia and/or SIADH, all medically confirmed with 6 coming from the published literature, and brought this signal to the attention of EMA and the Member States where its product is authorised. The United Kingdom confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of hyponatraemia and SIADH identified by Actavis, retrieved from the UK pharmacovigilance database and from the published

[6] Medical Dictionary for Regulatory Activities

literature particularly the articles by *Abadie et al.*[7] and *Fournier et al.*[8]. Taking into account the available post-marketing data, the published literature and a plausible biological mechanism via enhancement of serotonin release, the PRAC agreed to request the MAH for tramadol-containing products (Grünenthal) to provide a cumulative review of hyponatraemia associated with tramadol and discuss the need for any updates to product information for prescribers and patients.

The PRAC appointed Julie Williams as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for tramadol-containing products (Grünenthal) should submit to the EMA, within 60 days, a cumulative review of hyponatraemia associated with tramadol and discuss the need for any updates of the product information. The MAH should include all relevant data from spontaneous reports, clinical trials and relevant literature and evaluate the biological plausibility for a possible association.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Axitinib – INLYTA (CAP) - EMEA/H/C/002406/SDA/013

Applicant: Pfizer Limited

PRAC Rapporteur: Ingebjorg Buajordet

Scope: Signal of nephrotic syndrome
EPITT 18484 – Follow-up to November 2015

Background

For background, see PRAC minutes November 2015. The MAH replied to the request for information on the signal of nephrotic syndrome and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence from EudraVigilance, the literature and the data submitted by the MAH, the PRAC noted that the evidence for causality is weak (causality could not be excluded in 3 out of 15 cases but the rest of the cases had confounding factors or the information available was too limited to perform a causality assessment) but that there is a plausible biological mechanism suggesting that tyrosine kinase inhibitors (TKIs) may induce proteinuria and nephrotic syndrome. The PRAC therefore agreed that the product information should be updated to include that treatment with axitinib should be discontinued in the event that nephrotic syndrome develops.

Summary of recommendation(s)

[7] Abadie D , Durrieu G, Roussin A, Montastruc JL, Reseau francais des centres regionaux de pharmacovigilance. 'Serious adverse drug reactions with tramadol: a 2010-2011 pharmacovigilance survey in France'. Therapie. 2013 Mar-Apr; 68 (2): 77-84. Doi: 10.2515/therapie/2013021. EPUB 2013 Jun 18.

[8] Fournier JP, Yin H, Nessim S J, Montastruc J L, Azoulay L, 'Tramadol for non-cancer pain and the risk of hyponatraemia'. Am J Med. 2015 Apr; 128(4):418-25.e5. doi: 10.1016/j.amjmed.2014.10.046. Epub 2014 Nov 22

- The MAH for Inlyta (axitinib) should submit to the EMA, within 60 days, a variation to include in the current warning on proteinuria that axitinib should be discontinued if the patient develops nephrotic syndrome. In addition the MAH should continue to monitor nephrotic syndrome via routine pharmacovigilance.

For the full PRAC recommendations, see EMA/PRAC/135876/2016 published on 11/04/2016 on the EMA website.

4.3.2. Azathioprine (NAP); mercaptopurine - XALUPRINE (CAP), NAP

Applicant: Nova Laboratories Limited, Aspen Pharma, various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of lymphoproliferative disorders
EPITT 18503 – Follow-up to November 2015

Background

For background, see PRAC minutes November 2015. The MAH replied to the request for information on the signal of lymphoproliferative disorders and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence from spontaneous reports and the literature, the PRAC agreed that the product information of mercaptopurine- and azathioprine-containing medicinal products should be updated to include warnings related to lymphoproliferative disorders and macrophage activation syndrome. Moreover and considering the potential for carcinogenicity of these products, the PRAC agreed to include information about other malignancies in the product information for mercaptopurine-containing medicinal products in line with the information already included for azathioprine (pro-drug of mercaptopurine).

Summary of recommendation(s)

- The MAHs of mercaptopurine- and azathioprine-containing products should submit to the EMA or to the national competent authorities of the Member States, as applicable, within 60 days, a variation to include warnings related to lymphoproliferative disorders and macrophage activation syndrome. In addition the product information of mercaptopurine-containing medicinal products should be updated to include information about other malignancies in line with the information already included for azathioprine (pro-drug of mercaptopurine).

For the full PRAC recommendations, see EMA/PRAC/135876/2016 published on 11/04/2016 on the EMA website.

4.3.3. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP) - EMEA/H/C/000781/SDA/023; HIZENTRA (CAP) - EMEA/H/C/002127/SDA/019; HYQVIA (CAP) - EMEA/H/C/002491/SDA/005; KIOVIG (CAP) - EMEA/H/C/000628/SDA/039; PRIVIGEN (CAP) - EMEA/H/C/000831/SDA/027, NAP

Applicant: Instituto Grifols S.A. (Flebogamma DIF); CSL Behring GmbH (Hizentra, Privigen); Baxalta Innovations GmbH (HyQvia); Baxter AG (Kiovig); various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of posterior reversible encephalopathy syndrome (PRES)
EPITT 18512 – Follow-up to November 2015

Background

For background, see PRAC minutes November 2015. The MAHs replied to the request for information on the signal of posterior reversible encephalopathy syndrome (PRES) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. Having reviewed the available evidence from post-marketing data, clinical trials and the scientific literature, the PRAC agreed that a causal link between PRES and intravenous human normal immunoglobulins can be considered weak at this stage, taking into account that spontaneous and literature reports are confounded by the underlying disease (e.g. Guillain-Barre syndrome) and concomitant medications. The MAHs for intravenous normal human immunoglobulin should continue to monitor these events as part of routine safety surveillance and present updated information in an aggregated summary report within subsequent PSURs.

Summary of recommendation(s)

- The MAH of intravenous human normal immunoglobulin should continue to monitor events of posterior reversible encephalopathy syndrome (PRES) as part of routine safety surveillance and present updated information in an aggregated summary report within subsequent PSURs.

4.3.4. Loratadine (NAP)

Applicant: various

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of QT prolongation and Torsade de Pointe
EPITT 18576 – Follow-up to January 2016

Background

For background information, see PRAC minutes of January 2016.The additional analysis of the EudraVigilance data was assessed by the PRAC Rapporteur.

Discussion

The PRAC discussed the additional analysis of the EudraVigilance data performed by EMA on cetirizine, desloratadine, diphenhydramine and fexofenadine. As limited evidence to support a signal of QT prolongation and Torsade de Pointe is available, the PRAC did not support the extension of the proposed cumulative review to desloratadine, diphenhydramine, fexofenadine and/or cetirizine but agreed that the MAH of loratadine-containing medicinal products (Bayer) should submit in the next PSUR a cumulative review of all cases of Torsade de pointes/QT prolongation with loratadine.

Summary of recommendation(s)

- The MAH for loratadine-containing medicinal products (Bayer) should submit to the EMA and the national competent authorities in the Member States, in the next PSUR (DLP: 02/02/2017) (PSUSA/00001907/201702) a cumulative review of all cases of

Torsade de pointes/QT prolongation with loratadine. This cumulative review should include a review of spontaneous reports, published literature, epidemiological studies and clinical trials, as well as any relevant preclinical studies. The MAH should discuss the need for any potential amendment to the product information.

4.3.5. Recombinant factor VIII: antihemophilic factor (recombinant) (NAP) moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), KOGENATE (CAP)

Applicant: Baxter AG (Advate, Recombinate), Bayer Pharma AG (Kogenate, Helixate NexGen), Pfizer Limited (ReFacto AF), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of inhibitor development in previously untreated patients (PUP)
EPITT 18134 – Follow-up to January 2016

Background

For background information, see PRAC minutes November 2014, PRAC minutes December 2014, PRAC minutes January 2015, PRAC minutes March 2015, PRAC minutes May 2015 and PRAC minutes of January 2016.

Discussion

The PRAC discussed the assessment of the results of the meta-analysis by the co-Rapporteur for Kogenate (Ulla Wändel Liminga). The PRAC noted that comments on the meta-analysis report were received from the investigators of the studies included in the meta-analysis. The Rapporteur will update the meta-analysis report, considering those comments. The Co-Rapporteur will thereafter provide an updated assessment report. The PRAC will adopt a final recommendation during its April 2016 plenary meeting.

Summary of recommendation(s)

- The PRAC will adopt a final recommendation during its April 2016 plenary meeting.

4.3.6. Tigecycline – TYGACIL (CAP) - EMEA/H/C/000644/SDA/067

Applicant: Pfizer Limited

PRAC Rapporteur: Miguel-Angel Macia

Scope: Signal of hypofibrinogenaemia
EPITT 18479 – Follow-up to November 2015

Background

For background, see PRAC minutes November 2015. The MAH replied to the request for information on the signal of hypofibrinogenaemia and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence from post-marketing cases and the literature, and the data submitted by the MAH, the PRAC

agreed that the product information of Tygacil should be updated to include hypofibrinogenaemia as a new undesirable effect.

Summary of recommendation(s)

- The MAH for Tygacil (tigecycline) should submit to the EMA, within 60 days, a variation to include hypofibrinogenaemia as a new undesirable effect with a not-known frequency.

For the full PRAC recommendations, see EMA/PRAC/135876/2016 published on 11/04/2016 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 14.1.

5.1.1. Allogeneic T cells genetically modified to express suicide gene - EMEA/H/C/002801, Orphan

Applicant: MolMed SpA, ATMP

Scope: Treatment in haploidentical haematopoietic stem cell transplantation

5.1.2. Autologous CD34$^+$ enriched cell fraction that contains CD34$^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence - EMEA/H/C/003854, Orphan

Applicant: GlaxoSmithKline Trading Services, ATMP

Scope: Treatment of severe combined immunodeficiency

5.1.3. Bezlotoxumab - EMEA/H/C/004136

Scope (accelerated assessment): Prevention of *Clostridium difficile* infection (CDI) recurrence

5.1.4. Drisapersen - EMEA/H/C/003846, Orphan

Applicant: BioMarin International Limited

Scope: Treatment of Duchenne muscular dystrophy (DMD)

5.1.5. Emtricitabine, rilpivirine, tenofovir alafenamide - EMEA/H/C/004156

Scope: Treatment of human immunodeficiency virus (HIV)-1

5.1.6. Fluticasone propionate, salmeterol xinafoate - EMEA/H/C/002752; EMEA/H/C/004267

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

5.1.7. Pemetrexed - EMEA/H/C/003895

Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer (NSCLC)

5.1.8. Sofosbuvir, velpatasvir - EMEA/H/C/004210

Scope (accelerated assessment): Treatment of chronic hepatitis C virus

5.2. Medicines in the post-authorisation phase – PRAC-led procedures

See Annex I 14.2.

5.3. Medicines in the post-authorisation phase – CHMP-led procedures

See Annex I 14.3.

6. Periodic safety update reports (PSURs)

6.1. PSUR procedures including centrally authorised products (CAPs) only

See also Annex I 15.1.

6.1.1. Brimonidine – MIRVASO (CAP) - PSUSA/10093/201508 (with RMP)

Applicant: Galderma International

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Background

Brimonidine is a selective alpha$_2$-adrenergic receptor agonist indicated for the symptomatic treatment of facial erythema of rosacea in adult patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mirvaso, a centrally authorised medicine containing brimonidine, 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 Mirvaso (brimonidine) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

- In the next PSUR, the MAH should confirm whether a case number has been assigned to the relevant literature case by *Gillihan R et al.*[9]. The MAH should also provide an assessment of the 'wearing-off effect' taking into consideration the current posology. The MAH should finally provide an evaluation of the impact of including a warning about the occurrence of aggravated erythema, flushing and skin burning sensation and also to advice on treatment discontinuation and management of these conditions.
- The MAH should submit to the EMA, within 60 days, a clear evidence-based summary of the risk-benefit balance. This review should discuss the proportion of patients who benefit from Mirvaso, the magnitude and persistence of the improvement (i.e. clinical relevance) and take into account data from clinical trials (including pre-authorisation randomised clinical trials and more recent data, such as from the MIRACLE study, including information on drop-outs from these studies), post-marketing usage and survey data. This review should also discuss the frequency and severity of adverse reactions, with special emphasis on symptom aggravation and rebound effect, taking into account all relevant study and post-marketing ADR report data. The MAH should weigh the evidence for benefit against harmful effects reported, taking into account the frequency, severity and persistence of effects.
- The MAH should submit to the EMA, within 60 days, a discussion on whether the available evidence supports the use of an initial test dose in order to minimise risk. Details of the advice that could be offered to patients should be discussed. If further data are needed before a variation on test dose could be submitted, the MAH should discuss this, including strategies and timescales for gathering the necessary data. The MAH should provide a detailed discussion of whether any excipient(s) are potentially causing symptom aggravation or rebound and discuss whether the formulation can be adapted to remove relevant excipients without introducing new safety or efficacy issues. If further evidence is needed, the MAH should discuss proposals for collecting the necessary data. Finally the MAH should discuss any other possible risk minimisation strategies, including an outline of product information changes and a plan for their implementation. In case changes to the marketing authorisation annexes are considered necessary, the MAH should submit the appropriate variation.

