11 June 2015
EMA/PRAC/59170/2015
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 04 - 07 May 2015

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 4-7 May 2015 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Zane Neikena, replacing Inguna Adoviča, as the new alternate for Latvia. The PRAC Chair also noted that Harald Herkner and Arnaud Batz were to step down as members for Austria and France respectively and thanked them for their contribution to the work of the PRAC. Finally, the PRAC noted a further change in the membership for Romania: Roxana Stefania Stroe and Nicolae Fotin swapped roles. Roxana Stroe became the member and Nicolae Fotin became the alternate.

1.2. Adoption of agenda of the meeting of 04-07 May 2015

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

1.3. Adoption of minutes of the previous meeting of 07-10 April 2015

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 7-10 April 2015 were published on the EMA website on 20 May 2015 (EMA/PRAC/332948/2015).

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. 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); 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

The European Commission sent a letter of notification dated 27/04/2015 of a referral under Article 31 of Directive 2001/83/EC for the review of inhaled corticosteroids (ICS) indicated in the treatment of chronic obstructive pulmonary disease (COPD) alone or in combination with a long acting beta$_2$ acting agonist (LABA).
Following a review conducted in 2010, the CHMP Pharmacovigilance Working Party (PhVWP) concluded that ICS-containing products alone or in combination with LABAs increased the risk of pneumonia in COPD patients. Since 2010, new clinical trials, publications and meta-analysis considered individually in the context of national and European reviews for individual active substances may have led to a differential reflection of the risk of pneumonia in the COPD population in the product information.

Discussion

The PRAC noted the notification letter from the European Commission requesting a review of all available data for ICS-containing products indicated in the treatment of COPD in order to further characterise the risk of pneumonia in COPD patients and to assess whether the product information appropriately reflects this risk. The PRAC discussed a list of questions to be addressed by the relevant MAHs as well as a timetable for conducting the review.

The PRAC appointed Rafe Suvarna as Rapporteur and Jan Neuhauser as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions to the MAHs of ICS-containing products indicated in the treatment of COPD (EMA/PRAC/290016/2015) and a timetable for the procedure (EMA/PRAC/290163/2015).

3.1.2. Natalizumab – TYSABRI (CAP) - EMEA/H/A-20/1416/C/000603/0083

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski; PRAC Co-rapporteur: Carmela Macchiarulo

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 29/04/2015 of a referral under Article 20(8) of Regulation (EC) No 726/2004 for the review of Tysabri (natalizumab), a recombinant humanised anti-α4-integrin antibody, indicated as a single disease modifying therapy in highly active relapsing remitting multiple sclerosis under certain conditions. Natalizumab has been associated with an increased risk of progressive multifocal leukoencephalopathy (PML) and the following risk factors are known: presence of anti-John Cunningham virus (JCV) antibodies, treatment duration (especially beyond 2 years) and use of immunosuppressant prior to nataluzimab treatment. A number of risk minimisation measures have been previously put in place to mitigate these risks. However, new elements in relation to risk estimates, diagnosis of PML before the development of clinical symptoms and anti JCV antibodies have arisen in light of further evidence and scientific progress and their impact needs to be assessed to better define the risk of PML and identify measures to further minimise it.

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 appointed Brigitte Keller-Stanislawski as Rapporteur and Carmela Macchiarulo as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/293316/2015) and a timetable for the procedure (EMA/PRAC/293314/2015).

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

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[1]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Amikacin (NAP)

Applicant: Bristol-Myers Squib, B. Braun Melsungen AG

PRAC Rapporteur: Maia Uusküla

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)
EPITT 18304 – New signal
Lead Member State: EE

Background

Amikacin is a semi-synthetic aminoglycoside antibiotic active against a broad spectrum of Gram-negative organisms, including *pseudomonas* and some Gram-positive organisms. Amikacin is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including *Pseudomonas* species. Although amikacin is not the drug of choice for infections due to *staphylococci*, at times it may be indicated for the treatment of known or suspected staphylococcal disease. These situations include: the initiation of therapy for severe infections when the organisms suspected are either Gram-negative or *staphylococci*, patients allergic to other antibiotics, and mixed staphylococcal/Gram-negative infections.

The exposure for nationally authorised medicines containing amikacin is estimated to have been more than 93,641 patients worldwide during the period 01 April 2009 to 31 March 2012.

During routine signal detection activities, a signal of drug reaction with eosinophilia and systemic symptoms (DRESS) was identified by the EMA, based on 21 cases retrieved from EudraVigilance. Estonia confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

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

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account that DRESS is a serious event, that one case was reported with positive de-challenge and positive skin test with amikacin alone as well as four cases where the patch test was positive for amikacin with one or more co-suspected medications, the PRAC agreed to request the MAH for the originator product to provide a cumulative review of cases of DRESS, Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and toxic skin eruption.

The PRAC appointed Maia Uusküla as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for the originator product Amikin (amikacin) should submit to the EMA, within 60 days, a cumulative review of all cases of severe cutaneous adverse reaction reported with amikacin-containing products. For each of these cutaneous disorders, the MAH should discuss the confirmed diagnosis based on the available information (i.e. symptomatology, skin biopsy, estimation of Kardaun score or ALDEN[2] score) and should also discuss the plausible concomitant drugs. Cases with positive de-challenge and re-challenge with amikacin, or with positive skin patch tests performed several months after the events should also be presented. With this cumulative review the MAH should also provide a discussion of relevant non-clinical data and scientific literature.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Angiotensin-converting enzyme (ACE)-inhibitors: benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, zofenpril (NAP)

Applicant: various

PRAC Rapporteur: No need for appointment

Scope: Signal of hallucinations
EPITT 18286 – New signal
Lead Member States: IE, NL, PT

Background

Benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, zofenpril are angiotensin-converting enzyme (ACE)-inhibitors indicated for the treatment of hypertension and congestive heart failure.

During routine signal detection activities, a signal of hallucinations was identified by the Netherlands, based on 15 cases retrieved from the Netherlands Pharmacovigilance centre (Lareb) and an additional 5 cases reported in the literature. DE, ES, IE, IT, NL, PT and UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed all the available information on the reported cases of hallucinations (e.g. number with de-challenge or re-challenge, where an ACE-inhibitor was the only

[2] Algorithm of drug causality for epidermal necrolysis (EN)

suspected drug) and agreed that the number of possible cases of hallucinations with a temporal relationship to ACE-inhibitors was small in light of extensive usage and that the likelihood of a causal relationship between treatment with ACE-inhibitors and hallucinations was not sufficiently strong at this stage. The PRAC considered that the MAHs of ACE-inhibitors should continue to monitor adverse events of hallucinations as part of routine safety surveillance.

Summary of recommendation(s)

- MAHs for ACE-inhibitor-containing products should continue to monitor cases of hallucination as part of their routine safety surveillance.

4.1.3. Decitabine – DACOGEN (CAP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Patrick Maison

Scope: Signal of organising pneumonia
EPITT 18303 – New signal
Lead Member State: FR

Background

Decitabine is a cytidine deoxynucleoside analogue indicated for the treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia under certain conditions.

The post-marketing exposure for Dacogen, a centrally authorised medicine containing decitabine, is estimated to have been more than 94,601 treatment courses worldwide, in the period from first authorisation in 2012 until November 2014.

During routine signal detection activities, a signal of organising pneumonia was identified by the EMA, based on 4 cases retrieved from EudraVigilance and one additional case published in the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account the plausible temporal association between the reported cases of organising pneumonia and drug intake, that the diagnosis was supported by lung biopsy results and that in some cases no alternate explanations for the development of organising pneumonia have been identified, the PRAC agreed to request the MAH to provide a cumulative review of cases of organising pneumonia with the next upcoming PSUR.

Summary of recommendation(s)

- The MAH for Dacogen (decitabine) should submit to the EMA, with the next PSUR (DLP: 01/05/2015), a cumulative review of cases of organising pneumonia expanding the search terms as pertinent in order to study the possibility of pulmonary toxicity with no infectious aetiology. This review should include an evaluation of the literature, cases reported spontaneously and cases collected from studies. Finally, the MAH should discuss the need for any potential amendment to the product information and/or the risk management plan.

4.1.4. Lenalidomide – REVLIMID (CAP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Arnaud Batz

Scope: Signal of pulmonary alveolar haemorrhage
EPITT 18300 – New signal
Lead Member State: FR

Background

Lenalidomide is an anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory agent indicated for the treatment of adult patients with previously untreated multiple myeloma and is used in combination with dexamethasone for the treatment of multiple myeloma in adult patients under certain conditions and for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes under certain conditions.

The post-marketing exposure for Revlimid, a centrally authorised medicine containing lenalidomide, is estimated to have been more than 388,779 patients worldwide, in the period from first authorisation in 2007 until December 2014.

Following the publication of the article by *Sakai et al.*[3], a signal of pulmonary alveolar haemorrhage was identified by the EMA during routine signal detection activities, based on 3 publications and 36 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the literature and from case reports in EudraVigilance. Taking into account the known antiangiogenic effect of lenalidomide, the known risks of lenalidomide regarding thrombocytopenia and bleeding (especially epistaxis), the plausible temporal relationship between lenalidomide intake and occurrence of pulmonary alveolar haemorrhage in the available cases, the PRAC agreed to request the MAH to provide a cumulative review of cases of pulmonary alveolar haemorrhage reported with lenalidomide as well as with thalidomide or pomalidomide[4].

Summary of recommendation(s)

- The MAH for Revlimid (lenalidomide), Thalidomide Celgene (thalidomide) and Imnovid (pomalidomide) should submit to the EMA, within 60 days, a cumulative review of reported cases of pulmonary alveolar haemorrhage. The MAH should review cases of pulmonary alveolar haemorrhage, as well as pulmonary haemorrhage and hemoptysis in order to check if they meet the diagnostic criteria of pulmonary alveolar haemorrhage. This review should include cases reported spontaneously and collected from studies. A literature review should also be performed. In addition, the MAH should discuss plausible biological mechanisms and the role of the underlying disease, co-administered anticoagulation treatments and thrombocytopenia. Finally, the MAH

[3] Sakai M, Kubota T, Kuwayama Y, Ikezoe T, Yokoyama A. Diffuse alveolar hemorrhage associated with lenalidomide. Int J Hematol. 2011 Jun;93(6):830-1
[4] Lenalidomide and pomalidomide are thalidomide derivatives and case reports were reported with lenalidomide, pomalidomide and thalidomide in the multiple myeloma indication

should discuss the need for any potential amendment to the product information and/or the risk management plan.

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

4.1.5. Long acting glucagon-like peptide (GLP)-1 agonists: Albiglutide – EPERZAN (CAP); dulaglutide - TRULICITY (CAP); exenatide – BYDUREON (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP); liraglutide, insulin degludec - XULTOPHY (CAP)

Applicant: Novo Nordisk A/S (Saxenda, Victoza, Xultophy), AstraZeneca AB (Bydureon), GlaxoSmithKline Trading Services (Eperzan), Eli Lilly Nederland B.V. (Trulicity)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of medullary thyroid cancer
EPITT 18292 – New signal
Lead Member State: NL

Background

Albiglutide, dulaglutide, exenatide and liraglutide are acting glucagon-like peptide (GLP)-1 agonists indicated for the treatment of type 2 diabetes mellitus in adults to improve glycaemic control under certain conditions.