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. Crizotinib – XALKORI (CAP) - PSUSA/10042/201508

Applicant: Pfizer Limited

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

Crizotinib is a protein kinase inhibitor indicated for the treatment (first line and repeat treatment) of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

[9] Gillihan R, Nguyen T, Fischer R et al. Erythema skin adjacent to area of long-term brimonidine treatment for rosacea: a novel adverse reaction. JAMA Dermatol. Published online June 17, 2015. doi: 10.1001/jamadermatol.2015.1252

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xalkori, a centrally authorised medicine containing crizotinib, 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 Xalkori (crizotinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include that grade 4 visual defect with visual loss has been reported and that treatment should be discontinued during evaluation of severe vision loss in case of grade 4 ocular disorder in the 'Posology and method of administration', 'Special warnings and precautions' and 'Undesirable effects' sections. In addition the product information should be updated to include blood testosterone decreased and oesophagitis as new undesirable effects with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should provide a cumulative review of events of erythema multiforme reported with crizotinib, from post-marketing and clinical trials sources together with a literature review. The MAH should obtain follow up data and the outcome for two cases (to document pregnancies) and provide the health status of the newborn for a third case. In addition the MAH should prepare a summary of cases of pregnancy reported with crizotinib cumulatively: treated females; female partners of treated males; pregnancy outcome (normal outcome; spontaneous miscarriages; birth defect). Moreover, the MAH should discuss new cases of optic neuropathy, blindness, tumour lysis syndrome, rhabdomyolysis, posterior reversible encephalopathy syndrome (PRES), venous thromboembolic events, and provide the relevant CIOMs[11] forms. Finally the MAH should discuss geographic origin of cases of off-label use to try to quantify this in the EU and be more precise especially to put into perspective the patient's cancer status regarding ALK, c-MET/hepatocyte growth factor receptor (HGFR) or ROS1 and the type of cancer. The MAH should discuss whether crizotinib off-label use is driven by molecular considerations.

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. Florbetaben (^{18}F) – NEURACEQ (CAP) - PSUSA/10094/201508

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

[10] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[12] 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

Florbetaben (18F) is a diagnostic radiopharmaceutical indicated for positron emission tomography (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Neuraceq, a centrally authorised medicine containing florbetaben (^{18}F), 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 Neuraceq (florbetaben (^{18}F) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include injection/application site erythema as a new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[12].

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. Lamivudine – ZEFFIX (CAP) - PSUSA/01824/201507

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

Lamivudine is an antiviral agent of the nucleoside analogue reverse transcriptase inhibitor (NRTI) class indicated for the treatment of chronic hepatitis B in adults with compensated liver disease under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zeffix, a centrally authorised medicine containing lamivudine, 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 Zeffix (lamivudine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the switch to or addition of an alternative agent without cross-resistance to lamivudine based on therapeutic guidelines in the 'Posology and method of administration' and 'Special warnings and precautions' sections and to include that maintenance therapy of lamivudine monotherapy is not appropriate in patients with detectable hepatitis B virus (HBV) deoxyribonucleic acid (DNA) at or beyond 24 weeks of treatment in the

[12] 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

'Pharmacodynamic properties' section. Therefore, the current terms of the marketing authorisation(s) should be varied[13].

- In the next PSUR, in particular the MAH should provide the narratives of all cases of pancreatitis reported with lamivudine in HBV-treated patients during the PSUR period. If a relevant case is identified the MAH should provide a cumulative safety review on this issue including literature data, clinical trials and post-marketing data.

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

6.1.5. Linaclotide – CONSTELLA (CAP) - PSUSA/10025/201508

Applicant: Almirall S.A

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Background

Linaclotide is a guanylate cyclase-C receptor agonist (GCCA) with visceral analgesic and secretory activities indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Constella, a centrally authorised medicine containing linaclotide, 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 Constella (linaclotide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include lower gastrointestinal bleeding as a new warning and to include nausea, vomiting and lower gastrointestinal haemorrhage including haemorrhoidal haemorrhage and rectal haemorrhage as new undesirable effects with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[14].
- The MAH should be requested to include 'lower gastrointestinal haemorrhage' as an important identified risk within the next update of the RMP.

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

6.1.6. Pomalidomide – IMNOVID (CAP) - PSUSA/10127/201508 (with RMP)

Applicant: Celgene Europe Limited

[13] Update of SmPC sections 4.2, 4.4 and 5.1. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[14] 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

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Background

Pomalidomide is an immunomodulating agent indicated in combination for the treatment of adult patients with relapsed and refractory multiple myeloma under certain conditions.

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

An oral explanation with the MAH for Imnovid (pomalidomide) took place at the meeting. The MAH presented and discussed evidence relating to the risk of hepatitis B reactivation, and made proposals for risk minimisation during the oral explanation.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Imnovid (pomalidomide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include non-melanoma skin cancer in the existing warning on second primary malignancies and to include basal cell carcinoma of the skin and squamous cell carcinoma of the skin as new undesirable effects with an uncommon frequency. The product information should also be updated to include a new warning on infections and reactivation of hepatitis B and to include as new undesirable effects herpes zoster with a common frequency and hepatitis B reactivation with a not known frequency. Finally the product information should be updated to include gastrointestinal haemorrhage as a new undesirable effect with a common frequency, to specify bacterial, viral and fungal infections, including opportunistic infections under the undesirable effect 'pneumonia' and to include that haemorrhagic disorders have been reported with pomalidomide in the 'Undesirable effects' section. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- Furthermore, the PRAC considered that a direct healthcare professional communication (DHPC) should be distributed to relevant healthcare professionals to inform on the need to establish the hepatitis B status of patients before initiating treatment with pomalidomide as a new precaution for use in agreement with the communication plan.
- In the next PSUR, the MAH should provide an update on recruitment for the PASS (study CC-4047-MM-015) as well as a discussion on the feasibility of meeting the study milestones. The MAH should carefully review new cases of progressive multiple leukoencephalopathy in future PSURs and provide the relevant CIOMS forms.
- The MAH should be requested to update the RMP so that the existing safety concerns of 'infection', 'thrombocytopenia and bleeding' and 'second primary malignancies' include information on viral reactivation (varicella-zoster virus and hepatitis B virus), gastrointestinal haemorrhage and non-melanoma skin cancer, respectively within the next update of the RMP. 'Hepatic impairment' should remain as missing information until the final results of study CC-4047-CP-009 have been reviewed by the CHMP.

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

6.1.7. Vemurafenib – ZELBORAF (CAP) - PSUSA/09329/201508

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Vemurafenib is a protein kinase inhibitor indicated as monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zelboraf, a centrally authorised medicine containing verumafenib, 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 Zelboraf (vemurafenib) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should submit a review of all cases of palmoplantar fibromatosis including Peyronie's disease associated with vemurafenib. The MAH should submit a review on gingival hyperplasia in the next PSUR. In addition, the MAH should submit a full drug safety report on second primary malignancies. The MAH should also discuss the 12 cases of atrial fibrillation from the Phase III study (study NO25026) in previously untreated patients regarding causality taking into account time to onset, and confounding factors. The MAH should discuss the potential drug-drug interaction of vemurafenib with amiodarone and carvedilol through CYP3A4[16] suggested in the WHO newsletter (no. 1, 2016). Moreover, the MAH should also discuss the article by *Bellon T et al.*[17] relating to one case report concerning vemurafenib-induced toxic epidermal necrolysis. Finally, the MAH should finally provide a cumulative review and analysis of cases of enteritis.
- The MAH should be requested to submit to the EMA within 60 days a variation to update the product information to further reflect on hypersensitivity reactions and dermatologic reactions and to include myositis and rhabdomyolysis as consequences of severe hypersensitivity. If the MAH considers that the data does not support the need to vary the marketing authorisation, they should submit a legally binding post authorisation measure (LEG) in which they justify why the data do not necessitate amendments to the product information.

[16] Cytochrome P450 3A4
[17] Bellon T, Lema V, Gonzalez-Valle O et al. Vemurafenib-induced toxic epidermal necrolysis: Possible cross-reactivity with other sulphonamide compounds. Br J Dermatol. 2015 Sep 28. doi: 10.1111/bjd.14201.

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

6.2. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

See also Annex I 15.2.

6.2.1. Pioglitazone - ACTOS (CAP), GLUSTIN (CAP), NAP; pioglitazone, glimepiride – TANDEMACT (CAP); pioglitazone, metformin - COMPETACT (CAP), GLUBRAVA (CAP) - PSUSA/02417/201507

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Pioglitazone is a thiazolidinedione, indicated alone or in combination with glimepiride, a sulfonylurea antidiabetic or with metformin, a biguanide, and is indicated in the treatment of type 2 diabetes mellitus under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Actos and Glustin, centrally authorised medicines containing pioglitazone, and nationally authorised medicines containing pioglitazone, of Tandemact, a centrally authorised medicine containing pioglitazone and glimepiride and of Competact and Glubrava, centrally authorised medicines containing pioglitazone and metformin, 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 pioglitazone-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include that post-marketing bone fractures have been reported in both and female patients in the 'Undesirable effects' section with a cross-reference to the 'Special warnings and precautions' section. Therefore the current terms of the marketing authorisations should be varied[18].
- In the next PSUR, the MAH should review the finding from the non-clinical study in rats from *Ayuob et al.*[19] which investigated the effects of pioglitazone, metformin or sitagliptin on the structure of the male reproductive system and showed that histological structure and estrogen receptor (ER) and androgen receptor (AR) expression were significantly and adversely affected with all studied drugs and advised avoidance of pioglitazone and sitagliptin in young male diabetic patients. The MAH

[18] 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

[19] Ayuob NN, Murad HA, Ali SS. Impaired expression of sex hormone receptors in male reproductive organs of diabetic rat in response to oral antidiabetic drugs. Folia Histochem Cytobiol 2015;53(1):35-48.

should review this finding with respect to the cumulative relevant data available for pioglitazone and report in the next PSUR if there is any clinical relevance.

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.

6.3. PSUR procedures including nationally authorised products (NAPs) only

See also Annex I 15.3.

6.3.1. Albendazole (NAP) - PSUSA/00000073/201507

Applicant: various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Albendazole is a benzimidazole carbamate with anthelmintic and antiprotozoal activity licensed for the treatment of intestinal and tissue parasites (including cutaneous larva migrans).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing albendazole, 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 albendazole-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should include 'neurological disorders' as a potential risk in the summary of safety concerns and submit a detailed analysis of nervous system disorders and psychiatric disorders.
- The MAHs which have an RMP update should be requested in the next RMP update to include 'neurological disorders' as an important potential 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.

6.3.2. Chloroquine (NAP) - PSUSA/00000685/201508

Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Chloroquine is a 4-aminoquinoline derivative used in the treatment and prophylaxis of malaria and polymorphous light eruptions, systemic lupus erythematosus, rheumatoid arthritis and amebiasis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing chloroquine, 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 chloroquine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on prolongation of the QTc interval and on cardiomyopathy in the 'Special warnings and precautions' section, to include that chloroquine should be used with caution with drugs known to prolong QT interval or with the potential to induce cardiac arrhythmias in the 'Interaction with other medicinal products and other forms of interaction' section, to include as new undesirable effects 'cardiomyopathy' with a rare frequency, 'atrioventricular block', 'QT prolongation' with an unknown frequency and finally that cardiovascular adverse reactions may occur with serious intoxication in the 'Overdose' section. Therefore the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAHs should continue to closely monitor cases of toxic epidermal necrolysis (TEN) and all new cases should be presented. The MAH should also present all new cases of congenital anomaly-hearing disorder following administration of chloroquine for malaria prophylaxis to the mother.

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.

6.3.3. Everolimus (indicated for rejection of transplanted organs) (NAP) - PSUSA/00010269/201507

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant and in patients receiving a hepatic transplant.

[20] Update of SmPC sections 4.4, 4.5, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing everolimus (indicated for rejection of transplanted organs), 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 everolimus-containing medicinal products (indicated for rejection of transplanted organs) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the potential for everolimus to cause infertility in male and female patients in the 'Fertility, pregnancy and lactation' section and to include as new undesirable effects 'menstrual disorders (including amenorrhoea and menorrhagia)' with a common frequency and 'ovarian cyst' with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].

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.

6.3.4. Paracetamol, tramadol (NAP) - PSUSA/00002310/201508

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

Paracetamol is a para-aminophenol derivative with analgesic and antipyretic properties and tramadol is an opioid which acts on the central nervous system. The oral combination is indicated for the symptomatic treatment of moderate to severe pain in adults and children above 12 years of age.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of medicinal products containing paracetamol and tramadol in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to refine existing information on breast-feeding and excretion of tramadol into breast-milk in the 'fertility, pregnancy and lactation' section. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, all the MAHs should provide a cumulative review and analysis (including narratives) of the cases reported for paracetamol / tramadol-containing products and a literature review for the following ongoing signals: adverse drug reactions reported in ultra-rapid CYP2D6 metabolisers, hyponatremia, drug exposure in

[21] 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 CMDh for adoption of a position
[22] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

pregnancy, hiccups, miosis, mydriasis, speech disorder, syncope, interaction with some antiepileptics and rifampicin, interaction with flucloxacillin, and interaction with phenylephrine.

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.