The post-marketing exposure for Bydureon, a centrally authorised medicine containing exenatide, is estimated to have been more than 561,651 patient-years worldwide, in the period from first authorisation in 2011 until March 2014. The post-marketing exposure for Eperzan, a centrally authorised medicine containing albiglutide, is estimated to have been more than 63.5 patient-years worldwide, in the period from first authorisation in March 2014 until September 2014. The clinical trials exposure for Trulicity, a centrally authorised medicine containing dulaglutide, is estimated to have been more than 12,659 patients worldwide, in the period from first authorisation in November 2014 to March 2015. The exposure for Victoza, a centrally authorised medicine containing liraglutide, is estimated to have been more than 3,374,736 patient-years worldwide, in the period from first authorisation in 2009 until June 2014.

Following labelling changes in the US for long acting GLP-1 agonists (liraglutide, exenatide extended-release, albiglutide, and dulaglutide) to describe the first reported human cases of medullary thyroid cancer, a signal of medullary thyroid cancer was identified by the EMA during routine signal detection activities, based on 18 cases (including 16 for liraglutide only) retrieved from EudraVigilance. The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the reported cases in EudraVigilance. Medullary thyroid carcinoma is a potential risk in the RMP of long acting GLP-1 agonists and this safety concern is addressed in several ongoing studies. It was noted that the majority of cases were reported with liraglutide - including five cases in patients without a medical history of thyroid disorder or a family history of thyroid diseases, and that non-lethal thyroid C-cell tumours had been observed in the carcinogenicity studies. The PRAC agreed to request the MAH for liraglutide-containing products to provide a cumulative review of all

cases concerning medullary thyroid cancer, both from clinical trials and spontaneously reported with liraglutide.

The PRAC appointed Menno van der Elst as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Victoza (liraglutide) and Xultophy (liraglitude/insulin degludec) should submit to the EMA, within 60 days, a cumulative review of all cases of medullary thyroid cancer, both from clinical trials and spontaneous source reported with liraglutide-containing products. With this cumulative review, the MAH should also provide a discussion of relevant non-clinical data and scientific literature. Based on the review, the MAH should discuss the need for an update of the product information and risk management plan.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.6. Rivaroxaban – XARELTO (CAP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of pulmonary alveolar haemorrhage
EPITT 18291 – New signal
Lead Member State: SE

Background

Rivaroxaban is a highly selective direct factor Xa inhibitor indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) under certain conditions, for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in adult patients under certain conditions and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The exposure for Xarelto, a centrally authorised medicine containing rivaroxaban, is estimated to have been used for more than 3,753,911 patient-years worldwide, in the period from first authorisation in 2008 until September 2014.

During routine signal detection activities, a signal of pulmonary alveolar haemorrhage was identified by the EMA, based on 18 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the reported cases in EudraVigilance. Taking into account that in two of the five literature cases pulmonary alveolar haemorrhage progressed into respiratory failure, including one case with fatal outcome, that time to onset varied from three days to two years and that five suspected cases of pulmonary haemorrhage were retrieved in addition, the PRAC considered that a detailed review of all known cases was warranted. Therefore, the PRAC agreed to request the MAH to provide a

cumulative review of cases of pulmonary alveolar haemorrhage based on clinical trial and post marketing data, including the literature and preclinical and in vitro data.

Summary of recommendation(s)

- The MAH for Xarelto (rivaroxaban) should submit to the EMA, with the next PSUR (DLP: 15/09/2015), a cumulative review of pulmonary alveolar haemorrhage and other relevant MedDRA[5] preferred terms (PTs), based on clinical trials and post-marketing data, including the literature and pre-clinical and *in vitro* data. In the cumulative review, analysis should be performed with regard to risk factors for the reported events and discussions should be made on any experiences obtained in patients with high age, renal impairment, or other morbidity, or concomitantly treated with other medicines that may increase the risk, in the context of real-life. In addition, the MAH should discuss any possible mechanisms other than the pharmacological mechanism of action.

4.1.7. Tamsulosin (NAP)

Applicant: Astellas Pharma Europe B.V., various

PRAC Rapporteur: Sabine Straus

Scope: Signal of urinary incontinence
EPITT 18317 – New signal
Lead Member State: NL

Background

Tamsulosin is an alpha$_1$-adrenoceptor antagonist indicated for the treatment of functional symptoms of benign prostatic hyperplasia (BPH).

The exposure to tamsulosin containing medicines is estimated to have been more than 205,890 patients worldwide, in the period from first authorisation in 1993 to 2013.

During routine signal detection activities, a signal of urinary incontinence was identified by the Netherlands, based on 11 cases retrieved from the Netherlands Pharmacovigilance Centre (Lareb). The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the reported cases in Lareb. Taking into account that a positive de-challenge was reported in five cases and a positive re-challenge was reported in two cases, that urinary incontinence is currently not included in the product information and that no reports were retrieved in Lareb nor in EudraVigilance for other alpha$_1$-adrenoceptor antagonists, the PRAC agreed to request the MAH for Omnic to provide a cumulative review of 'urinary incontinence' and 'incontinence' cases in association with tamsulosin.

The PRAC appointed Sabine Straus as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Omnic (tamsulosin) should submit to the EMA, within 60 days, a cumulative review of 'urinary incontinence' and 'incontinence' cases in association with

[5] Medical dictionary for regulatory activities

tamsulosin. The review should include spontaneous reports, reports from clinical studies and the literature. In addition, the MAH should provide information on the underlying pharmacological mechanism. Finally, the MAH should discuss the need for any potential amendment to the product information, depending on the outcome of the review.

- 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. Digoxin (NAP)

Applicant: various

PRAC Rapporteur: Carmela Macchiarulo

Scope: Signal of increased mortality in patients with atrial fibrillation
EPITT 18259 – New signal
Lead Member State: IT

Background

Digoxin is a cardiac glycoside indicated in the management of chronic cardiac failure where the dominant problem is systolic dysfunction, and in the management of certain supraventricular arrhythmias, particularly chronic atrial flutter and fibrillation. It is specifically indicated where cardiac failure is accompanied by atrial fibrillation.

During routine signal detection activities, a recent publication of a retrospective, propensity-score matched, cohort study in 'Circulation: Arrhythmia and Electrophysiology'[6] on the risk of death in adults with atrial fibrillation treated by digoxin was identified by UK. Since the findings of the study were considered relevant, a signal was validated by the UK for further evaluation. Italy confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results of the retrospective, propensity-score matched, cohort study by *Freeman and al*, and considered the limitations of the study. The PRAC agreed to further explore this signal through a systematic review of the available literature, namely clinical trials and non-interventional studies, on mortality related to the use of digoxin in patients with atrial fibrillation, with or without heart failure. The review should focus particularly on risk factors such as age, gender, serum digoxin level and renal impairment.

The PRAC appointed Carmela Macchiarulo as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed to further assess the new information from this cohort study and to conduct a systematic review of the available literature, namely clinical trials and non-interventional studies, on mortality related to the use of digoxin in patients with atrial fibrillation, with or without heart failure. The review should focus particularly, but not

[6] Digoxin and Risk of Death in Adults with Atrial Fibrillation (AF), Freeman JV et al., Circ Arrhythm Electrophysiol. 2015 Feb;8(1):49-58

only, on risk factors such as age, gender, serum digoxin level and renal impairment. The PRAC Rapporteur will circulate an assessment report on this signal.

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

4.2.2. Mitotane – LYSODREN (CAP)

Applicant: Laboratoire HRA Pharma, SA

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of sex hormone disturbances and development of ovarian macrocysts
EPITT 18301 – New signal
Lead Member State: ES

Background

Mitotane is an adrenal cytotoxic active substance indicated in the symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma (ACC).

The exposure for Lysodren, a centrally authorised medicine containing mitotane, is estimated to have been more than 839 patient-years worldwide, in the period from first authorisation in 2004 until April 2014.

During routine signal detection activities, a signal of sex hormone disturbances and development of ovarian macrocysts was identified by the EMA, based on the article by *Salenave et al.*[7] published in the European Journal of Endocrinology in November 2014. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information provided in the literature article by *Salenave et al.* and considered that this signal merited further review. Therefore the PRAC agreed to request the MAH for Lysodren to provide a cumulative review of the effect of mitotane on sex hormone metabolism and also comment on the development of ovarian cysts observed in this study.

Summary of recommendation(s)

- The MAH for Lysodren (mitotane) should submit to the EMA, within 60 days, a cumulative review of the effect of mitotane on sex hormone metabolism and also comment on the development of ovarian cysts observed in this study. The MAH should review case reports from all sources and review the scientific literature.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[7] Salenave S et al. Ovarian macrocysts and gonadotrope-ovarian axis disruption in premenopausal women receiving mitotane for adrenocortical carcinoma or Cushing's disease. Eur J Endocrinol. 2015 Feb;172(2):141-9. doi: 10.1530/EJE-14-0670. Epub 2014 Nov 19.

4.3. Signals follow-up and prioritisation

4.3.1. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/SDA/033

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Arnaud Batz

Scope: Signal of progressive multifocal leukoencephalopathy (PML)
EPITT 18241– Follow-up to March 2015

Background

For background information, see PRAC Minutes March 2015. The MAH replied to the request for information on the signal of progressive multifocal leukoencephalopathy (PML) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses and additional information on the reported case of PML. Having considered the available evidence and taking into account that PML is a complex disease which may take a prolonged time before becoming clinically symptomatic, the PRAC considered that an update of the product information was warranted to include PML as a new warning and a new undesirable effect and that the RMP should be updated to include PML as an important identified risk. The prescriber's guide should also be updated with the risk of PML. The PRAC agreed to seek advice from the Scientific Advisory Group (SAG) neurology in the context of the ongoing PSUR procedure (PSUSA/001393/201502) regarding the risk factors and the monitoring (e.g. magnetic resonance imaging (MRI), John Cunningham virus (JCV) status, CD4+/CD8+ ratio) of patients treated with fingolimod, to identify patients at risk of developing PML and to aid earlier diagnosis.

Summary of recommendation(s)

- The MAH for Gilenya (fingolimod) should submit to the EMA, within 60 days, a variation to update the product information to include as a new warning that PML has been reported during post-marketing, to include PML as a new undesirable effect and to include the risk of PML in the prescriber's guide in Annex II. The MAH should also update the RMP to include the risk of PML as an important identified risk (under the risk of infections).
- The MAH should closely monitor the risk of PML in future PSURs.

For the full PRAC recommendations, see EMA/PRAC/277134/2015 published on the EMA website.

4.3.2. Latanoprost (NAP)

Applicant: Pfizer (Xalatan), various

PRAC Rapporteur: Julie Williams

Scope: Signal of increased reporting of eye disorders, in particular eye irritation, after change of formulation
EPITT 18068 – Follow-up to January 2015

Background

For background information, see PRAC Minutes September 2014 and PRAC Minutes January 2015. As agreed by the PRAC, further exploration and evaluation of relevant data sources was conducted by the PRAC Rapporteur.

Discussion

The PRAC discussed the severity and seriousness of the reported cases of eye irritation with the new formulation of Xalatan (latanoprost), available data from EudraVigilance and the available published literature on the influence of pH on ocular irritation. EudraVigilance data confirmed what had been seen from other data sources that there was a peak in reporting of eye irritation events following the launch of the new formulation of Xalatan. Review of the literature suggested that the increased incidence of eye irritation might be a result of the lower pH of the new formulation, although other factors cannot be excluded. Having considered the available evidence from spontaneous reports, EudraVigilance and the literature, the PRAC considered that patients receiving the new formulation of Xalatan should be warned about the importance of seeking medical advice if they experience excessive eye irritation.

Summary of recommendation(s)

- The MAH for Xalatan (latanoprost) should submit to the relevant EU national competent authorities (NCAs), within 60 days, a variation to update the package leaflet of the new formulation of Xalatan to advise patients to contact their healthcare professionals, should they experience excessive eye irritation.
- The MAH should continue to monitor events of eye irritation and present updated data in the next PSUR. A targeted follow-up questionnaire should be implemented to maximise the information obtained from future cases.

For the full PRAC recommendations, see EMA/PRAC/277134/2015 published on the EMA website.

4.3.3. Leflunomide – ARAVA (CAP) - EMEA/H/C/000235/SDA/053

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Sabine Straus

Scope: Signal of colitis
EPITT 18189 – Follow-up to January 2015

Background

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

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence from clinical trials, from spontaneous cases as well as supporting reports in literature, the PRAC agreed that the product information should be updated with respect to colitis.

Summary of recommendation(s)

- The MAHs for leflunomide-containing medicinal products should submit to the EMA or to the EU NCAs, as applicable, within 60 days a variation to update the product information to include a new warning that cases of colitis has been reported in patients treated with leflunomide and to include colitis as a new undesirable effect.

For the full PRAC recommendations, see EMA/PRAC/277134/2015 published on the EMA website.

4.3.4. Natalizumab – TYSABRI (CAP) - EMEA/H/C/000603/SDA/062

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of anaemia and haemolytic anaemia
EPITT 18137 – Follow-up to December 2014

Background

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

Discussion

The PRAC discussed the MAH's responses. Having considered the data submitted by the MAH, as well as the evidence from EudraVigilance cases and the literature, the PRAC agreed that the product information should be updated with respect to anaemia and haemolytic anaemia.

Summary of recommendation(s)

- The MAH for Tysabri (natalizumab) should submit to the EMA, within 60 days, a variation to update the product information to include anaemia and haemolytic anaemia as undesirable effects. The MAH should calculate the frequencies based on the data available in studies.

For the full PRAC recommendations, see EMA/PRAC/277134/2015 published on the EMA website.

4.3.5. Olanzapine – ZYPADHERA (CAP) - EMEA/H/C/000890/SDA/024, ZYPREXA (CAP) - EMEA/H/C/000115/SDA/045, ZYPREXA VELOTAB (CAP) - EMEA/H/C/000287/SDA/038

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Terhi Lehtinen

Scope: Signal of angle closure glaucoma
EPITT 18159 – Follow-up to January 2015

Background

For background information, see PRAC Minutes January 2015. The MAH replied to the request for information on the signal of angle closure glaucoma and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses and thorough overview of data related to olanzapine and glaucoma. Clinical trial data related to glaucoma is very limited and data from spontaneous reports indicated that events related to SMQ[8] narrow 'glaucoma' were very rarely reported. Given the background annual incidence rate of glaucoma events, and the limitations of spontaneous reports, the PRAC considered that the available data did not support a causal relationship between olanzapine and glaucoma. No relevant information was obtained from the literature. Having considered the available evidence, including data submitted by the MAH, the PRAC agreed that there was insufficient evidence to establish a causal relationship between olanzapine and glaucoma events. The current product information is considered sufficient in terms of contraindication regarding angle closure glaucoma (ACG) and the warnings related to anticholinergic effects.

Summary of recommendation(s)

- The MAHs for Zypadhera, Zyprexa and Zyprexa Velotab (olanzapine) should continue to monitor cases of angle closure glaucoma as part of the routine safety surveillance.

4.3.6. 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 March 2015

Background

For background information, see.PRAC Minutes November 2014, PRAC Minutes December 2014, PRAC Minutes January 2015 and PRAC Minutes March 2015. The PRAC Rapporteur presented a revised draft protocol for the analysis of the data from three published studies[9].

Discussion

The PRAC Rapporteur presented an updated draft protocol for the analysis of the data from three published studies, taking into account comments received from the PRAC and comments from the dedicated meeting with the study authors. Following the comments, the sections on aims, inclusion/exclusion criteria as well as the statistical methods have been updated. The PRAC endorsed the updated draft protocol and recommended proceeding with the analysis as planned. The PRAC will assess the results of the analysis when they become available.

Summary of recommendation(s)

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

- The PRAC endorsed the updated protocol for the analysis of the data from the three published studies and recommended to proceed with the analysis according to the updated action plan. The PRAC will assess the results of the analysis when they become available.

4.3.7. Sildenafil – REVATIO (CAP) - EMEA/H/C/000638/SDA/048

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Signal of pulmonary haemorrhage in off label paediatric use
EPITT 18183 – Follow-up to January 2015

Background

For background information, see PRAC Minutes January 2015. The MAH replied to the request for information on the signal of pulmonary haemorrhage in off-label paediatric use and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses and additional data from the literature, non-clinical data, clinical data, and post-marketing data. Having considered all the available evidence, the PRAC agreed that there is at present insufficient evidence to establish a causal relationship between pulmonary haemorrhage and sildenafil, therefore no update of the product information is warranted. The severe underlying disease, co-morbidities and co-medications of this vulnerable group of children may provide an alternative explanation for the events of pulmonary haemorrhage. In particular with regard to co-morbidities, it should be noted that the majority of the children were reported or assumed to be intubated and placed on mechanical ventilation. Barotrauma and free radical damage to lung tissue are well-recognised complications of mechanical ventilation and oxygenation, which might lead to a risk of acute respiratory distress syndrome (ARDS) which is an important causal factor for pulmonary haemorrhage. Nevertheless, due to the fact that the confounding factors hamper causality assessment and considering the seriousness and life threatening nature of pulmonary haemorrhage in premature children, the PRAC agreed that pulmonary haemorrhage should be included in the RMP as an important potential risk at the next regulatory opportunity and should be closely monitored in future PSURs.

Summary of recommendation(s)

- The MAH for Revatio (sildenafil in pulmonary arterial hypertension) should include pulmonary haemorrhage in the RMP as an important potential risk at the next regulatory opportunity and should closely monitor pulmonary haemorrhage in future PSURs. New cases of pulmonary haemorrhage should be evaluated and in case new relevant information is detected, the MAH should report this for further evaluation on a causal relationship of pulmonary haemorrhage and sildenafil.

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. Dinutuximab – EMEA/H/C/002800, Orphan

Applicant: United Therapeutics Europe Ltd

Scope: Treatment of neuroblastoma, treatment of high-risk neuroblastoma

5.1.2. Plasmodium falciparum circumsprozoite protein fused with hepatitis B surface antigen (rts) and combined with hepatitis B surface antigen(s) in the form of non-infectious virus-like particles (vlps) produced in yeast cells (saccharomyces cerevisiae) by recombinant DNA technology - EMEA/H/W/002300

Scope: Active immunisation against malaria

5.1.3. Pitolisant - EMEA/H/C/002616, Orphan

Applicant: Bioprojet Pharma

Scope: Treatment of narcolepsy

5.1.4. Recombinant L-asparaginase - EMEA/H/C/002661, Orphan

Applicant: Medac Gesellschaft fuer klinische Spezialpraeparate GmbH

Scope: Combination therapy for B/T cell lymphoblastic leukaemia (ALL) or B/T cell lymphoblastic lymphoma (LBL)

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

See also ANNE I 14.2.

5.2.1. Teduglutide – REVESTIVE (CAP) - EMEA/H/C/002345/II/0009

Applicant: NPS Pharma Holdings Limited

PRAC Rapporteur: Torbjorn Callreus

Scope: Updated RMP (version 6.0) to include the results of long-term study CL0600-021, the proposed use of nursing services as a risk minimisation measure effort to decrease adverse events associated with fluid overload and to include updated review of non-clinical risks, clinical exposure data and post-marketing exposure data

Background

Teduglutide is a glucagon-like peptide-2 (GLP-2) analogue indicated for the treatment of adult patients with short bowel syndrome (SBS) under certain conditions.

The PRAC is evaluating a type II variation procedure for Revestive, a centrally authorised product containing teduglutide, to reflect in the RMP the results of a long-term study CL0600-021, the use of nursing services as a risk minimisation measure to decrease adverse events associated with fluid overload and to include updated review of non-clinical risks, clinical exposure data and post-marketing exposure data. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. See PRAC Minutes October 2014, PRAC Minutes December 2014 and PRAC Minutes March 2015.

Summary of advice

- The RMP version 6.3 for Revestive (teduglutide) in the context of the variation under evaluation by the PRAC and CHMP could be considered acceptable provided that satisfactory responses to the fourth list of questions detailed in the adopted assessment report are submitted.
- Having reviewed the MAH's responses to the third list of questions, and considering the difficulty of identifying a clear justification for additional risk minimisation measures (aRMMs), the limited usage of the product and the disproportionate proposed approaches to evaluating the effectiveness of the proposed aRMMs, the PRAC did not endorse the proposed aRMMs and considered that routine pharmacovigilance and risk minimisation measures were sufficient for managing the risks of teduglutide. The MAH should submit a revised version of the RMP accordingly.

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

See also ANNEX I 14.3.

5.3.1. Infliximab – REMICADE (CAP) - EMEA/H/C/000240/II/0188

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of SmPC sections 4.4, 4.5, 4.6 and 4.8 to include updated pregnancy information following submission of the final report of the Pregnancy and Infant Outcomes Research Initiative (PRIORITY) study registry and additional reports on infections and agranulocytosis in neonates and infants who have been exposed to Remicade in utero. The package leaflet is updated accordingly. Furthermore, the patient alert card is updated accordingly. In addition, the Marketing authorisation holder took the opportunity to revise Annex II D to bring it in line with Annex 10 of the RMP

Background

Infliximab is a tumour necrosis factor alpha (TNF-α) inhibitor indicated for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis under certain conditions.