6.3.5. Thiocolchicoside (NAP) - PSUSA/00002927/201507

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Thiocolchicoside is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity indicated as an adjuvant for the treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16-years onwards.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing thiocolchicoside, 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 thiocolchicoside-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information of systemic formulations of thiocolchicoside-containing medicinal products should be updated to include a warning that post-marketing cases of liver injury have been reported with thiocolchicoside and a warning that convulsion can occur in particular in patients with epilepsy or at risk for seizures. In addition the product information of systemic formulations of thiocolchicoside-containing medicinal products should be updated to include as new undesirable effects 'anaphylactic reactions', 'drug-induced liver injury' and 'convulsions' with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAHs should continue to closely monitor any safety signal correlated with aneuploidy (i.e. teratogenicity, embryo-foetal toxicity / spontaneous abortion, impaired male fertility and cancer) and pregnancy reporting, to collect structured data on accidental exposure to the drug and provide a report about this in the future PSURs.

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.

[23] 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 CMDh for adoption of a position

6.3.6. Trimetazidine (NAP) - PSUSA/00003043/201508

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Trimetazidine (TMZ) is currently 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.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing trimetazidine, 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 trimetazidine-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should continue to closely monitor extrapyramidal symptoms, choreiform movements, and chorea. In addition the MAHs should closely monitor and discuss reported cases of patients with a known medical history of renal impairment and patients with coagulation disorders (including haemorrhage and stroke), extrapyramidal symptoms and falls, orthostatic hypotension/hypotension, hyponatremia and confusional state, parkinsonian symptoms (parkinsonism, extrapyramidal disorders, gait disturbance (particularly in elderly patients more than 75 years old)) and vertigo.

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.

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 15.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[24]

See also Annex I 16.1.

7.1.1. Afamelanotide – SCENESSE (CAP) - EMEA/H/C/PSP/0022.1.A.1

Applicant: Clinuvel (UK) Limited

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

PRAC Rapporteur: Valerie Strassmann

Scope: Revised PASS protocol for study CUV-PA001: disease registry to assess long-term safety and generate data on the clinical benefits of afamelanotide 16 mg implant in patients with erythropoietic protoporphyria (EPP)

Background

Scenesse is a centrally authorised medicine containing afamelanotide. It is indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

The PRAC adopted the draft protocol for a disease registry to assess long term safety data and outcome endpoints and generate data on the clinical benefits of afamelanotide 16 mg implant in patients with EPP in September 2015. Following a commitment to pre-test the Questionnaire named Daily Activity Inventory and to submit a statistical analysis plan for further evaluation 3 months after the approval of the protocol, the MAH submitted a substantial protocol amendment for this study to the PRAC.

Endorsement/Refusal of the protocol

The PRAC, having considered the amended protocol in accordance with Article 107o of Directive 2001/83/EC, endorsed by consensus the substantial amendments to the PASS protocol for the above listed medicinal product.

The PRAC also noted the status of submission and review of the educational materials and controlled access programme at a national level in different Member States.

7.1.2. Ferric citrate coordination complex – FEXERIC (CAP) - EMEA/H/C/PSP/0038

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Draft protocol for a non-interventional observational post-authorisation study to assess the safety of Fexeric as a phosphate binder in routine clinical practice

Background

Fexeric is a centrally authorised medicine containing ferric citrate coordination complex. It is indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD).

A protocol for a non-interventional observational PASS to assess the safety of Fexeric as a phosphate binder in routine clinical practice was submitted by the MAH in accordance with the conditions of the marketing authorisation(s).

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product, as the Committee considered that that the design of the study did not fulfil the study objectives. The PRAC noted that the MAH had not included a comparator arm as is currently required according to the current condition to the Marketing Authorisation. The PRAC noted and endorsed the arguments provided by the MAH as to why inclusion of a comparator arm was unlikely to better inform the PRAC's understanding of the risks with Fexeric. In particular, the MAH put forward the heterogeneity of the patient population treated with phosphate binders with

considerable variation amongst patients and different products used per region/country. The MAH also put forward that the selection bias with Fexeric patients likely to be refractory to other phosphate binders and also that treatment selection influenced by undocumented variables (preference, history of symptoms/ medical conditions and tolerability issues). Moreover, the MAH emphasized issues in capturing accurate exposure data given complex treatment regimen with interruptions, dose changes and treatment cross over, as well as the use of iron supplements even in the comparator arm. Before submitting a revised PASS protocol, the MAH should submit an appropriate variation to amendment the condition to the Marketing Authorisation as follows: 'Non-interventional long-term post-authorisation safety study (PASS): prospective, observational, multicentre in CKD patients treated with Fexeric in order to gain long term (2 years) safety data (including iron overload events, infective and gastrointestinal events) particularly in EU patients, elderly and very elderly patients, dialysed and non-dialysed patients in addition reflecting the specific risks in subgroups of serum ferritin levels >500 ng/ml and in patients in the range 200 to <500 ng/ml'.

- The PRAC agreed that the study should start in the EU first to ensure that 70% of the study population is from EU countries. The draft protocol should be amended to stratify the incidence rates of adverse events by country to assess any variation, to include a sub-group analysis to look at incidence rates of adverse events in the group of patients who have participated in previous Fexeric clinical trials and to amend the inclusion criteria in line with the approved indication. The MAH should specify the intended countries of study conduct in the revised study protocol. The PRAC therefore recommended that:
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied.

7.1.3. Ketoconazole – KETOCONAZOLE HRA (CAP) - EMEA/H/C/PSP/0040

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Drat protocol for a post-authorisation safety study: a multi-country, observational registry to collect clinical information on patients with Cushing syndrome patients exposed to ketoconazole (preferably using the existing European Registry on Cushing's syndrome (ERCUSYN) registry), to assess drug utilisation patterns and to document the safety and effectiveness of ketoconazole

Background

Ketoconazole HRA is a centrally authorised medicine containing ketoconazole, a steroidogenesis inhibitor, indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

A protocol for a multi-country, observational registry (PASS) to collect clinical information on patients with Cushing Syndrome exposed to ketoconazole (preferably using the existing European Registry on Cushing's syndrome (ERCUSYN) where feasible), to assess drug utilisation patterns and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole, was submitted by the MAH in accordance with the conditions to the marketing authorisation(s).

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 3 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal products, as the Committee considered that that the design of the study did not fulfil the study objectives. A number of concerns regarding the milestones, the endpoints, the expected product launch, the inclusion and exclusion criteria, the definition of exposures, outcomes and other variables, the case report forms, the study power for detecting patients with QTc prolongation, concomitant medication, handling of missing information, the statistical analysis plan, confounders and biases should be resolved before the final approval of the study protocol. The PRAC therefore recommended that:
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied.

7.1.4. Thiocolchicoside (NAP) - EMEA/H/N/PSP/j/0030.1

Applicant: Sanofi-Aventis Recherche & Développement and other companies involved in the consortium

PRAC Rapporteur: Amelia Cupelli

Scope: Revised protocol for a drug utilisation study to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription

Background

Thiocolchicoside is a semi-synthetic sulfurated colchicoside derivative indicated for the treatment of painful muscular contractures in different settings in rheumatological and/or orthopaedic conditions.

A revised protocol for a post-authorisation safety study (drug utilisation study) to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess the main reasons for prescription of thiocolchicoside, was submitted to the PRAC by a consortium of MAHs in accordance with the conditions to the marketing authorisation included in the EC decision (Annex IV) for the referral under Article 31 of Directive 2001/83/EC (EMA/H/A-31/1361) for thiocolchicoside-containing medicines. For further background, see PRAC minutes September 2015 and PRAC minutes October 2015.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 2.1 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal products, as the Committee considered that that the design of the study did not fulfil the study objectives. A number of concerns regarding the database study (on data management and the provision of an operational definition of off-label use, gaining access to prescription databases available through the Portuguese national competent authority) and regarding the survey (on the management and reporting of adverse events) should be resolved before the final approval of the study protocol. The PRAC therefore recommended that:
- The MAHs should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied.

7.1.5. Tolvaptan – JINARC (CAP) - EMEA/H/C/PSP/0028.2

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Revised PASS protocol for a prospective study of the safety of tolvaptan in autosomal dominant polycystic kidney disease (ADPKD) patients with an additional retrospective component to assess for risks associated with long term use

Background

Jinarc is a centrally authorised medicine containing tolvaptan. It is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.

A revised protocol for a non-interventional PASS was submitted by the MAH in accordance with the conditions to the marketing authorisation(s), to investigate the risks of hepatotoxicity, basal cell carcinoma, glaucoma associated with the use of Jinarc and to provide information on pregnancy outcomes in patients treated with Jinarc, patterns of drug utilisation, especially with regards to off-label use and use in patients over 50 years old, and adverse drug reactions associated with long term use.

For further background, see PRAC minutes July 2015 and PRAC minutes November 2015.

Endorsement/Refusal of the protocol

- The PRAC, having considered the joint draft protocol versions B and C in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for the PASS study for the above listed medicinal product.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[25]

See Annex I 16.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[26]

None

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

See also Annex I 16.4.

7.4.1. Abacavir – ZIAGEN (CAP) - EMEA/H/C/000252/WS/0769 lamivudine – EPIVIR (CAP) - EMEA/H/C/000107/WS/0769, LAMIVUDINE VIIV (Art 58[28]) - EMEA/H/W/000673/WS/0769 lamivudine, abacavir – KIVEXA (CAP) - EMEA/H/C/000581/WS/0769

[25] 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
[26] In accordance with Article 107p-q of Directive 2001/83/EC
[27] 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
[28] Article 58 of Regulation (EC) No 726/2004 allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO), on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

lamivudine, abacavir, zidovudine – TRIZIVIR (CAP) - EMEA/H/C/000338/WS/0769 lamivudine, zidovudine – COMBIVIR (CAP) - EMEA/H/C/000190/WS/0769 (without RMP)

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Isabelle Robine

Scope: Submission of final clinical study report (CSR) for mitochondrial toxicity in children (MITOC) study (WE027/WWE112888). The MAH took also the opportunity to respond to a LEG on mitochondrial dysfunction to address the request on revision of class labelling of antiretrovirals on mitochondrial toxicity

Background

Combination antiretroviral therapy (cART) consists of any combination regimen of antiretroviral medicines that include nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs), with non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs) or integrase inhibitors for the treatment of patients affected by the human immunodeficiency virus (HIV-1).

In the context of the reviews initiated in July 2014 evaluating new evidence with respect to mitochondrial toxicity, lactic acidosis and lipodystrophy associated with antiretroviral medicines, the PRAC concluded the review on lactic acidosis and lipodystrophy in October 2015 and provided advice to the CHMP. For further background, see PRAC minutes October 2015.

The class labelling wording on mitochondrial toxicity was introduced 10 years ago in the relevant product information following a signal raised on cases of mitochondrial dysfunction in HIV negative children following exposure in utero. During that review, the need for a cohort at the EU level was established to explore the issue. An observational study entitled 'Mitochondrial Toxicity in Children (MITOC)' study was set up accordingly.

In the context of the evaluation of a type II work-sharing variation procedure on the results of the ongoing MITOC study, the PRAC discussed these results together with further analysis from the MAH of existing data on mitochondrial dysfunction. For further background, see PRAC minutes September 2015 and PRAC minutes January 2016.

Summary of advice

- Based on the assessment of the available non-clinical and clinical data and given the significant limitations of the MITOC study, in particular, the inconclusive results relating to the prevalence of unexplained neurological symptoms and the association between NRTI exposures in utero or the post-natal period and mitochondrial disorders, the PRAC concluded that the class labelling wording currently in place should be maintained. Nevertheless, the PRAC considered that minor revisions of the wording should be implemented to reflect the current scientific knowledge, especially the variable degree of mitochondrial dysfunction caused by nucleoside and nucleotide analogues, namely zidovudine, stavudine (and also didanosine) with the highest potency for inhibition of mitochondrial function.

See also under 10.1.1.

7.4.2. Tacrolimus – PROTOPIC (CAP) - EMEA/H/C/000374/II/0063

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final clinical study report of the non-interventional, registry PASS study JOELLE (JOint European Longitudinal Lymphoma and skin cancer Evaluation) final results. The RMP was updated accordingly

Background

Topical tacrolimus is a calcineurin inhibitor. It is indicated for the flare (second-line to topical corticosteroids) and maintenance treatment of moderate to severe atopic dermatitis. It is not to be used in children less than 2 years of age.

The MAH for Protopic (tacrolimus) committed to perform the following non-interventional PASS: the JOELLE (JOint European Longitudinal Lymphoma and skin cancer Evaluation) study to assess the risk of malignancies in adults and children using 4 European population healthcare databases, as listed in the RMP. The Rapporteur assessed the final results of the JOELLE study.