The CHMP is evaluating a type II variation procedure for Remicade, a centrally authorised product containing infliximab, to include updated pregnancy information in the product

information following the submission of the final report of the Pregnancy and Infant Outcomes registry and additional reports on infections and agranulocytosis in neonates and infants who have been exposed to Remicade in utero. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 11.0 for Remicade (infliximab) in the context of the variation under evaluation by the CHMP was considered acceptable provided that an updated risk management plan and satisfactory responses to the list questions adopted by the PRAC are submitted.
- The PRAC considered that 'disseminated BCG[10] infection after BCG vaccination of infants up to 6 months of age who were exposed in utero to infliximab' could not be added as a separate risk in the safety specifications. Instead, the MAH should update the important identified risk 'tuberculosis' accordingly. The MAH should also add 'adverse effects related to TNF alpha inhibition in infants who have been exposed to infliximab in utero' as a new important identified risk. In addition, the PRAC considered that the PRIORITY[11] cohort study could not be removed from the list of ongoing pharmacovigilance activities, since it is not yet complete. The MAH should provide details as to when data from longer follow-up can be made available. Moreover, the PRAC noted that approximately 30% of infliximab exposed pregnancies were lost to follow up at 12 months. The MAH should therefore discuss this issue, including a comparison of the characteristics of those who were maintained in the study with those who were lost to follow up. The MAH should also discuss whether further examples of live vaccines in addition to BCG should be added to the product information and the educational material, in association with the recommendation not to administer live vaccines within 6 months after birth to an infant who has been exposed in utero to infliximab.
- The PRAC adopted a list of questions to the Vaccine Working Party (VWP) to be further considered at CHMP in May 2015, regarding whether there is a need to further optimise the recommendations related to the administration of a live vaccine to an infant previously exposed in utero to a TNF inhibitor.

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. Arsenic trioxide – TRISENOX (CAP) - PSUSA/00235/201409

Applicant: Teva B.V.

PRAC Rapporteur: Arnaud Batz

Scope of procedure: Evaluation of a PSUSA procedure

[10] Bacille Calmette-Guérin
[11] Exposure-based, prospective cohort study, following patients in the USA

Background

Arsenic trioxide is an antineoplastic agent indicated for induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Trisenox, a centrally authorised medicine containing arsenic trioxide, 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 Trisenox (arsenic trioxide) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a cumulative review of cases reporting off-label use with arsenic trioxide, in particular regarding its use in first line therapy (concomitant chemotherapies should be provided), as well as a cumulative review of cases pertaining to hepatic disorders, in particular acute hepatitis and hepatic failure.
- The MAH should submit to the EMA, within 60 days, an estimation of the incidence of haemorrhage events in patients with an acute promyelocytic leukaemia disease, especially the incidence of cerebral haemorrhage. The MAH should also provide information on the search criteria used for the cumulative review of cerebral haemorrhage. Amongst the 22 cases of haemorrhage presented by the MAH, only 9 cases were considered as possibly related to arsenic trioxide. The MAH should discuss why the other 13 cases were excluded. Finally, the MAH should present and discuss the arsenic trioxide non clinical data concerning the risk of haemorrhage and especially of cerebral haemorrhage. A mechanistic explanation of the effects of arsenic trioxide on the risk of haemorrhage should also be discussed. Based on the information provided in response to these questions, the MAH should consider whether an update of the product information is warranted.

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

6.1.2. Deferasirox – EXJADE (CAP) - PSUSA/00939/201410

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Arnaud Batz

Scope of procedure: Evaluation of a PSUSA procedure

Background

Deferasirox is an orally active chelator highly selective for iron (III) indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major aged 6 years and older, and when deferoxamine therapy is contraindicated or inadequate under certain conditions and for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or

inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Exjade, a centrally authorised medicine containing deferasirox, 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 Exjade (deferasirox) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new warning on deferasirox reintroduction after a hypersensitivity reaction (due to the risk of anaphylactic shock) to reinforce the existing contraindication on hypersensitivity. Therefore the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should address some issues, in particular, it should provide clarifications on risk factors for renal disorders and risk factors for gastrointestinal haemorrhages, detailed reviews on haemorrhagic and ischemic events and long-term safety data. Moreover, the MAH should provide additional safety data for iron chelators combination by adequately analysing results from study CICL670A2214 (HYPERION[2]) and a comprehensive clinical review of cases with iron chelators combinations, including a literature review on combination therapy.
- The MAH should consider upgrading 'hepatic failure' from an important potential risk to an important identified risk in the RMP within the next regulatory procedure affecting 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.

6.1.3. Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis b (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) – HEXACIMA (CAP); HEXAXIM (Art 58[13]); HEXYON (CAP) - PSUSA/10091/201410

Applicant: Sanofi Pasteur

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

Background

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type b conjugate vaccine (adsorbed) (DTaP-IPV-HB-Hib) is indicated for primary and booster vaccination of infants and toddlers from six

[12] Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

[2] Efficacy and safety of deferasirox in combination with deferoxamine followed by deferasirox monotherapy in severe cardiac iron overload

[13] 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)

weeks to 24 months of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae type b* (Hib). Hexaxim is exclusively intended for markets outside the European Union.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Hexacima, Hexyon and Hexaxim, centrally authorised/approved medicines containing DTaP-IPV-HB-Hib, and issued a recommendation on their marketing authorisations and scientific opinion.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Hexacima, Hexyon and Hexaxim (diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type b) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations and of the scientific opinion should be maintained.
- In the next PSUR, the MAH/SOH[14] should comment on the one case of death, one case of convulsion, one case of epilepsy and one case of febrile convulsion reported from clinical trials during the covering period of this PSUR.

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. Eribulin – HALAVEN (CAP) - PSUSA/01254/201411

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope of procedure: Evaluation of a PSUSA procedure

Background

Eribulin is a non-taxane, microtubule dynamics inhibitor indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Halaven, a centrally authorised medicine containing eribulin, 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 Halaven (eribulin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new warning on the need for flushing the intravenous line to ensure administration of the complete

[14] Scientific Opinion Holder

dose in the 'special precautions for disposal and other handling' section. Therefore the current terms of the marketing authorisation(s) should be varied[15].

- In the next PSUR, the MAH should discuss the events of QT prolongation observed in completed clinical trials. In addition, the MAH should closely monitor severe cutaneous adverse reactions, any new events should be discussed. Furthermore, the MAH should report any new safety data on combination therapy, if available. Finally, the MAH should discuss the case of aplasia reported in the SOC[16] 'congenital, familial and genetic disorders'.

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. Eslicarbazepine – ZEBINIX (CAP) - PSUSA/01267/201410

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Martin Huber

Scope of procedure: Evaluation of a PSUSA procedure

Background

Eslicarbazepine is an antiepileptic indicated as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zebinix, a centrally authorised medicine containing eslicarbazepine, 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 Zebinix (eslicarbazepine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include drug reaction with eosinophilia and systemic symptoms (DRESS) as a new undesirable effect with an unknown frequency and delete the statement that no second or higher degree atrioventricular block has been observed in eslicarbazepine treated patients, under the description of selected adverse reactions. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should address the following issues: serious dermatologic reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis and DRESS, as well as hyponatraemia, potential for suicidality, convulsion, aggression, severe anaemia, pancytopenia, or agranulocytosis, cases of liver injury (increase of Gamma-glutamyltransferase), cardiovascular/cerebrovascular ischemia, congenital anomalies, thyroid function

[15] Update of SmPC section 6.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[16] MedDRA System Organ Class
[17] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

changes, INR[18] and aPTT[19] increase and finally second or third degree atrioventricular block.

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. Granisetron – SANCUSO (CAP) - PSUSA/10101/201410

Applicant: ProStrakan Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope of procedure: Evaluation of a PSUSA procedure

Background

Granisetron is a highly selective antagonist of 5-hydroxytryptamine (5-HT_3 receptors) and granisetron transdermal patch is indicated in adults for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy, for a planned duration of 3 to 5 consecutive days, where oral anti-emetic administration is complicated by factors making swallowing difficult.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sancuso, a centrally authorised medicine containing granisetron, 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 Sancuso (granisetron) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide an analysis of cases of patch adhesion failure with emphasis on information on whether these patches were used correctly and whether specific situations were more frequently reported under which the patch failed to adhere to the patients' skin, and the nature of adverse drug reactions reported.

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. Lurasidone – LATUDA (CAP) - PSUSA/10114/201410

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

Background

[18] international normalised ratio
[19] activated partial thromboplastin time

Lurasidone is a selective blocking agent of dopamine and monoamine effects indicated for the treatment of schizophrenia in adults aged 18 years and over.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Latuda, a centrally authorised medicine containing lurasidone, 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 Latuda (lurasidone) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to revise the current warning on neuroleptic malignant syndrome and reflect that it has been reported with antipsychotics including lurasidone, and to include neuroleptic malignant syndrome as new undesirable effect with a rare frequency.
- In the next PSUR, the MAH should review cases of hyperactivity and should update the pharmacovigilance plan table to include more specific safety concerns that are to be addressed in the PASS study.

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

6.1.8. Macitentan – OPSUMIT (CAP) - PSUSA/10115/201410

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope of procedure: Evaluation of a PSUSA procedure

Background

Macitentan is an orally active potent endothelin receptor antagonist indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of World Health Organization (WHO) functional class II to III.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Opsumit, a centrally authorised medicine containing macitentan, 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 Opsumit (macitentan) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include as new undesirable effects nasal congestion with a common frequency and oedema and fluid retention with a very common frequency, and to amend the current information on oedema/fluid retention from clinical trials in the description of selected adverse reactions. Therefore the current terms of the marketing authorisation(s) should be varied[20].

[20] 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

- In the next PSUR, the MAH should clarify whether the pregnancy cases detected with macitentan treatment were reported in the EU or not, in order to assess the effectiveness of educational material of macitentan in the EU. The MAH should also provide a discussion regarding safety data collected in the DUAL-2[21] study in patients with ischaemic digital ulcer associated with systemic sclerosis.

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

6.1.9. Micafungin – MYCAMINE (CAP) - PSUSA/02051/201410

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope of procedure: Evaluation of a PSUSA procedure

Background

Micafungin is an antimycotic which inhibits the synthesis of 1,3-β-D-glucan (an essential component of the fungal cell wall) indicated for the treatment of invasive candidiasis, oesophageal candidiasis, in the prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mycamine, a centrally authorised medicine containing micafungin, 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 Mycamine (micafungin) in the approved indication(s) remains favourable.
- Nevertheless, Annex II should be updated to include a further key element to the checklist for prescribers to highlight the restricted nature of the indications authorised due to the important potential risk of hepatocellular carcinoma. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should provide stratified and extrapolated exposure data from the MYRIADE study, a French national observational prospective study on the use of micafungin as prophylactic or curative treatment for invasive fungal infections (e.g. for age groups) for EU only region without including other non-EU countries.
- The MAH should perform, in the next update of the RMP, surveys to measure physicians' knowledge and behaviour, including in Greece based on the apparent off-label usage and extensive exposure in this EU Member State and to update the RMP in line with the above amendment to Annex II.

[21] Prospective, randomized, placebo-controlled, double-blind, multicentre, parallel group study to assess the efficacy, safety and tolerability of macitentan in patients with ischemic digital ulcers associated with systemic sclerosis
[22] Update of Annex II. 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.

6.1.10. Ocriplasmin – JETREA (CAP) - PSUSA/10122/201410

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

Background

Ocriplasmin has proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (VRI) and is indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with a macular hole of diameter less than or equal to 400 microns.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jetrea, a centrally authorised medicine containing ocriplasmin, 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 Jetrea (ocriplasmin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include new undesirable effects: night blindness and pupillary reflex impaired with uncommon frequencies, and cystoid macular oedema as part of the undesirable effect macular oedema. Occurrence of visual symptoms perceived in the contralateral eye or bilaterally should also be added. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should discuss a number of issues, especially the MAH should present an analysis of data from studies TG-MV-014 and TG-MV-022 and propose an update of the product information to give useful information to prescribers regarding events of photoreceptor alteration. This should include available information on frequency of events, the nature, severity and duration of associated clinical effects and any long term clinical implications. Additional risk minimisation measures should be proposed as necessary.