Summary of advice

- The PRAC discussed the final results from the JOELLE study. The primary objective of this study was to evaluate the risk of lymphoma, malignant melanoma and non-melanoma skin cancer (NMSC) among paediatric and adult users of topical tacrolimus and of topical pimecrolimus compared with paediatric and adult users of topical moderate-high potency corticosteroids. From 4 European population healthcare databases (PHARMO in the Netherlands, CPRD in the UK, Danish databases and Swedish databases), 19,948 paediatric and 66,127 adult new users of topical tacrolimus were identified, who were matched at a 1:4 ratio to paediatric and adult users of moderate-to-high potency topical corticosteroids, respectively. Similarly paediatric and adult new users of topical pimecrolimus were matched to users of moderate-high potency topical corticosteroids. Matching was based on propensity scores, which included a large number of variables associated with the outcomes of interest to address potential residual confounding. The pooled corrected incidence rate ratios (IRR) indicated an almost fourfold increased rate of lymphoma among paediatric users of topical tacrolimus compared with paediatric users of topical corticosteroids (pooled IRR 3.74 95% CI 1.00-14.06). However, there was only a small and non-significant excess of lymphoma among children using topical tacrolimus (7.9 events 95% CI -1.1-16.9 per 100,000 person-years of follow-up). Results among paediatric users of topical pimecrolimus were less noteworthy, as the IRR for lymphoma was non-significant (pooled corrected IRR 1.07 95% CI 0.25-4.60). Among adult users of topical tacrolimus compared with adult users of topical corticosteroids the pooled corrected IRR for lymphoma was non-significantly increased, although the rate difference indicated a small but significant excess of lymphoma (12.7 events 95% CI 2.4-22.9 per 100,000 person-years of follow-up). The predominant subtype of lymphoma among adult users of topical tacrolimus was cutaneous T-cell lymphoma, of which there was a small but significant excess rate (5.8 events 95% CI 1.2-10.4 per 100,000 person-years of follow-up). Among adults using topical pimecrolimus, the pooled corrected IRR and adjusted rate difference for lymphoma were both non-significant. With regard to cutaneous malignancy, there was a significant excess of non-melanoma skin cancer

among adults using topical tacrolimus (34.2 events 95% CI 3.5-64.9 per 100,000 person-years of follow-up) and adults using topical pimecrolimus (93.6 events 95% CI 60.9-126.2 per 100,000 person-years of follow-up). The PRAC noted however some inherent limitations of the study: the possibility of multiplicity; inadequate power due to the rarity of outcomes especially among children; approximations of dose; confounding by indication given that topical tacrolimus is a second-line treatment for atopic dermatitis; inclusion of prevalent users resulting in healthy adherer effect; and residual confounding particularly due to lack of information on sun-related risk factors associated with cutaneous malignancy. Nonetheless; the duration-response relationships observed in the study among adult users of topical tacrolimus for the outcomes lymphoma and cutaneous T-cell lymphoma appear to be somewhat consistent with observations from pre-clinical studies. Additionally, the results of the study appear to be supportive of information in relation to a possible association with malignancy contained in the Protopic SmPC. Finally, the study highlighted a number of patterns of use, including some ongoing use of topical tacrolimus in children under the age of 2 years, as a first line agent, and in off-label indications; and use as maintenance treatment among some children for longer than the recommended 12 months.

- Considering these results, the PRAC agreed on a list of questions to the MAH. This will include a discussion of current drug utilisation data in relation to the patterns of use highlighted by the PASS in the next PSUR for topical tacrolimus.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[29]

See Annex I 16.5.

7.6. Others

See Annex I 16.6.

7.7. New Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

7.8. Ongoing Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

7.9. Final Scientific Advice (Reports and Scientific Advice letters)

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

See also Annex I 16.9.

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

8. Renewals of the marketing authorisation, conditional renewal and annual reassessments

8.1. Annual reassessments of the marketing authorisation

None

8.2. Conditional renewals of the marketing authorisation

See Annex I 17.2.

8.3. Renewals of the marketing authorisation

See Annex I 17.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the agenda.

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/WS/0792 elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP) - EMEA/H/C/002574/WS/0792 emtricitabine – EMTRIVA (CAP) - EMEA/H/C/000533/WS/0792 emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/WS/0792 emtricitabine, tenofovir disoproxil – TRUVADA (CAP) - EMEA/H/C/000594/WS/0792 tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/WS/0792

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd., Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.4 of the SmPC in order to delete the human immunodeficiency virus (HIV) class label wording for mitochondrial dysfunction following the review of existing data on mitochondrial toxicity including the Mitochondrial Toxicity in Children (MITOC) study. The Package Leaflets for Viread, Truvada and Emtriva are updated accordingly

Background

Combination antiretroviral therapy (cART) consists of any combination regimen of antiretroviral medicines that include nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs), with non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs) or integrase inhibitors for the treatment of patients affected by the human immunodeficiency virus (HIV-1).

The class labelling wording on mitochondrial toxicity was introduced 10 years ago in the relevant product information following a signal raised on cases of mitochondrial dysfunction in HIV negative children following exposure in utero. During that review, the need for a cohort at the EU level was established to explore the issue. An observational study entitled 'Mitochondrial Toxicity in Children (MITOC)' study was set up accordingly.

In the context of the reviews initiated in July 2014 evaluating new evidence with respect to mitochondrial toxicity, lactic acidosis and lipodystrophy associated with antiretroviral medicines, the PRAC concluded the review on lactic acidosis and lipodystrophy in October 2015 and provided advice to the CHMP. For further background, see PRAC minutes October 2015.

In the context of the evaluation of a type II work-sharing variation procedure on the review of the existing data on mitochondrial toxicity including results from the Mitochondrial Toxicity in Children (MITOC) study together with further analysis from the MAH of existing data on mitochondrial dysfunction, the CHMP requested PRAC advice. For further background, see PRAC minutes September 2015 and PRAC minutes January 2016.

Summary of advice

- Based on the assessment of the available non-clinical and clinical data and given the significant limitations of the MITOC study, in particular, the inconclusive results relating to the prevalence of unexplained neurological symptoms and the association between NRTI exposures in utero or the post-natal period and mitochondrial disorders, the PRAC concluded that the class labelling wording currently in place should be maintained. Nevertheless, the PRAC considered that minor revisions of the wording should be implemented to reflect the current scientific knowledge, especially the variable degree of mitochondrial dysfunction caused by nucleoside and nucleotide analogues[30].

See also under **Error! Reference source not found.**

10.1.2. Posaconazole – NOXAFIL (CAP) - EMEA/H/C/000610/II/0044

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.2 of the SmPC in order to strengthen the information about non-interchangeability of the oral formulations based on new reports of medication errors related to confusion between posaconazole tablets and oral suspension in prescribing. The Package Leaflet and the RMP are updated accordingly

Background

[30] Namely zidovudine, stavudine (and also didanosine) with the highest potency for inhibition of mitochondrial function

Posaconazole is a lanosterol 14α-demethylase (CYP51) inhibitor indicated for the treatment of fungal infection in adults (invasive aspergillosis, fusariosis, chromoblastomycosis and mycetoma, coccidioidomycosis as well as oropharyngeal candidiasis under certain conditions). It is also indicated for the prophylaxis of invasive fungal infections in patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) as well as in hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease under certain conditions.

A type II variation proposing to update the product information of Noxafil is under evaluation at the CHMP in order to strengthen the wording on non-interchangeability of the oral formulations based on new reports of medication errors related to confusion in prescribing posaconazole tablets and oral suspension. The PRAC was requested to provide advice on this variation, beyond the RMP solely. See also under **Error! Reference source not found.**

Summary of advice

- The PRAC considered that the MAH's proposed changes in the product information wording are not sufficient to minimise the risk of medication errors concerning the substitution of the two oral formulations of Noxafil. Therefore, the PRAC proposed further amendments to highlight differences between the two formulations in terms of dose, frequency of dosing and administration in relation to food. The PRAC also advised further improvements to the outer packaging of both the tablet and oral suspension presentations in order to highlight that they are not to be used interchangeably, and to improve visual differentiation of the two formulations. Furthermore, the PRAC recommended that for the tablet formulation, the foil on the blister strips should include the following above each blister cavity: name, dosage, batch number and expiry date. Moreover, the PRAC considered that the distribution of a Direct Healthcare Professional Communication (DHPC) is necessary to communicate on the non-interchangeability of Noxafil tablets and Noxafil oral suspension.
- The PRAC also considered that the proposed updates to the RMP are acceptable providing the MAH removes the word 'potential' from the identified risk of 'medication errors related to potential substitution between different formulations (tablet and oral suspension)'.

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

None

10.3. Other requests

None

10.4. Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

12.2.1. Joint Paediatric Committee (PDCO)-PRAC Working Group – summary of the joint PDCO-PRAC strategic review and learning meeting, 28-29 May 2015

PRAC lead: June Raine

At the organisational matters teleconference held on 31 March 2016, the PRAC was presented with a report of the joint PRAC-PDCO session on pharmacovigilance held at the May 2015 strategic and learning meeting in Langen, Germany, summarizing the action points agreed during the session. The PRAC agreed to the proposed review of the mandate of the joint PDCO/PRAC WG, and to plan an appropriate meeting schedule. The PRAC also agreed with exploring strategies to facilitate the interactions between PRAC and PDCO, focussing on RMP assessment and paediatric issues, to plan a presentation at PRAC of PDCO-related topics of mutual relevance in order to further enhance collaboration, and to plan a stocktake on delivered improvements. In line with the PRAC work plan 2016, the PRAC will further support the ongoing revision of the 'Guideline on conduct of pharmacovigilance for medicines used by the paediatric population' as well as the work of the PDCO/PRAC working group. A call for nomination to join the PDCO/PRAC working group alongside Jolanta Gulbinovič was made.

12.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

12.3.1. Scientific Advice Working Party (SAWP) – consultation procedure: criteria and process

As a follow-up to the February 2016 PRAC preliminary discussion (see PRAC minutes February 2016) on a proposal for PRAC consultation on scientific advice outside the ongoing pilot for non-imposed post-authorisation studies, the EMA informed the PRAC of the organisation of break-out sessions[31] in the margins of the April 2016 PRAC meeting in order

[31] To be organised with PRAC delegates and relevant EMA staff

to discuss a process and criteria to involve PRAC in the scientific advice procedure when pharmacovigilance (e.g. RMP and PASS planning) questions are posed. Further updates will be provided in due course.

12.4. Cooperation within the EU regulatory network

12.4.1. EMA reflection paper on extrapolation across age groups

PRAC lead: Jolanta Gulbinovič
As announced in January 2016 (see PRAC minutes January 2016), the EMA presented to the PRAC for adoption the draft consolidated EMA extrapolation reflection paper across age groups, following agreement at the level of the CHMP Biostatistics Working Party, Modelling and Simulation Working Group, Pharmacokinetic Working Party (PKWP) and Scientific Advice Working Party (SAWP). The PRAC adopted the reflection paper for release for public consultation. Following adoption at the PDCO and CHMP, the reflection paper will be published on the EMA website for public consultation. The PRAC was also reminded that the 'Workshop on extrapolation of efficacy and safety in medicine development across age group' will take place on 17-18 May 2016.

Post-meeting note: On 1 April 2016, the draft 'Reflection paper on extrapolation of efficacy and safety in paediatric medicine development' (EMA/199678/2016) was released on the EMA website. After the workshop in May 2016, the draft will be finalised and released for public consultation.

12.4.2. Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE)

At the organisational matters teleconference held on 31 March 2016, the PRAC was presented with an update on the SCOPE Joint Action project initiated by the European Commission following the implementation of the revised EU pharmacovigilance legislation in 2012 to help medicines regulators to operate pharmacovigilance systems to the EU legislative requirements. EU Regulators are collaborating to share expertise and best practice, to deliver practical tools and guidance and to operate pharmacovigilance efficiently in Europe. A description of the eight Work Packages (WP)[32] was presented with their deliverables, timelines and planned training together with an overall sustainability plan (including a 6-month extension of the project until April 2017). The PRAC discussed the possibility to use the EU Network Training Centre (EU NTC) platform to ensure that relevant training materials can be shared within the EU regulators network and discussed possible ways forward to ensure that a maintenance structure is in place to keep these training materials up-to-date and ensure links are made with relevant initiatives and enhance GVP modules. The PRAC welcomed receiving regular updates on the progress of SCOPE.

12.5. Cooperation with International Regulators

None

[32] WP1: Governance; WP2: Dissemination; WP3: Evaluation; WP4: ADR collection; WP5: Signal management; WP6: Risk communications; WP7: Quality management systems; WP8: Lifecycle pharmacovigilance

12.6. Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections - inspectors/assessors' collaboration and sharing of pharmacovigilance inspection information

In line with the EU pharmacovigilance legislation[33], GVP Module III on 'Pharmacovigilance inspections' states that *'a common repository, accessible to all Member States, the Agency and the Commission, should be created to facilitate this information sharing on pharmacovigilance inspections'*. The common repository[34] for pharmacovigilance inspection reports has been tested by the EMA and NCAs inspectors as part of a pilot phase. At the current PRAC meeting, the EMA secretariat informed the Committee that the repository had successfully passed its pilot phase and was ready to be extended to PRAC delegates/ assessors and the European Commission as of April 2016 in order to standardise and strengthen the communication between interested parties. To this purpose, the EMA secretariat proposed to set up a subgroup gathering members from the Pharmacovigilance Inspectors Working Group and pharmacovigilance assessors from NCAs in order to support the development and updating of guidance documents of common interest and to provide recommendations and advice on topics referred to the subgroup and/or on topics of common interest to inspectors and assessors. The EMA secretariat launched a call for nominations to participate in this subgroup. The PRAC delegates will be invited by email to send any nominations to participate in the subgroup by 10/05/2016. Further information on the subgroup meeting's planned format and frequency of subgroup meetings will be also shared with the PRAC together with a draft mandate.

12.9.3. Pharmacovigilance audits

None

[33] Article 111(1) of Directive 2001/83/EC
[34] EMA's Managing Meeting Documents system (MMD) selected as the common repository, until a system is in place for the EU Member States to be able to update directly their information and upload documents to be shared within the EU network

12.10. Periodic safety update reports (PSURs) & Union reference date (EURD) list

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst; Margarida Guimarães

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and welcomed the progress being made.

12.10.3. PSUR action group - roadmap for PSUR issues: draft outcome and next steps

PRAC lead: Almath Spooner; Jolanta Gulbinovic; Margarida Guimaraes; Menno van der Elst

Following the February 2016 PRAC discussion (see PRAC minutes February 2016) on the outcome of the workshop of the joint PRAC /CMDh PSUR action group action group held in January 2016 and the resulting 'draft joint PRAC/CMDh recommendation paper on a common understanding on the EU PSUR single assessment for nationally authorised products', the EMA secretariat presented to PRAC the key recommendations further agreed at the CMDh and PRAC Strategic Review and Learning Meetings held in Utrecht, Netherlands in early March 2016. The PRAC was also presented with a calendar detailing the planned steps for the proposed implementation activities. The PRAC welcomed the substantial progress being made and further discussion is scheduled in April 2016.

12.10.4. PSURs repository

None

12.10.5. Union reference date list – consultation on the draft list

The PRAC endorsed the draft revised EURD list version March 2016 reflecting the PRAC comments impacting on the DLP and PSUR submission frequencies of the substances/combinations.
The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting in March 2016, the updated EURD list was adopted by the CHMP and CMDh at their March 2016 meetings and published on the EMA website on 07/04/2016, see:

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

12.11. Signal management

12.11.1. Signal management – feedback from Signal Management Review Technical (SMART) Working Group

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the March 2016 SMART Working Group (SMART WG) work stream WS1. The SMART WG WS1 had been updated on SCOPE[35] Work Package 5 on Signal Management examining processes in place at NCAs and EU levels and aiming at elaborating recommendations in this field. A best practice guide from WP5 is expected at the end of March 2016 and will be shared with PRAC for comments. It was underlined that GVP module IX on signal management will be impacted by the best practice guide. Draft revision 1 of GVP module IX as well as GVP IX – Addendum I on 'Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions' are planned for PRAC discussion in April 2016, with the aim to adopt them in May/June 2016 before their release on the EMA website for public consultation. As a follow-up from February 2016 (see PRAC minutes February 2016), the SMART WSG WS1 also continued its discussion on homeopathic medicinal products, traditional herbal medicinal products and PRAC recommendations for signals follow-up, and concurred that PRAC recommendations made in the context of signal assessments should not cover such products (respectively authorised under Article 14 and Article 16a of Directive 2001/83/EC). The MAHs of homeopathic medicinal products and of traditional herbal medicinal products should consider product information updates based on scientific grounds and NCAs may also consider actions at national level as appropriate. The SMART WG WS 1 agreed to revisit this position within 3 years as needed and in the light of the experience gained.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products - collecting and reporting information on off-label use - discussion paper

As a follow-up to previous PRAC discussions (see PRAC minutes July 2015 and PRAC minutes December 2015), the EMA secretariat updated the PRAC on the status of the discussion paper (previously known as Q&A) developed to address the Industry's questions on MAH's management of reports of off-label use with medicinal products that do not result in harm to patients. The draft paper incorporates the legal interpretation of the requirements pursuant to Article 23(2) of Directive 2001/83/EC and previous PRAC comments. Following further discussion and points for clarifications, the EMA secretariat plans to finalise the document with a final agreement from the European Commission, include a cover note to inform relevant GVP modules and to release it on the EMA website for public consultation.

Post-meeting note: On 29 April 2016, the reflection paper on 'collecting and reporting information on off-label use in pharmacovigilance' (EMA/293194/2016) was published on the EMA website for a 3-month-public consultation.

[35] Strengthening Collaborations for Operating Pharmacovigilance in Europe

12.12.2. Management and reporting of adverse reactions to medicinal products – guidance Additional monitoring

None

12.12.3. List of products under additional monitoring – consultation on the draft list

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

Post-meeting note: The updated additional monitoring list was published on 30/03/2016 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

12.14.2. Tools, educational materials and effectiveness measurement of risk minimisations

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

12.15.2. Post-authorisation Safety Studies – non-imposed PASS

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public hearings - draft rules of procedure

Following the 2014 public consultation on the draft Rules of Procedure (RoP) for Public hearings, further discussion at various fora in 2015 (including PRAC, Heads of Medicines Agencies (HMA), EMA Management Board, EMA Scientific Coordination Board (SciCoBo)) (see PRAC minutes May 2015) as well as the feedback from the European Commission, the EMA secretariat prepared an impact assessment including a retrospective analysis of safety related referral procedures further discussed at the HMA and European Commission levels. At the current meeting, the EMA secretariat presented the draft revised RoP together with the impact assessment in order to identify any outstanding issues before final adoption of the RoP at the March 2016 EMA Management Board and at the April 2016 PRAC meeting. In April 2016, the EMA Secretariat will present to PRAC further details on the organisation of a 'mock-up' (or 'dry-run') public hearings planned in July 2016.

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. EMA emergency notification system

The EMA Secretariat updated the PRAC on the EMA emergency notification system, a service that can simultaneously and rapidly reach a group of people (i.e. CHMP, PRAC, CAT) to provide information and/or instructions in case of emergency situations. A test is to be conducted in the course of 2016 to ensure that the notification system is running efficiently.

12.20.2. Initial marketing authorisation(s) - revised accelerated assessment procedural timetables – follow up

PRAC lead: Ulla Wändel Liminga

As a follow-up to the January 2016 PRAC discussion (see PRAC minutes January 2016), Ulla Wändel Liminga together with EMA secretariat presented to PRAC further details relating to the proposed revised procedural timetable for the evaluation of marketing authorisation applications under accelerated assessment, giving particular emphasis to the need for early dialogue with PRAC rapporteurs during the procedure but also in the pre-submission phase as well as criteria for PRAC plenary discussion. The PRAC agreed with the proposed procedural timetable, the criteria for plenary discussion, together with the reinforcement of early dialogue with PRAC Rapporteurs and applicants in order to plan appropriately for the RMP including any studies, and risk minimisation measures. The PRAC requested to be kept informed of progress in these areas.

12.20.3. Pharmacovigilance programme and revised implementation

As a follow-up to previous PRAC meetings (see PRAC minutes January 2016 and PRAC minutes February 2016), the EMA secretariat updated the PRAC at the organisational matters teleconference held on 31 March 2016 on the Heads of Medicines Agencies (HMA)'s adoption in February 2016 of the streamlined EU network governance for pharmacovigilance with operation and implementation overseen by PRAC (in collaboration with CHMP, CMDh, CAT) and key operational issues supported by a dedicated pharmacovigilance business team where all NCAs can be represented. A call to HMA was issued on 29 February 2016 for members of the new pharmacovigilance business team on information systems.
The revised EU network governance structure for pharmacovigilance implementation and operation will commence as of April 2016 and related topics will generally be scheduled at the monthly organisational matters teleconferences in a streamlined manner, following a calendar for implementation and in line with the PRAC work plan 2016.

13. Any other business

None

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(s) will be made available following the CHMP opinion on their marketing authorisation(s).

14.1.1. Atazanavir - EMEA/H/C/004048

Scope: Treatment of human immunodeficiency virus (HIV)-1

14.1.2. Bortezomib - EMEA/H/C/004076

Scope: Treatment of multiple myeloma

14.1.3. Daclizumab - EMEA/H/C/003862

Scope: Treatment of multiple sclerosis

14.1.4. Glycopyrronium bromide - EMEA/H/C/003883

Scope: Treatment of sialorrhoea

14.1.5. Mercaptamine - EMEA/H/C/004038, Orphan

Applicant: Lucane Pharma

Scope: Treatment of corneal cystine deposits

14.1.6. Miglustat - EMEA/H/C/004016

Scope: Treatment of Gaucher disease

14.1.7. Pandemic influenza vaccine H5N1 (live attenuated, nasal) - EMEA/H/C/003963

Scope: Prophylaxis of influenza

14.1.8. Sacubitril, valsartan - EMEA/H/C/004343

Scope: Treatment of heart failure (New York Heart Association (NYHA) class II-IV)

14.2. Medicines in the post-authorisation phase – PRAC-led procedure

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the variation procedure for the below mentioned medicine(s).

14.2.1. Catridecacog – NOVOTHIRTEEN (CAP) - EMEA/H/C/002284/II/0012/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Isabelle Robine

Scope: Update of the RMP to include exposure and safety data following finalisation of trial F13CD-3835 (to evaluate the long term safety of monthly replacement therapy with recombinant Factor XIII (rFXIII) when used for prevention of bleeding episodes in paediatric subjects with congenital FXIII A-subunit deficiency). F13CD-3835 was listed as additional pharmacovigilance activity. Update of the RMP to include the final study report of the PRO-RBDD registry (prospective data collection on congenital FXIII deficiency) in the RMP. PRO-RBDD was listed as additional pharmacovigilance activity. The MAH took the opportunity to correct the classification of the additional pharmacovigilance activity PASS NN1841-3868 from category 2 to category 3, as this study is not a specific obligation and is not listed in the Annex II of the Marketing Authorisation

14.2.2. Colistimethate sodium – COLOBREATHE (CAP) - EMEA/H/C/001225/II/0021

Applicant: Forest Laboratories UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of the RMP (version.6.0) in order to add information on the first interim report for study CLB-MD-05 (an open-label observational safety study of Colobreathe compared with other inhaled antipseudomonal antibiotics in cystic fibrosis patients using cystic fibrosis registries, MEA 009) and the protocol for study CLB-MD-08 (a post-authorisation registry based safety study to evaluate the effectiveness of the risk minimisation educational materials, including DVD and patient and healthcare professional guide, implemented in the EU for Colobreathe)

14.2.3. Pioglitazone – ACTOS (CAP) - EMEA/H/C/000285/WS/0875; GLUSTIN (CAP) - EMEA/H/C/000286/WS/0875 pioglitazone, glimepiride – TANDEMACT (CAP) - EMEA/H/C/000680/WS/0875 pioglitazone, metformin – COMPETACT (CAP) - EMEA/H/C/000655/WS/0875; GLUBRAVA (CAP) - EMEA/H/C/000893/WS/0875

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Update of the RMP in order to extend the due date for the category 3 drug utilisation study Pioglitazone_5019: from '31 December 2015' to '29 July 2016'

14.2.4. Piperaquine tetraphosphate, artenimol – EURARTESIM (CAP) - EMEA/H/C/001199/II/0020

Applicant: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP with regards the delay in starting resistance monitoring, collection of off label use data, submission of reports of imposed addition pharmacovigilance activities. The MAH also took this opportunity to reformat the RMP to the new template

14.2.5. Roflumilast – DALIRESP (CAP) - EMEA/H/C/002398/WS/0924; DAXAS (CAP) - EMEA/H/C/001179/WS/0924; LIBERTEK (CAP) - EMEA/H/C/002399/WS/0924

Applicant: Takeda GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope: To change the final due date to 'Q2 2016' for study RO-2455-302-RD

14.2.6. Teriparatide – FORSTEO (CAP) - EMEA/H/C/000425/II/0042/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 4) and revised protocol for post authorisation safety studies (PASS) B3D-MC-GHBX[2.2] and B3D-MC-GHBX[2.3]. In addition, the RMP has been updated to include non-uraemic calciphylaxis as a potential important risk as requested by PRAC

14.3. Medicines in the post-authorisation phase – CHMP-led procedure

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

14.3.1. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/II/0094/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information with data from the long-term final clinical study report for study IM101174. In addition, the Product Information is being aligned to the latest QRD template (version 9.1). The timelines for study IM101537, aimed at evaluating the effectiveness of risk minimisation measure (alert card) have been updated

14.3.2. Aflibercept – EYLEA (CAP) - EMEA/H/C/002392/II/0027/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: Grouped variations to include: 1) 3-year data of the pivotal trials VIVID-DME and VISTA-DME; 2) protocol T data with a consequential update to section 5.1 of the SmPC. Furthermore, the MAH took the opportunity to condense the SmPC section 4.8 text relating to antiplatelet trialists' collaboration (APTC) as recommended by EMA during II/018 variation (diabetic macular oedema (DME) 2 year data), to shorten SmPC section 5.1 as committed by the MAH during II/021 variation (indication myopic choroidal neovascularisation (mCNV)), to align the annexes with the latest QRD templates (version 9.1, June 2015) and to implement minor changes within age-related macular degeneration (AMD) and DME posology sections

14.3.3. Amifampridine – FIRDAPSE (CAP) - EMEA/H/C/001032/II/0038

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4, 4.5, 5.2 and 5.3 of the SmPC to update the safety information with new data available following the completion of the clinical study report (CSR) REN-002 on renal impairment