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.

6.1.11. Pazopanib – VOTRIENT (CAP) - PSUSA/02321/201410

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

[23] 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

Scope of procedure: Evaluation of a PSUSA procedure

Background

Pazopanib is a tyrosine kinase inhibitor indicated for the treatment of advanced renal cell carcinoma under certain conditions and selective subtypes of advanced soft tissue sarcoma under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Votrient, a centrally authorised medicine containing pazopanib, 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 Votrient (pazopanib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning on the need for contraception during treatment and at least 2 weeks after treatment in the fertility, pregnancy and lactation section. Therefore the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should closely monitor cases of paediatric off-label use.

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

6.1.12. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – AFLUNOV (CAP); prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - FOCLIVIA (CAP), PREPANDEMIC INFLUENZA VACCINE (H5N1) (SURFACE ANTIGEN, INACTIVATED, ADJUVANTED) NOVARTIS VACCINES AND DIAGNOSTIC (CAP) - PSUSA/10008/201410

Applicant: Novartis Vaccines and Diagnostics S.r.l.

PRAC Rapporteur: Carmela Macchiarulo

Scope of procedure: Evaluation of a PSUSA procedure

Background

Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) is indicated for the prophylaxis of influenza in an officially declared pandemic situation. Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) is indicated for active immunisation against H5N1 subtype of influenza A virus.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Foclivia, a centrally authorised vaccine containing pandemic influenza (H5N1) (surface antigen, inactivated, adjuvanted) and of Aflunov and Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostic, centrally authorised vaccines containing prepandemic influenza (H5N1) (surface antigen, inactivated, adjuvanted), and issued a recommendation on their marketing authorisations.

[24] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Foclivia (pandemic influenza (H5N1) (surface antigen, inactivated, adjuvanted)), Aflunov and Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostic (prepandemic influenza (H5N1) (surface antigen, inactivated, adjuvanted)) in the approved indications remains favourable.
- With regard to Foclivia, the current terms of the marketing authorisation(s) should be maintained.
- With regard to Aflunov and Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostic, the product information should be updated to include a new warning on syncope as a psychogenic response to needle injection. Therefore the current terms of the marketing authorisations should be varied[25].

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.

6.1.13. Regadenoson – RAPISCAN (CAP) - PSUSA/02616/201410

Applicant: Rapidscan Pharma Solutions EU Ltd.

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

Background

Regadenoson is a selective coronary vasodilator (agonist for the A_{2A} adenosine receptor) for use as a pharmacological stress agent for radionuclide myocardial perfusion imaging (MPI) in adult patients unable to undergo adequate exercise stress.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rapiscan, a centrally authorised medicine containing regadenoson, 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 Rapiscan (regadenoson) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include in the current warning on bronchoconstriction that respiratory arrest and bronchoconstriction can occur with regadenoson treatment and to clarify that appropriate bronchodilator therapy and resuscitative measures should be available for all patients prior to regadenoson administration (not just those with a history of bronchoconstrictive disease). In addition, the product information should be updated to include as new undesirable effects respiratory arrest and bronchospasm with unknown frequencies and

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

wheezing with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[26].

- In the next PSUR, the MAH should carefully monitor cases of bronchoconstriction and respiratory arrest. In particular, the MAH should ensure that strenuous efforts are made to obtain follow up information on cases involving patients with respiratory disease to determine if bronchoconstriction or respiratory arrest in this group results in more serious adverse outcomes, especially death.
- The MAH should be requested within the next regulatory procedure affecting the RMP to update the RMP to include respiratory arrest and bronchoconstriction as important identified risks, preferably combined under a single risk, and to amend accordingly all relevant sections 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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.2. PSUR procedures including Centrally Authorised Products (CAPs) and Nationally Authorised Products (NAPs)

See also ANNEX I 15.2.

6.2.1. Melatonin – CIRCADIN (CAP), NAP - PSUSA/01963/201409

Applicant: Rad Neurim Pharmaceuticals EEC Ltd., various

PRAC Rapporteur: Magda Pedro

Scope of procedure: Evaluation of a PSUSA procedure

Background

Melatonin is a naturally occurring hormone produced by the pineal gland (structurally related to serotonin) indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Circadin, a centrally authorised medicine containing melatonin, 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 Circadin (melatonin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include information on severe post-marketing cases of overdose. Therefore the current terms of the marketing authorisation(s) should be varied[27].

[26] 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

- In the next PSUR, the MAH should keep open the signal on 'blood prolactin increased' and evaluate any further additional reports, since hyperprolactinaemia is an important potential risk with three cumulative reported cases.
- Within the next update of the RMP, the MAH should remove the risk 'hyperammonaemia' from the list of important potential risks..

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

6.3. PSUR procedures including Nationally Approved Products (NAPs) only

6.3.1. Adapalene, benzoyl peroxide (NAP) – PSUSA/00000059/201409

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Adapalene is a naphthoic acid derivative with retinoid-like activity and benzoyl peroxide an antibacterial agent, the combination is indicated for the topical treatment of *acne vulgaris* when comedones, papules and pustules are present.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing adapalene/benzoyl peroxide, 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 adapalene/benzoyl peroxide in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should submit the results of the foetal biopsy and clarify the reason why the pregnancy was considered at high risk for the one case of hydrops foetalis reported in a patient exposed to several drugs including adapalene/benzoyl peroxide.
- The MAHs which have an RMP in place should be requested to include bullous dermatitis as an important potential risk in the RMP within the next upcoming regulatory opportunity.

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

[27] Update of SmPC section 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.3.2. Atenolol, chlortalidone (NAP) – PSUSA/00000260/201409

Applicant: various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

Background

Atenolol is a cardio-selective beta-blocker and chlortalidone a diuretic, the combination is indicated for the treatment of hypertension, particularly suited to older patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing atenolol/chlortalidone, 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 atenolol/chlortalidone in the approved indications remains favourable.
- Nevertheless, the product information should be updated to include as a new undesirable effect lupus-like syndrome with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[28].

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

6.3.3. Hexaminolevulinate hydrochloride (NAP) – PSUSA/00001606/201409

Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Hexaminolevulinate hydrochloride is a diagnostic agent indicated as adjunct to standard white light cystoscopy to contribute to the diagnosis and management of bladder cancer in patients with known or high suspicion of bladder cancer.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing hexaminolevulinate hydrochloride, and issued a recommendation on its marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of hexaminolevulinate hydrochloride in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.

[28] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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

6.4. Follow-up to PSUR procedures

See ANNEX I 15.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[29]

See also ANNEX I 16.1.

7.1.1. Afamelanotide – SCENESSE (CAP) - EMEA/H/C/PSP/0022

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: 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) and for a retrospective study comparing long term safety data and outcome endpoints in patients receiving and not receiving afamelanotide, or having discontinued the use of Afamelanotide

Background

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

A protocol for a disease registry to assess long-term safety and generate data on the clinical benefits of afamelanotide 16 mg implant in patients with EPP and to assess long term safety data and outcome endpoints was submitted to the PRAC 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 1 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that the design of the study did not fulfil the study objectives. The MAH submitted a single protocol to address both the requirement to conduct a disease registry and to perform a retrospective chart review to assess off-label use. The PRAC agreed that the MAH should conduct two separate studies (a disease registry and a retrospective chart review). A number of concerns regarding study objectives, study design, variables, data sources, planned analysis and study size 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 day-assessment timetable will be applied.

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

7.1.2. Dexamfetamine (NAP) - EMEA/H/N/PSP/0018

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Julie Williams

Scope: Protocol for a post-authorisation safety study to evaluate the long-term safety profile of dexamfetamine in children with attention deficit hyperactivity disorder (ADHD), specifically targeting key issues such as cardiovascular events, growth and psychiatric related adverse events

Background

Dexamfetamine is indicated as a second line treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6 years up to 18 years.

A protocol for a post-authorisation safety study to evaluate the long-term safety profile of dexamfetamine in children with ADHD, specifically targeting key issues such as cardiovascular events, growth and psychiatric related adverse events was submitted to the PRAC by the MAH in accordance with conditions to the marketing authorisation included in the EC decision Annex IV for the referral under Article 29(4) of Directive 2001/83/EC (EMA/709170/2013) for dexamfetamine-containing medicines.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 2.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that that the design of the study did not fulfil the study objectives. The stated objective was considered to adequately reflect the safety issues to be addressed with such a study, but the PRAC considered there were issues identified in the protocol regarding the sample size and the duration of follow up that could impact on the meaningfulness of the results. The PRAC therefore recommended that:

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

7.1.3. Ivabradine – CORLENTOR (CAP), PROCORALAN (CAP) - EMEA/H/C/PSP/J/0019

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope: PASS protocol for a drug utilisation study (DUS) in selected European countries: multinational, retrospective, observational study to assess the effectiveness of risk-minimisation measures

Background

Procoralan and Corlentor are centrally authorised medicines containing ivabradine. They are indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease in adults with normal sinus rhythm and heart rate ≥ 70 bpm under certain conditions and in chronic heart failure New York Heart Association (NYHA) classes II to IV with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

A protocol for a drug utilisation study to assess the effectiveness of risk-minimisation measures implemented as the outcome of the Article 20 of Regulation (EC) No 726/2004 (EMA/676096/2014) for ivabradine-containing medicines was submitted to the PRAC by the MAH in accordance with the condition to the marketing authorisations.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.1 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 some aspects of the design of the study did not fulfil the obligations. The overall research objectives and methods were considered acceptable but a number of concerns regarding study design, milestones, variables, setting and data analysis 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 14 days to the EMA. A 15 day-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[30]

See also ANNEX I 16.2.

7.2.1. Voriconazole – VFEND (CAP) - EMEA/H/C/000387/MEA 087.2

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 087.1 as adopted in November 2014, including revised PASS protocol for study A1501102, evaluating the effectiveness of risk minimisation measures (RMMs) that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in the EU

Background

Vfend is a triazole antifungal agent used in the treatment under certain conditions of invasive aspergillosis, candidaemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* infections, serious fungal infections caused by *Scedosporium* and *Fusarium* and prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant recipients.

As part of the RMP for Vfend, a centrally authorised medicine containing voriconazole, the MAH was required to conduct a PASS in order to measure the effectiveness of the additional risk minimisation measures to mitigate the important identified risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity. The MAH submitted a revised protocol for study A1501102[31] (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

[30] 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

[31] Evaluation of the effectiveness of additional risk minimisation measures (aRMMs) that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in the European Union (EU)

- The study protocol for the proposed PASS for Vfend (voriconazole) could be acceptable provided that the MAH sets the minimum acceptable percentage of Healthcare Professionals providing correct answers for each of the study objectives in order to consider the overall programme to be adequately successful for each of the risks. The MAH is requested by the PRAC to start the survey as soon as possible and should provide the final study report within 90 days after the completion of the data collection.

7.3. Results of PASS imposed in the marketing authorisation(s)[32]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[33]

See ANNEX I 16.4.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[34]

See ANNEX I 16.5.

7.6. Others

See also ANNEX I 16.6.

7.6.1. Ketoconazole – KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/ANX 002

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Viola Macolić Šarinić

Scope: Submission of a feasibility study for a PASS: multi-country, observational registry to collect clinical information on patients with Cushing's syndrome patients 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

Background

Ketoconazole HRA is an imidazole derivative and potent inhibitor of cortisol synthesis indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

As part of the RMP for Ketoconazole HRA, there was a request to conduct a post-authorisation study (PASS) to collect clinical information on patients with Cushing's syndrome exposed to ketoconazole (preferably considering the existing *European Registry on Cushing's syndrome (ERCUSYN) registry where feasible*), to assess drug utilisation patterns and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole (category 1 study).

[32] In accordance with Article 107p-q of Directive 2001/83/EC
[33] 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
[34] In line with the revised variations regulation for any submission before 4 August 2013

The MAH submitted the results of a feasibility study of adding safety items to the existing ERCUSYN[35] database.

Summary of advice

- The PRAC discussed the results of the study on the feasibility of adding safety items to the existing ERCUSYN database submitted by the MAH and agreed that the proposed PASS to collect clinical information in patients with Cushing's syndrome exposed to ketoconazole using the ERCUSYN to assess drug utilisation patterns and to document the safety and effectiveness of ketoconazole is feasible taking into account the views from the physicians. The MAH should provide satisfactory responses to a list of questions agreed by the PRAC along with a revised study report for this PASS feasibility study within 30 days.

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

8.1. Annual reassessments of the marketing authorisation

See ANNEX I 17.1.

8.2. Conditional renewals of the marketing authorisation

See ANNEX I 17. 17.2.

8.3. Renewals of the marketing authorisation

8.3.1. Vernakalant – BRINAVESS (CAP) - EMEA/H/C/001215/R/0023 (without RMP)

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Five-year renewal of the marketing authorisation

Background

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

Brinavess, a centrally authorised medicine containing vernakalant, was authorised in 2010.

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

Summary of advice

- Based on the review of the available pharmacovigilance data for Brinavess (vernakalant) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation was warranted based on

[35] European register on Cushing's syndrome

some important risks (bradycardia, ventricular arrhythmia and atrial flutter, and severe hypotension) not yet fully characterised. This advice is supported by the need to fully assess the effectiveness of the additional risk minimisation measures implemented in the ongoing SPECTRUM[36] PASS study.

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 minutes.

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

10.3.1. Saxagliptin – ONGLYZA (CAP) – EMEA/H/C/001039/LEG 038; saxagliptin, metformin - KOMBOGLYZE (CAP) – EMEA/H/C002059/LEG 015

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: PRAC consultation on the assessment of data on mortality from the SAVOR study

Background

Saxagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, used alone or in combination with metformin, a biguanide, is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control under certain conditions.

[36] SPECTRUM: prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant IV sterile concentrate

In 2014, the CHMP assessed a Type II variation (WS/0529/G[37]) to reflect data outcomes from the SAVOR[38] study in the product information. In April 2015, new FDA analyses relating to the SAVOR study were made available. Based on the new data and the assessment of the MAH's responses to a CHMP list of questions adopted in April 2015, the CHMP requested advice from the PRAC.

Summary of advice

- Based on the review of the available information, the PRAC agreed that further clarification was needed regarding the underlying reasons for the observed imbalance in all-cause mortality before any conclusions on causality can be drawn. The PRAC agreed a list of questions to be addressed to the MAH to be further considered at CHMP in May 2015. The PRAC will provide CHMP with further advice in September 2015 following the assessment of the MAH's responses to the list of questions.

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

11.2.1. Gadolinium-containing contrast agents (GdCA): gadoversetamide – OPTIMARK (CAP) Gadobenate dimeglumine; gadobutrol; gadodiamide; gadopentetic acid dimeglumine, gadoteric acid (intra articular formulation); gadoteric acid (intrvenous and intravascular formulations); gadoteridol; gadoxetic acid disodium (NAP)

Applicant: various

Lead member: Rafe Suvarna

Scope: PRAC consultation on a post-authorisation measure resulting from the 2010 Article 20 and Article 31 referral procedures for gadolinium-containing contrast agents

Background

Gadolinium containing contrast agents (GdCAs) are used intravenously as an enhancement for magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). A referral procedure under Article 31 of Directive 2001/83/EC, completed in 2010 (EMEA/H/A-31/1097), focused on measures to minimise the risk of nephrogenic systemic fibrosis (NSF) in specific patient groups, and concerns regarding accumulation of gadolinium in bone and

[37] CHMP opinion dated July 2014: update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC with regard to posology recommendations and warnings for use in elderly patients and patients with renal impairment, minor amendment of the existing warning on skin disorders, lack of inhibition of CYP2C8 by saxagliptin and inclusion of safety and efficacy information from study D1680C00003 (SAVOR), a cardiovascular outcome study, and study D1680L00002 (GENERATION), a study comparing saxagliptin with glimepiride in elderly patients

[38] Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) study: large, randomised, double-blind, placebo-controlled postmarketing study designed to evaluate the cardiovascular effects of Onglyza when added to current type 2 diabetes background therapy in adult patients with type 2 diabetes mellitus at risk for cardiovascular disease

skin tissue. As part of the outcome of the referral procedure, the CHMP agreed that further clinical studies were warranted to assess the retention of gadolinium in bone and skin. Studies were initiated, ALS-Gd64-001[39] led by a consortium of MAHs, including the MAH for Optimark (gadoversetamide), and GMRA-102 concerning two products authorised by national procedures. In October 2014, MAHs responsible for ALS-Gd64-001 requested an extension to the submission deadline (deadline for submission of the final study report for ALS-Gd64-001 initially planned for Q2 2015) due to slow rates of patient recruitment. GMRA-102 is also affected by the same issue.
With regard to ALS-Gd64-001, following a list of questions the CHMP reviewed in April 2015 the proposals made by the relevant MAHs to change the protocol to accelerate recruitment, or other measures to ensure timely delivery of study data while measuring their impact on the study objectives. At its April 2015 meeting, the CHMP reviewed the MAHs' responses and considered that GMRA-102 should be also reviewed in parallel by the PRAC and suggested to consult the Scientific Advice Working Party (SAWP) as the WP was involved in reviewing the initial study design.
UK requested PRAC advice on the issue of recruitment for GMRA-102, while considering the position of the CHMP.

Summary of advice

- Based on the available data, the PRAC agreed with the UK on the possible protocol changes that were most suitable to be explored further, and also agreed to consult the SAWP by addressing a combined list of questions with the CHMP for ALS-Gd64-001 and GMRA-102 studies. The PRAC adopted the consolidated list of questions in order to explore options for accelerating recruitment and timely delivery of meaningful data. Follow-up discussion will take place in July 2015 once the SAWP responses are made available.

- The PRAC discussed recent publications[40] suggesting evidence of gadolinium accumulation in the brain. In the next PSUR, MAHs for products containing gadobenate dimeglumine, gadobutrol, gadodiamide, gadopentetic acid dimeglumine, gadoteric acid (intra articular formulation), gadoteric acid (IV and intravascular formulations), gadoteridol and gadoxetic acid disodium should submit detailed reviews of all relevant information on brain accumulation that has become available since the finalisation of the referral procedure along with a discussion of the possible safety implications, as per the requirements set out in the EURD list (DLP for all substances: 30/04/2015, with a submission date by: 29/07/2015). With regard to gadoversetamide, the MAH should

[39] Exploratory evaluation of the potential for long-term retention of Gadolinium in the bones of patients who have received Gadolinium based Contrast Agents according to their medical history
[40] Errante Y et al. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. Invest Radiol. 2014 Oct;49(10):685-90
Kanda T et al. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology. 2014 Mar;270(3):834-41
Kanda T et al. High signal intensity in dentate nucleus on unenhanced T1-weighted MR images: association with linear versus macrocyclic gadolinium chelate administration. Radiology. 2015 Jan 27:140364.
Kanda T et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. Radiology. 2015 May 5:142690
McDonald RJ et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. radiology. 2015 Mar 5:150025
Quattrocchi CC et al. Gadodiamide and dentate nucleus T1 hyperintensity in patients with meningioma evaluated by multiple follow-up contrast-enhanced magnetic resonance examinations with no systemic interval therapy. Invest Radiol. 2015 Mar 11
Radbruch A et al. Gadolinium retention in the Ddentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology. 2015 Apr 6:150337.

submit the same detailed review as part of the ongoing PSUSA procedure (DLP: 31/01/2015).

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. Competence and experience of Committee members - recommendation to National Competent Authorities in appointment process

The EMA Secretariat presented to the PRAC proposed criteria for experience and expertise for nominating authorities to take into consideration when appointing new CHMP and PRAC members and alternates. PRAC members were invited to review the proposed criteria and send any comments by 3 June 2015. The criteria will be presented for recommendations at the EMA Management Board scheduled on 11 June 2015.

12.2. Coordination with EMA scientific committees or CMDh-v

12.2.1. Appointment of CHMP liaison person for PRAC-led variations

The topic was deferred to June 2015 PRAC meeting.

12.3. Coordination with EMA working parties/working groups/drafting groups

12.3.1. Biostatistics Working Party - statistical reporting of safety data in product information

The EMA Secretariat presented to the PRAC the outcome of the Biostatistics Working Party (BSWP) analysis on how safety data are expressed in product information (PI) and further consideration to address them in PI. Further discussion will take place at PRAC as necessary.

12.3.2. Blood Products Working Party - Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products and Guideline on core SmPC for human plasma-derived and recombinant coagulation factor VIII products – revision

The EMA Secretariat presented to the PRAC the draft revised guideline applying to the clinical investigation of recombinant and human plasma-derived factor VIII products and guideline on core SmPC for human plasma-derived and recombinant coagulation factor VIII products. The proposed changes relate to the assays for potency assignment and clinical monitoring, including RMP aspects. The PRAC supported the changes. Following CHMP adoption in May 2015, the guidelines will be released for one-month public consultation: EMA/CHMP/BPWP/144533/2009 rev 1 and EMA/CHMP/BPWP/1619/1999 rev. 2 (end of consultation: 1 July 2015).

12.3.3. Blood Products Working Party - Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products and overview of comments – revision

The EMA Secretariat presented to the PRAC a further revised guideline applying to the clinical investigation of recombinant and human plasma-derived factor IX products and a brief overview of comments. As previously discussed, the proposed changes relate to the assays for potency assignment and clinical monitoring, including RMP aspects. The PRAC supported the changes. The guideline is due for CHMP adoption in May 2015 and will be published on the EMA website: EMA/CHMP/BPWP/144552/2009 rev 1 (dated 21 May 2015).

12.3.4. Blood Products Working Party - Haemophilia registries – workshop

The EMA Secretariat presented to the PRAC the draft programme for the EMA workshop on haemophilia registries organised on 1-2 July 2015. PRAC members were invited to express interests in participating in the workshop either physically or remotely by 19 June 2015.