14.3.4. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0019

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final results from the non-clinical study PTC124-15055: assessment of uncoupling protein 1 (UCP1) protein levels in brown adipose tissue (BAT) in weanling rats administered ataluren via oral gavage for two weeks, in order to address MEA 007. Part II: module SII of RMP (version 4.4) was updated to reflect in tumor findings that in-vivo exposure to ataluren and the M4 metabolite does not activate BAT. Other sections of the RMP were updated to reflect completion of the study

14.3.5. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0020

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.4, 4.6, 4.7, 4.8, and 5.1 of the SmPC and Annex II in order to reflect the results from study TC124-GD-020-DMD (SOB 001). The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to include some minor editorial changes throughout the Product Information

14.3.6. Belimumab – BENLYSTA (CAP) - EMEA/H/C/002015/II/0037

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.1 of the SmPC in order to update pharmacodynamic information as the result of completion of efficacy/safety phase 3 continuation study BEL112233 (HGS1006-C1066) which fulfils MEA 011. The RMP has been updated to reflect the completed milestone for this study and to update the information on long-term effects of belimumab on B cells which represents 'missing information' in the current approved RMP

14.3.7. Bevacizumab – AVASTIN (CAP) - EMEA/H/C/000582/II/0086

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication for the use of Avastin in combination with erlotinib for the first line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations. As a consequence sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and RMP are updated accordingly

14.3.8. Brentuximab vedotin – ADCETRIS (CAP) - EMEA/H/C/002455/II/0025

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of adult patients at increased risk of relapse or progression following autologous stem cell transplant (ASCT). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly

14.3.9. Canakinumab – ILARIS (CAP) - EMEA/H/C/001109/II/0043

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to amend the systemic juvenile idiopathic arthritis (SJIA) indication to include treatment of active Still's disease including adult-onset Still's disease (AOSD) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the annexes in line with the latest QRD template. An updated RMP (version 10) was provided as part of the application

14.3.10. Darunavir – PREZISTA (CAP) - EMEA/H/C/000707/II/0078

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report of the clinical study GS-US-236-0118: phase 3 open-label safety study of cobicistat-containing highly active antiretroviral regimens in human immunodeficiency virus (HIV-1) infected patients with mild to moderate renal impairment (category 3 study in the RMP) in order to update the relevant information on the RMP

14.3.11. Darunavir, cobicistat – REZOLSTA (CAP) - EMEA/H/C/002819/II/0007

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final study report of the clinical study GS-US-236-0118: phase 3 open-label safety study of cobicistat-containing highly active antiretroviral regimens in human immunodeficiency virus (HIV-1) infected patients with mild to moderate renal impairment (category 3 study in the RMP) in order to update the relevant information in the RMP

14.3.12. Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/WS/0829

emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/WS/0829
emtricitabine, tenofovir disoproxil – TRUVADA (CAP) - EMEA/H/C/000594/WS/0829

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd., Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Update of section 4.5 of the SmPCs for Viread, Truvada, Atripla and Eviplera regarding the potential drug interaction with ledipasvir/sofosbuvir (LDV/SOF), as well as that of LDV and SOF as single agents with tenofovir disoproxil fumarate (TDF). The RMP is updated accordingly. In addition, the MAH took the opportunity to update the Product Information according to the latest QRD template (version 9.1) and implement minor linguistic corrections

14.3.13. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP) - EMEA/H/C/002574/II/0054

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.5 of the SmPC in order to update the safety information regarding the potential drug interaction with ledipasvir/sofosbuvir (LDV/SOF), as well as that of LDV and SOF as single agents with tenofovir disoproxil fumarate (TDF). The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 9.1)

14.3.14. Entecavir – BARACLUDE (CAP) - EMEA/H/C/000623/II/0049

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of sections 4.8 and 5.1 of the SmPC to add long term efficacy, safety and resistance data on the paediatric population from study AI463189 'expanded cohort' (180 subjects). In adition, the MAH took the opportunity to combine the SmPCs of Baraclude 0.5 mg tablets and Baraclude 1 mg tablets

14.3.15. Eribulin – HALAVEN (CAP) - EMEA/H/C/002084/II/0028

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication for Halaven 0.44 mg/ml solution for injection for the treatment of soft tissue sarcoma, following the outcome of phase 3 study 309. As a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated in order to update the safety information. The Package Leaflet and RMP are updated accordingly. In addition, the MAH took the opportunity to update the product information in line with the latest QRD template (version 9.1)

14.3.16. Fentanyl, fentanyl citrate – INSTANYL (CAP) - EMEA/H/C/000959/X/0030/G

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Isabelle Robine

Scope: Line extension to add a new strength of 400 micrograms/dose in a multi-dose nasal spray in pack size of 10's, 20's, 30's and 40 doses; to replace the current multi-dose nasal

spray by a new improved child resistant multi-dose nasal spray; to add a new packsize of 30 doses for each current strength (50 micrograms/dose, 100 micrograms/dose and 200 micrograms/dose)

14.3.17. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/II/0063

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to reflect the data from a multicentre, placebo-controlled, double-blind, randomised-withdrawal, parallel group study (GO KIDS) in children (2 to 17 years of age) with active polyarticular juvenile idiopathic arthritis (pJIA). The Package leaflet is updated accordingly. This procedure includes also an update to the RMP

14.3.18. Human coagulation factor VIII, human von Willebrand factor – VONCENTO (CAP) - EMEA/H/C/002493/II/0017/G

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.8 of the SmPC in order to update the frequencies of undesirable effects to reflect the final clinical study report from study CSLCT-BIO-08-53 in haemophilia A paediatric patients. The Package Leaflet is updated accordingly. The submission of the final clinical study report for study CSLCT-BIO-08-53 also leads to changes to the RMP (version 6.1) in order to update the Company Core Safety Information (CCSI). Submission of a revised RMP in order to remove the commitment to conduct a post-marketing study for haemophilia A patients (study CSLCT-BIO-12-78) for Voncento as a consequence of new data from study CSLCT-BIO-08-53. In addition, the MAH took the opportunity to combine different strengths in the SmPC and Package Leaflet

14.3.19. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - EMEA/H/C/000721/II/0067

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include the prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the RMP (version 11.0) including the new indication

14.3.20. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0016

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to broaden the existing indication for chronic lymphocytic leukaemia (CLL) to include all previously untreated patients including those with 17p deletion or TP53 mutation based on the results from the final clinical stuyd report of study PCYC-1115-CA (MEA 021). As a consequence, sections 4.1, 4.6, 4.8, 5.1 and 5.3 of the SmPC are being updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC and to bring Annex II in line with the latest QRD template (version 9.1). Moreover, the updated RMP (version 5.0) has been submitted

14.3.21. Liraglutide – VICTOZA (CAP) - EMEA/H/C/001026/II/0038

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include second-line monotherapy in type 2 diabetes for Victoza. Additionally, the MAH updated information related to hepatic and renal impairment. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated with new efficacy and safety information. The Package Leaflet is updated in accordance. Furthermore, the MAH took the opportunity to align the PI with the latest QRD template (version 9.1)

14.3.22. Lixisenatide – LYXUMIA (CAP) - EMEA/H/C/002445/II/0013

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update information on patient with congestive heart failure following submission of the final clinical study report for study EFC11319 (ELIXA) in fulfilment of MEA 001

14.3.23. Lumacaftor, ivacaftor – ORKAMBI (CAP) - EMEA/H/C/003954/II/0005/G

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final study reports for the following studies in order to address MEA 006: 1. Report L240: In vitro evaluation of the substrate and inhibitor potential of lumacaftor (VX-809) for breast cancer resistance protein and multidrug resistance protein 2. 2. Report L242: evaluation of the inhibition potential of VX-809 for uptakes transporters OAT1, OAT3, OCT1 and OCT2. 3. L239: In vitro drug-drug interaction studies of the sponsor's test article, VX-770. 4. L241: evaluation of the inhibition potential of VX-770 for uptake transporters OAT1, OAT3, OCT1 and OCT2. An updated RMP (version 2.1) is provided with this variation and includes all the new results of these non-clinical studies. The RMP Public Summary has also been updated to align with the published RMP summary European Public Assessment Report

14.3.24. Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP) - EMEA/H/C/001095/II/0056

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC in order to add facial paresis as a new adverse drug reaction and to provide further safety information based on the final clinical study report for study V59_34OB in order to fulfil MEA 023. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 8.2 has been submitted

14.3.25. Natalizumab – TYSABRI (CAP) - EMEA/H/C/000603/II/0077

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adults with highly active relapsing remitting multiple sclerosis with high disease activity despite treatment with at least one modifying therapy (DMT). As a consequence, sections 4.1 and 4.4 of the SmPC are updated

in order to provide physicians with more options for treating relapsing remitting multiple sclerosis (RRMS) patients with high disease activity who fail an initial disease modifying therapy (DMT). Consequential changes to sections 4.2, 4.3, 5.1 and Package Leaflet are submitted accordingly

14.3.26. Nepafenac – NEVANAC (CAP) - EMEA/H/C/000818/II/0032

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include the indication 'reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients' also for the 3 mg/ml strength based on data from the phase III studies C-12-067 and C-12-071. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in SmPC and to update the annexes in line with the latest QRD template. An updated RMP (version 7) was provided as part of the application

14.3.27. Paliperidone – PALIPERIDONE JANSSEN (CAP) - EMEA/H/C/004066/X/0007/G

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variation consisting of an extension application to introduce four new strengths of a once-every-3-month paliperidone injection formulation (175 mg, 263 mg, 350 mg and 525 mg). In addition, extension of indication to revise the injection frequency to ' once-every-3-months' following prior adequate treatment with paliperidone for at least four months. Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 are updated. The Package Leaflet and RMP are updated accordingly. In addition, section 1 of SmPC is updated to change the name of the medicinal product from 'Paliperidone Janssen' to 'Trevicta'. Finally, deletion of authorised dosage strengths (i.e. Paliperidone Janssen 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 150 mg / 100 mg - EU/1/14/971/001-006)

14.3.28. Pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/II/0002

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC with safety and pharmacokinetic (PK) data based on the clinical study report (CSR) of study P006v01. Further, the adverse drug reaction (ADR) Guillain-Barré Syndrome (GBS) has been added to sections 4.4 and 4.8 of the SmPC. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to revise the text referring to fatal cases of pneumonitis in section 4.4 of the SmPC, to implement minor editorial changes in the annexes, to align the SmPC, Annex II, labelling and Package Leaflet with the latest QRD template (version 9.1), and to update the contact details of the local representative in Luxemburg in the Package Leaflet. A revised RMP (version 2.0) was provided as part of the application

14.3.29. Ponatinib – ICLUSIG (CAP) - EMEA/H/C/002695/II/0029/G

Applicant: Ariad Pharma Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 5.3 of the SmPC in order to add pre-clinical information on fertility and early embryonic development to implantation (study 2424-001) and on carcinogenity (study 805826). In addition, the MAH has submitted final study results for pre-clinical

studies ARP590, ARP591, ARP592, ARP593, ARP593 on vascular occlusion mechanism and study ARP598 on effects of ponatinib and its metabolites on in vitro kinase activity and cellular viability following commitments taken during the Article 20 referral procedure (EMEA/H/C/002695/A-20/0003, EC decision on 15 January 2015). No impact in the Product information is proposed for these 6 studies. The RMP has been updated accordingly to the grouped variations

14.3.30. Posaconazole – NOXAFIL (CAP) - EMEA/H/C/000610/II/0044

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.2 of the SmPC in order to strengthen the information about non-interchangeability of the oral formulations based on new reports of medication errors related to confusion between posaconazole tablets and oral suspension in prescribing. The Package Leaflet and the RMP are updated accordingly

14.3.31. Radium-223 – XOFIGO (CAP) - EMEA/H/C/002653/II/0014/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Rafe Suvarna

Scope: 1) Submission of clinical study report for study BC1-06, 'a double-blind, randomized, multiple dose, Phase III, multicentre study of alpharadin in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases' (MEA 001) 2) Submission of clinical study report for study 15995 'Radium-223 dichloride in castration-resistant (hormone-refractory) prostate cancer patients with bone metastases', an early access clinical trial in the USA. (MEA 002) 3) Submission of a clinical study report (based on primary completion) for study 16216 'Radium-223 dichloride in castration-resistant (hormone-refractory) prostate cancer patients with bone metastases' an early access clinical trial outside USA. (MEA 003) 4) The RMP (version 2.0) is updated with regard to the clinical study reports submitted, the due dates in part III section 4, and additionally to reflect the change in SmPC based on the recent reassessment of the primary reference standard for radium-223 (issued by the National Institute of Standards and Technology (NIST)), the active moiety of Xofigo (recently approved EMEA/H/C/2653/II/011)

14.3.32. Rituximab – MABTHERA (CAP) - EMEA/H/C/000165/X/0101/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Line extension to add a new strength: 1,600 mg solution for subcutaneous injection, a new indication is also proposed (different from 1,400 mg strength). Update to the product information of the existing strenghts as a consequence of the line extension application. Update of the RMP to include 'new information' relevant to chronic lymphocytic leukaemia (CLL) and update of the educational materials

14.3.33. Simeprevir – OLYSIO (CAP) - EMEA/H/C/002777/II/0015

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to amend the safety information regarding the use of Olysio in interferon-free regimens, based on the primary analysis (SVR12) of studies HPC3017 and HPC3018. The Package Leaflet and Labelling are updated accordingly

14.3.34. Teduglutide – REVESTIVE (CAP) - EMEA/H/C/002345/II/0020

Applicant: NPS Pharma Holdings Limited

PRAC Rapporteur: Torbjorn Callreus

Scope: Extension of indication to include the paediatric population. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to update the safety information. The Package Leaflet is updated accordingly

14.3.35. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/II/0057

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX) in the SmPC for the subcutaneous formulation. As a consequence, section 4.1 of the SmPC is updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. Moreover, the updated RMP (version 18) has been submitted

14.3.36. Ulipristal – ESMYA (CAP) - EMEA/H/C/002041/II/0037

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update the safety information based on the results of phase III study PGL11-024

14.3.37. Varenicline – CHAMPIX (CAP) - EMEA/H/C/000699/II/0062

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: The MAH submitted the final study report of study A3051123 and updated sections 4.4 and 5.1 of the SmPC to reflect these study results. The Annex II, the Package Leaflet and the RMP were also updated accordingly. The MAH took the opportunity to remove the black triangle and to introduce minor amendments to the Labelling

14.3.38. Vorapaxar – ZONTIVITY (CAP) - EMEA/H/C/002814/II/0005

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include treatment of patients with peripheral arterial disease (PAD) and as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the contact details of local representative in Luxembourg in the Package Leaflet. Furthermore, the Product Information is brought in line with the latest QRD template (version 9.1). Moreover, revised RMP version 2.0 was provided as part of the application

15. ANNEX I - Periodic safety update reports (PSURs)

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

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

15.1. PSUR procedures including centrally authorised products only

15.1.1. Antithrombin alfa – ATRYN (CAP) - PSUSA/00224/201507

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.1.2. Asenapine – SYCREST (CAP) - PSUSA/00256/201508

Applicant: N.V. Organon

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.3. Bedaquiline – SIRTURO (CAP) - PSUSA/10074/201509

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.4. Cobicistat – TYBOST (CAP) - PSUSA/10081/201508

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.5. Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil – STRIBILD (CAP) - PSUSA/10082/201508

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.6. Collagenase clostridium histolyticum – XIAPEX (CAP) - PSUSA/00871/201508

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

15.1.7. Copper (^{64}Cu) chloride – CUPRYMINA (CAP) - PSUSA/10040/201508

Applicant: Sparkle S.r.l.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.8. Dabrafenib – TAFINLAR (CAP) - PSUSA/10084/201508

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope of procedure: Evaluation of a PSUSA procedure

15.1.9. Deferiprone – FERRIPROX (CAP) - PSUSA/00940/201508 (with RMP)

Applicant: Apotex Europe BV

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.1.10. Dronedarone – MULTAQ (CAP) - PSUSA/01180/201507

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.1.11. Elosulfase alfa – VIMIZIM (CAP) - PSUSA/10218/201508

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.12. Elvitegravir – VITEKTA (CAP) - PSUSA/02577/201508

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.13. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - PSUSA/09142/201508

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.1.14. Enzalutamide – XTANDI (CAP) - PSUSA/10095/201508 (with RMP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.1.15. Ex vivo expanded autologous human corneal epithelial cells containing stem cells – HOLOCLAR (CAP) - PSUSA/10352/201508

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.16. Human coagulation factor VIII, von Willebrand factor complex – VONCENTO (CAP) - PSUSA/10102/201508

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.1.17. Idelalisib – ZYDELIG (CAP) - PSUSA/10303/201509

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.18. Influenza vaccine (split virion, inactivated) – IDFLU (CAP); INTANZA (CAP) - PSUSA/01743/201508

Applicant: Sanofi Pasteur

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

15.1.19. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP) - PSUSA/01745/201508

Applicant: Novartis Influenza Vaccines Marburg GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.1.20. Interferon beta-1b – BETAFERON (CAP); EXTAVIA (CAP) - PSUSA/01759/201507

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.21. Lenvatinib – LENVIMA (CAP) - PSUSA/10380/201508

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

15.1.22. Loxapine – ADASUVE (CAP) - PSUSA/10113/201508

Applicant: Ferrer Internacional S.A.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.1.23. Maraviroc – CELSENTRI (CAP) - PSUSA/01934/201508

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.24. Mecasermin – INCRELEX (CAP) - PSUSA/01942/201508

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

15.1.25. Metformin hydrochloride, sitagliptin – EFFICIB (CAP); JANUMET (CAP); RISTFOR (CAP); VELMETIA (CAP) - PSUSA/02003/201508

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.1.26. Midazolam – BUCCOLAM (CAP) - PSUSA/10118/201509

Applicant: Shire Services BVBA

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.1.27. Natalizumab – TYSABRI (CAP) - PSUSA/02127/201508

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.28. Nonacog alfa – BENEFIX (CAP) - PSUSA/02183/201508

Applicant: Pfizer Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.29. Ospemifene – SENSHIO (CAP) - PSUSA/10340/201508

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.30. Pandemic influenza vaccine H5N1 (whole virion, vero cell derived, inactivated), prepandemic influenza vaccine H5N1 (whole virion, vero cell derived, inactivated) – PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP); VEPACEL (CAP) - PSUSA/02282/201508

Applicant: Nanotherapeutics Bohumil Sro

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.31. Pembrolizumab – KEYTRUDA (CAP) – PSUSA/10403/201509

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.1.32. Pyronaridine, artesunate – PYRAMAX (Art 58[36]) – EMA/H/W/002319/PSUV/0012

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.1.33. Safinamide – XADAGO (CAP) - PSUSA/10356/201508

Applicant: Zambon SpA

[36] Article 58 of Regulation (EC) No 726/2004 allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO), on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

15.1.34. Teduglutide – REVESTIVE (CAP) - PSUSA/09305/201508

Applicant: NPS Pharma Holdings Limited

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

15.1.35. Vernakalant hydrochloride – BRINAVESS (CAP) - PSUSA/03109/201508 (with RMP)

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.1.36. Zoledronic acid – ACLASTA (CAP) - PSUSA/09334/201508

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

15.2. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

15.2.1. Eflornithine – VANIQA (CAP), NAP - PSUSA/01202/201507

Applicant: Almirall S.A

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

15.2.2. Human protein C – CEPROTIN (CAP), NAP - PSUSA/02563/201507

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.3. PSUR procedures including nationally approved products (NAPs) only

15.3.1. Alprostadil (patency of the ductus arteriosus) (NAP) - PSUSA/00010021/201507

Applicant: various

PRAC Lead: Marianne Lunzer

Scope: Evaluation of a PSUSA procedure

15.3.2. Cisatracurium (NAP) - PSUSA/00000777/201507

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.3. Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed); diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed) reduce antigens content (NAP) - PSUSA/00001126/201507

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.3.4. Escherichia coli lysate (NAP) - PSUSA/00001263/201507

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.3.5. Ethinylestradiol, gestodene (transdermal application) (NAP) - PSUSA/00010145/201508

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.3.6. Fluticasone propionate, formoterol fumarate dihydrate (NAP) - PSUSA/00010339/201507

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.7. Fosinopril (NAP) - PSUSA/00001474/201507

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.3.8. Fosinopril, hydrochlorothiazide (NAP) - PSUSA/00001475/201507

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.3.9. Gaxilose (NAP) - PSUSA/00010283/201507

Applicant: various

PRAC Lead: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

15.3.10. Lisdexamfetamine (NAP) - PSUSA/00010289/201508

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.11. Lubiprostone (NAP) - PSUSA/00010290/201507

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.12. Magnesium sulfate, sodium sulfate, potassium sulfate (NAP) - PSUSA/00010239/201508

Applicant: various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

15.3.13. Montelukast (NAP) - PSUSA/00002087/201507

Applicant: various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

15.3.14. Poliovirus type 1, poliovirus type 3 (oral, live, attenuated) vaccine (NAP) - PSUSA/00002460/201507

Applicant: various

PRAC Lead: Jean-Michel Dogne

Scope: Evaluation of a PSUSA procedure

15.3.15. Ribavirin (aerosol application) (NAP) - PSUSA/00010003/201508

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.3.16. Tiapride (NAP) - PSUSA/00002944/201507

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.3.17. Ziprasidone (NAP) - PSUSA/00003146/201507

Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.4. Follow-up to PSUR procedures

15.4.1. Caspofungin – CANCIDAS (CAP) - EMEA/H/C/000379/LEG/062

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Veerle Verlinden

Scope of procedure: Following PSUSA/00000576/201412, the MAH was requested to provide a cumulative analysis of the risk of serious cutaneous adverse reactions (SCARs) (including Stevens–Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms) with the cut-off date 30.09.2015

15.4.2. Human rotavirus, live attenuated – ROTARIX (CAP) - EMEA/H/C/000639/LEG 086

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: The MAH provided updated analyses on hypersensitivity case of clinical data and post-marketing data and provided a case definition for hypersensitivity taking into account the definition of the international consensus on drug allergy for the case review, as requested during the renewal procedure R/0079. The search for cumulative analysis should include MedDRA[37] preferred terms (PTs) for narrow Standardised MedDRA Queries (SMQ) narrow for hypersensitivity excluding PTs indicative of a site-specific reaction (injection site, vaccination site)

15.4.3. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/LEG 007.1

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's responses to LEG 007 on prevention of administration of expired Fluenz Tetra as per request for supplementary information adopted in June 2015: the MAH should suggest measures to increase attention to expiration dates, although spontaneous reports

[37] Medical Dictionary for Regulatory Activities

are not a reliable basis for assessing actual incidence rates, by end of Q4 2015 (deadline proposed by MAH)

15.4.4. Vildagliptin – GALVUS (CAP) - EMEA/H/C/00771/LEG 042 ; JALRA - EMEA/H/C/001048/LEG 026; XILIARX - EMEA/H/C/001051/LEG 026; Vildagliptin, metformin hydrochloride – EUCREAS (CAP) - EMEA/H/C/000807/LEG 024; ICANDRA (CAP) - EMEA/H/C/001050/LEG 022; ZOMARIST (CAP) - EMEA/H/C/001049/LEG 022

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's responses to the request from PRAC following the assessment of PSUSA/00003113/201502 regarding acute renal failure cases with vildagliptin (Galvus/Eucreas)

16. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

16.1. Protocols of PASS imposed in the marketing authorisation(s)[38]

16.1.1. Deferasirox – EXJADE (CAP) - EMEA/H/C/PSP/0010.4.A.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Revised PASS protocol for study CICL670E2422: observational cohort study in paediatric non transfusion dependant-thalassaemia (NTDT) patients over 10 years

16.1.2. Ethinylestradiol and ethinylestradiol, levonorgestrel (NAP) - EMEA/H/N/PSP/0037

Applicant: Teva Pharma B.V. (Seasonique)

PRAC Rapporteur: Isabelle Robine

Scope: Draft protocol for a post-authorisation safety study to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique: a retrospective longitudinal cohort study assessing the safety of short and long-term use of Seasonique

16.1.3. Pitolisant – WAKIX (CAP) - EMEA/H/C/PSP/0039

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Draft protocol for a non-interventional post-authorisation safety study (PASS): a multi-centre, observational post-authorisation safety study to document the drug utilisation

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

of Wakix and to collect information on the safety of Wakix when used in routine medical practice

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[39]

16.2.1. Dasabuvir – EXVIERA (CAP) - EMEA/H/C/003837/MEA/001.2

Applicant: AbbVie Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: MAH's responses to MEA 001.1 [PASS protocol for a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of Grade 3+ ALT elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (3 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (2-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA Regimens in a real world setting)] as per request for supplementary information adopted in October 2015

16.2.2. Edoxaban – LIXIANA (CAP) - EMEA/H/C/002629/MEA/005.1

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 005 [drug utilisation study DSE-EDO-01-14-EU: edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study] as per request for supplementary information adopted in October 2015

16.2.3. Edoxaban – LIXIANA (CAP) - EMEA/H/C/002629/MEA/006.1

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 006 [PASS Protocol Study DSE-EDO-04-14-EU] as per request for supplementary information as adopted in October 2015

16.2.4. Edoxaban – LIXIANA (CAP) - EMEA/H/C/002629/MEA/007.1

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 007 [PASS protocol study DSE-EDO-05-14-EU] as per request for supplementary information adopted in October 2015

16.2.5. Evolocumab – REPATHA (CAP) - EMEA/H/C/003766/MEA/009

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

[39] 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

Scope: Draft protocol for study 20150162: a multi-national observational study to evaluate the safety of Repatha in pregnancy

16.2.6. Filgrastim – NIVESTIM (CAP) - EMEA/H/C/001142/MEA 015.1

Applicant: Hospira UK Limited

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's responses to MEA 015 [revised protocol for study ZOB-NIV-1513: a multinational, multicentre, prospective, non-interventional, post-authorisation safety study in healthy donors (HDs) exposed to Nivestim for haematopoietic stem cell (HSC) mobilisation (NEST)] as per request for supplementary information adopted in January 2016