12.3.5. Cardiovascular Working Party – Reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases

The PRAC was presented the draft reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases for comments. The paper covers products intended for the treatment of cardiovascular diseases (hypertension, chronic heart failure and chronic coronary artery disease), and metabolic diseases (type 2 diabetes, obesity and lipid disorders) and provides guidance for approaches to assessment of clinical outcome data enabling an evaluation and quantification of the cardiovascular risk. PRAC delegates were invited to provide written comments by 15 May 2015. The reflection paper is due for adoption at the May 2015 CHMP before the launch of a 3-month public consultation: EMA/CHMP/50549/2015 (end of consultation: 30 September 2015).

12.3.6. Post-authorisation efficacy study (PAES) - Scientific guidance

At the organisational matters teleconference on 27 May 2015, the EMA secretariat updated the PRAC on progress with the preparation of the draft guidance on post-authorisation efficacy studies (PAES). The aim of this draft is to provide scientific guidance for MAHs and NCAs on the general need for such studies, on general methodological considerations, on specific situations and on study conduct. It will shortly be shared with PRAC, CHMP, CAT and CMDh for comments in advance of its adoption by the PRAC. Following its adoption this draft guidance will be released for public consultation (foreseen after the summer 2015).

12.4. Cooperation within the EU regulatory network

12.4.1. European Union network training centre

At the organisational matters teleconference on 27 May 2015, the EMA secretariat presented a briefing on the EU Network Training Centre (NTC) including its mission, vision, governance structure, a demonstration of its online interim platform, upcoming key

activities and finally highlighting the main benefits for the EU network. The PRAC welcomed this development which is important for pharmacovigilance in EU.

12.5. Cooperation with international regulators

None

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

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic Safety Update Reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

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

12.10.3. PSURs repository

At the organisational matters teleconference on 27 May 2015, the EMA Secretariat provided an update on the pilot phase for the PSURs repository. The first phase of the pilot included

PSUR procedures involving CAPs only which started in February and March 2015. The second phase of the pilot will also include involve procedures containing NAPs starting in May 2015. The second phase of the pilot will expand the number of procedures running in the system and the number of EU National Competent Authorities (NCAs) participating. 33 procedures have been selected bringing a total of 12 NCAs participating in the pilot.

12.10.4. Periodic safety update single assessment (PSUSA) - publication

The EMA secretariat presented to the PRAC a proposal for the publication of PSUR outcomes for procedures involving NAPs in order to make them publicly available. Following a written consultation, the PRAC supported the proactive publication of the final PRAC outcome for mixed CAPs and NAPs and NAPs only PSUSAs on the EMA website via a dedicated webpage. At present, the PRAC outcomes are published only for PSUR procedures involving CAPs (via the European public assessment reports (EPAR) update). The proposal is to start first with the roll out of the new dedicated EMA webpage which will include a table listing all the mixed CAPs and NAPs and NAPs only PSUSAs procedures (with the active substance(s) name(s), data lock point, date of PRAC recommendation, procedure number and the regulatory outcome) along with some annexes and appendix. At a later stage, it is foreseen to publish the actual final PRAC assessment report. A call for interest for PRAC sponsors to develop a best practice guide, elaborate a workflow and arrange training for assessors was launched.

12.10.5. Union Reference Date List – Consultation on the draft list

The PRAC endorsed the draft revised EURD list version May 2015 reflecting the PRAC comments impacting on the DLP and PSUR submission frequencies of the substances/combinations. The PRAC reviewed the allergen related entries in the EURD list. As these entries cannot provide an adequate degree of clarity with regard to the scope of the single assessment procedure and no immediate safety concerns were identified with regard to the benefit-risk balance of allergen products that would be addressed in a PSUR single assessment, the PRAC endorsed the temporary removal of these entries from the EURD List. The removal facilitates the continuation of PSUR assessment at national level, where applicable. The GPAG (see 12.10.2.) will work in order to introduce single assessment procedures for allergens in the EURD list over time.

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 May 2015, the updated EURD list was adopted by the CHMP and CMDh at their May 2015 meeting and published on the EMA website on 16/06/2015, see:

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

12.11. Signal management

12.11.1. Guideline on Screening for Adverse Drug Reactions in EudraVigilance

The EMA Secretariat provided an update on the statistical guideline and the screening of adverse drug reactions in EudraVigilance and presented the key aspects, in particular the selection of a disproportionality method, thresholds for defining a signal of disproportionate reporting (SDR) as well as stratification and subgroup analysis. Follow-up discussion will be held in June 2015. In the meantime, PRAC delegates were invited to provide written comments on the draft guideline by 5 June 2015.

12.11.2. Medical literature monitoring project - inclusion and exclusion criteria in support of the screening and review process

The EMA presented an update to the PRAC on the project on monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the EMA. Following the recent PRAC adoption of the detailed guide (see PRAC Minutes February 2015), supplemented by several aspects, including inclusion/exclusion criteria in support of literature screening activities, the PRAC was informed that the detailed guide and supporting documents were due for publication on the EMA website on 12 May 2015 following communication to HMA, NCAs and industry associations.

12.11.3. Medical literature monitoring project - launch of the EMA service - status update

See 12.11.2.

12.11.4. Signal Management: feedback from Signal Management Review Technical (SMART) Working Group

The PRAC was updated on the outcome of the May 2015 SMART Working Group (SMART WG) meeting. The SMART discussed single recommendations concluding on the need for MAHs to submit variations to implement an agreed wording for an active substance (innovator as well as generics). Following agreement and confirmation by the CMDh, and considering that the PRAC agrees the full updated wording (both SmPC and PIL) for the requested variation, that innovator MAHs are consulted on the text of the wording[41], that the translations are also available, it was supported to request all MAHs for the products containing the relevant active substance should submit variations concurrently, instead of sequentially.

In addition, the SMART discussed future MAHs' validated signals from EudraVigilance monitoring. In line with the legal requirements, MAHs shall monitor data in EV to the extent of their access and should validate newly detected signals and inform forthwith the Agency and the NCAs. EV access for MAHs is foreseen for mid-2017 and is linked to the implementation of the revision of the EV access policy. The SMART discussed the outline of the process. A draft concept paper will be further discussed and the output will be reflected in the GVP module IX on Signal Management ultimately.

[41] Preliminary signal assessment report is shared with innovator MAHs and MAHs that provided data

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. 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 27/05/2015 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

12.15.1.1. Facilitating joint post-authorisation studies between marketing authorisation holders (MAHs)

The EMA secretariat presented to the PRAC a proposal to facilitate the conduct of joint post-authorisation studies involving more than one MAH. It proposes to reflect in the assessment report at the time of imposing a PASS affecting more than one MAH, encouragement to conduct a joint study, for EMA to send a letter to all MAHs affected offering to act as a platform to exchange contact details and when meeting certain criteria to offer to organise a webinar/teleconference to help facilitate collaboration by MAHs to facilitate prompt progress and delivery of the study. A webinar/teleconference would be proposed if further clarification of the study objectives/specification are considered useful, if it is considered

crucial for all products to be captured in the same study, if this may catalyse bringing together the MAHs, if the joint PASS needs to start as soon as possible or if regulators can facilitate the identification of existing data sources. The PRAC endorsed the proposal and agreed to a pilot of the new facility.

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: outcome of the public consultation

The EMA Secretariat presented to the PRAC the outcome of the public consultation on the draft rules of procedure (RoP) on the organisation and the conduct of public hearings at the PRAC. The PRAC discussed the main comments received from different stakeholders (patient organisations, learned societies/academia, individual and associations of pharmaceutical industries and media organisations) and the proposed way to address them. The PRAC's input will be reflected in a revised version of the draft rules of procedures that will be presented subsequently at the next meeting of the Heads of Medicines Agencies (HMA) in May 2015, the EMA Management Board and the EMA Scientific Coordination Board (SciCoBo) in June 2015. With regard to the finalisation for the Rules of Procedure, the EMA Secretariat announced the development of a guidance document to accompany the RoP, training plan and communications plan. The revised RoP and the additional material is planned for consideration at PRAC in September/October 2015.

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

None

13. Any other business

13.1. European Commission report on the performance of pharmacovigilance tasks

The EC explained to the PRAC that the legislation foresees a report on the performance of the EU Member States activities relating to the pharmacovigilance. A draft structure of the report covering activities completed between 2012 to December 2014 was presented. The PRAC suggested some refinements that will be taken into consideration during the preparation of the report.

14. Annex I – Risk Management Plans

14.1. Medicines in the pre-authorisation phase

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

14.1.1. Asfotase alfa - EMEA/H/C/003794, Orphan

Applicant: Alexion Europe SAS

Scope: Treatment of paediatric-onset hypophosphatasia

14.1.2. Atazanavir - EMEA/H/C/004048, Generic

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

14.1.3. Atazanavir, cobicistat - EMEA/H/C/003904

Scope: Treatment of human immunodeficiency virus (HIV)-1, in combination with other antiretroviral medicinal products

14.1.4. Bortezomib - EMEA/H/C/003984, Generic

Scope: Treatment of multiple myeloma

14.1.5. Cinacalcet - EMEA/H/C/004014, Generic

Scope: Treatment of secondary hyperparathyroidism and hypercalcaemia

14.1.6. Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type B conjugate vaccine (adsorbed) - EMEA/H/C/003982

Scope: Vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib)

14.1.7. Evolocumab - EMEA/H/C/003766

Scope: Treatment of hypercholesterolaemia and mixed dyslipidaemia and homozygous familial hypercholesterolaemia

14.1.8. Idebenone - EMEA/H/C/003834, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

Scope: Treatment of Leber's hereditary optic neuropathy (LHON)

14.1.9. Isavuconazole - EMEA/H/C/002734, Orphan

Applicant: Basilea Medical Ltd

Scope: Treatment of aspergillosis and mucormycosis

14.1.10. Lesinurad - EMEA/H/C/003932

Scope: Treatment of hyperuricaemia

14.1.11. Lopinavir, ritonavir - EMEA/H/C/004025, Generic

Scope: Treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children above the age of 2 years

14.1.12. Nivolumab - EMEA/H/C/003840

Scope: Treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy

14.1.13. Panobinostat - EMEA/H/C/003725, Orphan

Applicant: Novartis Pharmaceuticals UK Limited

Scope: Treatment of multiple myeloma

14.1.14. Pembrolizumab - EMEA/H/C/003820

Scope: Treatment of melanoma

14.1.15. Pregabalin - EMEA/H/C/004024, Generic

Scope: Treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD)

14.1.16. Pregabalin - EMEA/H/C/003900, Generic

Scope: Treatment of epilepsy and generalised anxiety disorder (GAD)

14.1.17. Sacubitril, valsartan - EMEA/H/C/004062

Scope: Treatment of heart failure (NYHA class II-IV)

14.1.18. Sufentanil - EMEA/H/C/002784, Hybrid

Scope: Management of moderate to severe acute pain

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 these updated versions of the RMP for the below mentioned medicines.