16.2.7. Infliximab – REMICADE (CAP) - EMEA/H/C/000240/MEA/133.10

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eighth annual paediatric inflammatory bowel disease (IBD) registry (DEVELOP) report

16.2.8. Insulin lispro – HUMALOG (CAP) - EMEA/H/C/000088/MEA/028.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 028.1 [US surveillance programme] as per request for supplementary information adopted in October 2015

16.2.9. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/MEA/021.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 028.1 [US surveillance programme] as per request for supplementary information adopted in October 2015

16.2.10. Interferon beta-1a – AVONEX (CAP) - EMEA/H/C/000102/MEA/084.4

Applicant: Biogen Idec

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's responses to MEA 084.3 [PASS protocol: pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon-beta – a register-based study in the Nordic countries] as per request for supplementary information adopted in November 2015

16.2.11. Interferon beta-1a – REBIF (CAP) - EMEA/H/C/000136/MEA/039.4

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's responses to MEA 039.3 [PASS protocol: pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon-beta – a register-based study in the Nordic countries] as per request for supplementary information adopted in November 2015

16.2.12. Interferon beta-1b – BETAFERON (CAP) - EMEA/H/C/000081/MEA/021.4

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 021.3 [PASS protocol: pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon-beta – a register-based study in the Nordic countries] as per request for supplementary information adopted in November 2015

16.2.13. Interferon beta-1b – EXTAVIA (CAP) - EMEA/H/C/000933/MEA/019.4

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 019.3 [PASS protocol: pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon-beta – a register-based study in the Nordic countries] as per request for supplementary information adopted in November 2015

16.2.14. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/MEA/008.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's responses to MEA 008 [Protocol for study CA209234, a non-interventional category 3 PASS: pattern of use, safety, and effectiveness of nivolumab in routine oncology practice] as per request for supplementary information adopted in November 2015

16.2.15. Ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP) - EMEA/H/C/003839/MEA/001.2

Applicant: AbbVie Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: MAH's responses to MEA 001.1 [observational, cohort study utilising the hepatitis C therapeutic registry & research network (HCV-TARGET)] as per request for supplementary information adopted in October 2015

16.2.16. Ustekinumab – STELARA (CAP) - EMEA/H/C/000958/MEA/044

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Draft protocol for an adolescent registry: an observational post-authorisation safety study of ustekinumab in the treatment of pediatric patients aged 12 years and older with moderate to severe plaque psoriasis

16.2.17. Vernakalant – BRINAVESS (CAP) - EMEA/H/C/001215/MEA/026.1

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 026 [Amendment to PASS protocol for vernakalant intravenous (IV) sterile concentrate prospective safety registry study: a prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant IV sterile concentrate (study 6621 049-00)] as per request for supplementary information adopted in September 2015

16.3. Results of PASS imposed in the marketing authorisation(s)[40]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[41]

16.4.1. Dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/II/0092

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final study report for observational study 1160. 157 comparing the safety and efficacy of Pradaxa versus warfarin in the real world in patients with non-valvular atrial fibrillation. The RMP (version 31.3) has been updated with results from the observational study 1160.157 and inclusion of information on study 1160.207. In addition, the MAH took the opportunity to consolidate previous RMP versions and add information on study 1160.118 as the results were submitted with procedure II/91

16.4.2. Eptacog alfa (activated) – NOVOSEVEN (CAP) - EMEA/H/C/000074/II/0089

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study teport for study NN7025-3601 : a prospective observational study on NovoSeven room temperature (VII25) in patients with haemophilia A and B. The submission of this study report addresses MEA 046.4 and an updated RMP (version 6.1) is provided accordingly

16.4.3. Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP) - EMEA/H/C/001095/II/0062

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report for study V59_54OB, a post-licensure observational safety surveillance study of Menveo vaccination in children 2 through 10 years of age, in order to update the safety information of Menveo in subjects aged 2-10 years of age to fulfil MEA 024

[40] In accordance with Article 107p-q of Directive 2001/83/EC
[41] 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

16.4.4. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/WS/0897 saxagliptin, metformin hydrochloride – KOMBOGLYZE (CAP) - EMEA/H/C/002059/WS/0897

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a final clinical study report for an epidemiological study CV181-102 with the aim to assess risk factors associated with low lymphocyte count in patients with T2DM (PASS study category 3 currently in the RMP) together with an updated RMP (version 10)

16.4.5. Voriconazole – VFEND (CAP) - EMEA/H/C/000387/II/0115

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study report for a non-interventional post authorisation safety study A1501097: evaluation of the potential association between voriconazole use and squamous cell carcinoma (SCC) of the skin among patients with lung or lung/heart transplants in order to fulfil MEA 071.11. Consequently, the RMP (version 4.0) was updated

16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[42]

16.5.1. Catridecacog – NOVOTHIRTEEN (CAP) - EMEA/H/C/002284/MEA/015

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Isabelle Robine

Scope: First interim study report for study NN1841-3868: use of recombinant factor XIII in treatment of congenital factor XIII deficiency, a prospective multicentre observational study

16.5.2. Mannitol – BRONCHITOL (CAP) - EMEA/H/C/001252/ANX/002.8

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Sixth interim analysis of the cystic fibrosis (CF) study

16.5.3. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP) - EMEA/H/C/000758/MEA/050.2

Applicant: Novartis Influenza Vaccines Marburg GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Interim results of the enhanced passive safety surveillance of the seasonal cell culture trivalent influenza vaccine (Optaflu) for the 2015-16 influenza season in England in the pharmacies setting (V58_41OB)

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

16.5.4. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/002494/ANX/001.3

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Third interim study results of a five-year long-term observational study with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints

16.5.5. Oseltamivir – TAMIFLU (CAP) - EMEA/H/C/000402/LEG/087.3

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Third annual review on pregnancy cases

16.5.6. Oseltamivir – TAMIFLU (CAP) - EMEA/H/C/000402/MEA/102.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Annual review of the safety and efficacy of oseltamivir in immunocompromised patients up to final submission of the clinical trial NV20234 study report (treatment) as flu and season permits

16.5.7. Perampanel – FYCOMPA (CAP) - EMEA/H/C/002434/MEA/004.3

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Annual progress report for a post-marketing observational safety study to evaluate the long-term safety and tolerability of Fycompa as add-on therapy in epilepsy patients (PASS study E2007-G000-402)

16.5.8. Plasmodium falciparum and hepatitis b vaccine (recombinant, adjuvanted) – MOSQUIRIX (Art 58[43]) - EMEA/H/W/002300/MEA/001

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: First annual report for study Malaria-076, an open extension to the study Malaria-055 to evaluate long-term efficacy, safety and immunogenicity of the RTS,S/AS01E candidate vaccine (Mosquirix) against malaria disease caused by Plasmodium falciparum in infants and children in Africa, describing the incidence of severe malaria in the long-term over a 3-year period (from January 2014 to December 2016) of follow-up pooled across transmission settings, in both age categories: infants 6-12 weeks and children aged 5 to 17 months

16.5.9. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/000944/ANX/033.1

Applicant: Bayer Pharma AG

[43] Article 58 of Regulation (EC) No 726/2004 allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO), on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

PRAC Rapporteur: Qun-Ying Yue

Scope: Interim results from pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany, the Netherlands, the UK and Sweden

16.5.10. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/000944/ANX/035.1

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Second interim report an observational post-authorization Modified Prescription-Event Monitoring safety study (M-PEM) to monitor the safety and utilisation of rivaroxaban for the prevention of stroke in patients with atrial fibrillation (AF), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England – including an extension to the rivaroxaban M-PEM study to include acute coronary syndrome patients

16.5.11. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/000944/MEA/023.2

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Interim results (wave 1) of study SN 16167, a survey regarding educational materials for prescriber and patients receiving rivaroxaban for stroke prevention or deep vein thrombosis treatment post-launch

16.5.12. Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/MEA/256.6

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Interim results for a drug utilisation study (DUS) GS-EU-104-0433 in paediatric patients with human immunodeficiency virus (HIV-1) infection, to describe the characteristics of HIV-1 infected patients up to 18 years of age treated with Viread within the EU in order to determine if they are being managed in accordance with the European SmPC

16.5.13. Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/MEA/265.5

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Interim results for study GS-EU-174-1403, a pharmacoepidemiology study to define the long-term safety profile of tenofovir disoproxil fumarate and describe the management of associated renal and bone toxicity in Chronic Hepatitis B -infected adolescents aged 12 to <18 years in Europe

16.6. Others

16.6.1. Eliglustat – CERDELGA (CAP) - EMEA/H/C/003724/ANX/001.1

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's responses to ANX 001 [Safety sub-registry study OBS14099: concept protocol for a prospective multicentre observational post authorisation safety sub-registry to characterize the long-term safety profile of eliglustat of adult patients with Gaucher disease] as per request for supplementary information adopted in september 2015

16.6.2. Pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) – PANDEMRIX (CAP) - EMEA/H/C/000832/MEA 122

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Rafe Suvarna

Scope: Final study report for PASS study EPI-FLU H1N1-014 VS: an observational retrospective database analysis to estimate the risk of multiple sclerosis following vaccination with Arepanrix in Manitoba, Canada

16.7. New Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

16.8. Ongoing Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

16.9. Final Scientific Advice (Reports and Scientific Advice letters)

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

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. Annual reassessments of the marketing authorisation

None

17.2. Conditional renewals of the marketing authorisation

17.2.1. Fampridine – FAMPYRA (CAP) - EMEA/H/C/002097/R/0029 (without RMP)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

17.3. Renewals of the marketing authorisation

17.3.1. Abiraterone – ZYTIGA (CAP) - EMEA/H/C/002321/R/0038 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

17.3.2. Aztreonam – CAYSTON (CAP) - EMEA/H/C/000996/R/0058 (without RMP)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

17.3.3. C1-esterase inhibitor, human – CINRYZE (CAP) - EMEA/H/C/001207/R/0040 (without RMP)

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

17.3.4. Dexmedetomidine – DEXDOR (CAP) - EMEA/H/C/002268/R/0019 (with RMP)

Applicant: Orion Corporation

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

17.3.5. Levetiracetam – LEVETIRACETAM TEVA (CAP) - EMEA/H/C/002316/R/0021 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

17.3.6. Levodopa, carbidopa, entacapone – LEVODOPA, CARBIDOPA, ENTACAPONE ORION (CAP) - EMEA/H/C/002441/R/0019 (without RMP)

Applicant: Orion Corporation

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

17.3.7. Midazolam – BUCCOLAM (CAP) - EMEA/H/C/002267/R/0032 (with RMP)

Applicant: Shire Services BVBA

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

17.3.8. Perflutren – LUMINITY (CAP) - EMEA/H/C/000654/R/0021 (without RMP)

Applicant: Lantheus MI UK Ltd

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

17.3.9. Telavancin – VIBATIV (CAP) - EMEA/H/C/001240/R/0025 (without RMP)

Applicant: Clinigen Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

17.3.10. Vismodegib – ERIVEDGE (CAP) - EMEA/H/C/002602/R/0023 (without RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 14-17 March 2016 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Marianne Lunzer	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to meetings	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement
Yuliyan Eftimov	Alternate	Bulgaria	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Marina Dimov Di Giusti	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Isabelle Robine	Member	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests	Full

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	involvement
Ingebjørg Buajordet	Member	Norway	No interests declared	Full involvement
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Leonor Chambel	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Miguel-Angel Macia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Jane Ahlqvist Rastad	Member	Independent scientific expert	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent	No interests	Full

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
		scientific expert	declared	involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable	Full involvement
Filip Babylon	Expert - in person*	Belgium	No restrictions applicable to this meeting	Full involvement
Pierre Demolis	Expert - in person*	France	No interests declared	Full involvement
Alexandre Moreau	Expert - in person*	France	No interests declared	Full involvement
Nathalie Morgensztejn	Expert - via telephone*	France	Full involvement	Full involvement
Elke Stahl	Expert - via telephone*	Germany	Full involvement	Full involvement
Eleanor Carey	Expert - via telephone*	Ireland	Full involvement	Full involvement
Anna Marie Coleman	Expert - in person*	Ireland	Full involvement	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Pieter de Graeff	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Marcel S.G. Kwa	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Eirik Hagtvet	Expert - via telephone*	Norway	No interests declared	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Kristina Dunder	Expert - via telephone*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Bertil Jonsson	Expert - via telephone*	Sweden	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Bengt Ljungberg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jan Sjöberg	Expert - in person*	Sweden	No interests declared	Full involvement
Karolina Törneke	Expert - via telephone*	Sweden	No interests declared	Full involvement
Craig Allen	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Alison Banner-Simpson	Expert - in person*	United Kingdom	No interests declared	Full involvement
Inga Bellahn	Expert - in person*	United Kingdom	No interests declared	Full involvement
Mattia Calissano	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jo Lynn Chooi	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Michael Foy	Expert - via telephone*	United Kingdom	No restrictions applicable	Full involvement
Leigh Henderson	Expert - in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - in person*	United Kingdom	No interests declared	Full involvement
Gary Peters	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Andrew Ruddick	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Catherine Tregunno	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.

19. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

20. Explanatory notes

The Notes give a brief explanation of relevant minute's 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 minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC 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 summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC 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 management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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