14.2.1. Abacavir – ZIAGEN (CAP) - EMEA/H/C/00252/II/0082

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Arnaud Batz

Scope: Updated RMP to remove the important potential risk of viral resistance in children

14.2.2. Linagliptin – TRAJENTA (CAP) – EMEA/H/C/002110/II/0018

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Updated RMP to add cardiac failure as important potential risk

14.2.3. Linagliptin, metformin – JENTADUETO (CAP) - EMEA/H/C/002279/II/0026

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Updated RMP to add cardiac failure as important potential risk

14.2.4. Pioglitazone – ACTOS (CAP) - EMEA/H/C/000285/WS0705/0067; GLUSTIN (CAP) - EMEA/H/C/000286/WS0705/0065 pioglitazone, glimepiride – TANDEMACT (CAP) - EMEA/H/C/000680/WS0705/0042 pioglitazone, metformin – COMPETACT (CAP) - EMEA/H/C/000655/WS0705/0052; GLUBRAVA (CAP) - EMEA/H/C/000893/WS0705/0038

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Change of the due date for reporting of the pan-European multiple database bladder cancer risk characterisation study ER12-9433 from 30 December 2014 to 31 July 2015. In addition, an administrative change has been introduced to include mention of a drug utilisation study using the medical registries in Denmark (Pioglitazone 5019) and associated timelines

14.2.5. Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0021/G

Applicant: Roche Registration Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Updated RMP in order to update the following information: proposal to consider fulfilled MEA 004 (category 3) and MEA 018 (Category 4); proposal to extend the timelines of MEA 006 (category 3); to include amendments as required in procedure EMEA/H/C/2409/II/018 (opinion in March 2015) and MEA 015 (opinion in December 2012). Furthermore, the MAH take the opportunity to provide data on the ongoing study for MEA010 for information, to correct a mistake found in RMP v.7 and v.8 where study GO27826 had been misclassified as a category 3 PAM being instead a category 4 PAM and to update data in modules S.I, S.III, S.V and S.VI up to DLP of PBRER 1057994 (16 August 2014)

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

14.3.1. Bosutinib – BOSULIF (CAP) - EMEA/H/C/002373/II/0014/G

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Update of SmPC section 4.5 to include further information related to concomitant use of Bosulif with CYP3A inhibitors based on the results of study B1871041, and to reflect the results of study B1871043, submitted to fulfil MEA 003.2, and undertaken to investigate the drug interaction potential with regard to bosutinib being a P-gp inhibitor. The package leaflet is updated accordingly

14.3.2. Buprenorphine, naloxone – SUBOXONE (CAP) - EMEA/H/C/000697/X/0029

Applicant: RB Pharmaceuticals Ltd

PRAC Rapporteur: Martin Huber

Scope: Line extension to add 12mg/3mg and 16mg/4mg sublingual tablets

14.3.3. Enzalutamide – XTANDI (CAP) - EMEA/H/C/002639/II/0015

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of SmPC sections 4.2, 4.4 and 5.2 to update the safety and pharmacokinetic information on hepatic impairment after finalisation of study 9785-CL-0404. The package leaflet is updated accordingly

14.3.4. Fingolimod – GILENYA (CAP) - EMEA/H/C/002202/II/0032

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Arnaud Batz

Scope: Update of SmPC section 4.4 to include precautionary statements on cryptococcal meningitis and of section 4.8 to reflect cryptococcal infections, including isolated cases of cryptococcal meningitis. In addition, the marketing authorisation holder took the opportunity to make minor editorial change in SmPC section 4.5 to align with other SmPC sections

14.3.5. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/II/0061

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 to add a new therapeutic indication for non-radiographic axial spondyloarthritis. The package leaflet is updated accordingly

14.3.6. Human coagulation factor VIII, human von Willebrand factor – VONCENTO (CAP) - EMEA/H/C/002493/II/0008/G

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include prophylactic treatment of patients with von Willebrand disease (VWD). In addition the MAH submitted data to support the treatment of paediatric patients with VWD

14.3.7. Human thrombin, human fibrinogen – TACHOSIL (CAP) - EMEA/H/C/000505/II/0057

Applicant: Takeda Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication for the use of Tachosil as suture line sealing in dura mater closure. SmPC sections 4.1, 4.2, 4.4, 4.8, and 5.1 and the package leaflet are updated accordingly

14.3.8. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0001

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Extension of indication for the treatment of adult patients with Waldenström macroglobulinaemia (WM). SmPC sections 4.1, 4.2, 4.8 and 5.1 and the package leaflet are updated accordingly

14.3.9. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0007/G

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Group of variations to submit several non-clinical studies reports. Accordingly, update of section 4.5 of the SmPC regarding BRCP inhibition, update of section 4.5 of the SmPC to delete the CYP3A4 inhibition statement, update of wording regarding the coadministration with transport substrates/inhibitors in section 5.2 of the SmPC.
The Package Leaflet has been updated accordingly and an updated RMP version 3.5 is proposed

14.3.10. Insulin glargine – ABASAGLAR (CAP) - EMEA/H/C/002835/II/0003/G

Applicant: Eli Lilly Regional Operations GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Introduction of a new KwikPen capable of delivering a maximum dose of 80 units (1 pre-filled pen), a new pack-size of 2 pre-filled pens (Kwikpen, 1 to 80 unit injection), a new pack-size of 5 pre-filled pens (Kwikpen, 1 to 80 unit injection) and of a new multipack of 10 (2x5) pre-filled pens (Kwikpen, 1 to 80 unit injection)

14.3.11. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/002494/X/0034/G

Applicant: Vertex Pharmaceuticals (U.K.) Ltd

PRAC Rapporteur: Miguel-Angel Macia

Scope: Line extension to include a new pharmaceutical form (granules) in two new strengths (50 mg and 75 mg unit doses) to enable administration of Kalydeco to patients aged 2 to less than 6 years of age. SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.2 as well as the package leaflet are updated accordingly

14.3.12. Nelarabine – ATRIANCE (CAP) - EMEA/H/C/000752/II/0027

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Final study report from a post-marketing surveillance study in the indicated patient population under 21 years of age receiving 650 mg/m^2 dose of nelarabine (study PGA111081) and data from drug use investigation of ArranonG intravenous injection 250mg (paediatric study OTH112279). This variation intends to fulfil ANX II specific obligation SOB 004.2 and Article 46 of the paediatric legislation

14.3.13. Nonacog alfa – BENEFIX (CAP) - EMEA/H/C/000139/II/0131

Applicant: Pfizer Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of SmPC sections 4.2, 5.1, and 5.2 to update the posology with once-weekly prophylaxis regimen. The package leaflet is also updated

14.3.14. Perampanel – FYCOMPA (CAP) - EMEA/H/C/002434/II/0016

Applicant: Eisai Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication as adjunctive treatment of primary generalised tonic-clonic seizures in patients with epilepsy aged 12 years and older. SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 and the package leaflet are updated accordingly

14.3.15. Pertuzumab – PERJETA (CAP) - EMEA/H/C/002547/II/0010

Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope: Extension of the indication in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with human epidermal growth factor receptor (HER) 2-positive, locally advanced, inflammatory, or early stage breast cancer (> 2 cm in diameter) as part of the treatment for early breast cancer. SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 are updated accordingly

14.3.16. Pneumococcal polysaccharide conjugate vaccine (adsorbed) – SYNFLORIX (CAP) - EMEA/H/C/000973/II/0096/G

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations to update SmPC section 5.1 with effectiveness data against pneumococcal vaccine serotypes and against vaccine related serotype 19A, and to update SmPC section 4.4 to include information on the immune response against serotype 19A observed in infants and children. In addition, extensions of the due dates for MEA 009: study 10PN-PD-DIT-034 (111634) and MEA 018.5: study 10PN-PD-DIT-064 (114056)

14.3.17. Ramucirumab – CYRAMZA (CAP) - EMEA/H/C/002829/II/0003, Orphan

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with progression after platinum-based chemotherapy. SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 and the package leaflet are updated accordingly

14.3.18. Regorafenib – STIVARGA (CAP) - EMEA/H/C/002753/II/0008

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Update of SmPC section 5.1 to reflect final results from study 15808 (Concur; randomized, double blind, placebo controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic CRC who have progressed after Standard therapy)

14.3.19. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP) - EMEA/H/C/000674/X/0085

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Line extension to add a new route of administration 'intramuscular' to all presentations

14.3.20. Thiotepa – TEPADINA (CAP) - EMEA/H/C/001046/II/0018

Applicant: Adienne S.r.l. S.U.

PRAC Rapporteur: Arnaud Batz

Scope: Update of SmPC section 4.8 to update the safety information on pulmonary arterial hypertension with an uncommon frequency. The package leaflet is updated accordingly

14.3.21. Trastuzumab – HERCEPTIN (CAP) - EMEA/H/C/000278/II/0092

Applicant: Roche Registration Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of SmPC sections 4.4, 4.8 and 5.1 to reflect the new study report BO22227 (Hannah) regarding non inferior trastuzumab exposure and clinical efficacy of a q3w regimen of Herceptin subcutaneous compared to Herceptin intravenous

14.3.22. Ustekinumab – STELARA (CAP) - EMEA/H/C/000958/II/0042

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to add the treatment of moderate to severe plaque psoriasis in paediatric patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. SmPC sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 and the package leaflet are updated accordingly

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 agreed in the relevant PSUR procedure(s).

15.1. PSUR procedures including centrally authorised products only

15.1.1. Abiraterone – ZYTIGA (CAP) - PSUSA/00015/201410

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope of procedure: Evaluation of a PSUSA procedure

15.1.2. Alipogene tiparvovec – GLYBERA (CAP) - PSUSA/10056/201410

Applicant: uniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.3. Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T) – PROVENGE (CAP) - PSUSA/10065/201410

Applicant: Dendreon UK Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

15.1.4. Bazedoxifene – CONBRIZA (CAP) - PSUSA/00302/201410

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope of procedure: Evaluation of a PSUSA procedure

15.1.5. Budesonide, formoterol – BIRESP SPIROMAX (CAP), DUORESP SPIROMAX (CAP) - PSUSA/10202/201410

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Torbjorn Callreus

Scope of procedure: Evaluation of a PSUSA procedure

15.1.6. Ceftaroline fosamil – ZINFORO (CAP) - PSUSA/10013/201410

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.7. Cholic acid – KOLBAM (CAP) - PSUSA/10182/201410

Applicant: ASK Pharmaceuticals GmbH

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.8. Dapagliflozin – FORXIGA (CAP) - PSUSA/10029/201410

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.9. Decitabine – DACOGEN (CAP) - PSUSA/09118/201411

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Patrick Maison

Scope of procedure: Evaluation of a PSUSA procedure

15.1.10. Defibrotide – DEFITELIO (CAP) - PSUSA/10086/201410

Applicant: Gentium S.p.A.

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.11. Delamanid – DELTYBA (CAP) - PSUSA/10213/201410

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.12. Dihydroartemisinin, piperaquine – EURARTESIM (CAP) - PSUSA/01069/201410

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

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.13. Eltrombopag – REVOLADE (CAP) - PSUSA/01205/201409

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Dolores Montero Corominas

Scope of procedure: Evaluation of a PSUSA procedure

15.1.14. Empagliflozin – JARDIANCE (CAP) - PSUSA/10219/201410

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

15.1.15. Fenofibrate, pravastatin – PRAVAFENIX (CAP) - PSUSA/01363/201410

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Arnaud Batz

Scope of procedure: Evaluation of a PSUSA procedure

15.1.16. Human fibrinogen, human thrombin – EVICEL (CAP) - PSUSA/01627/201410

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

15.1.17. Hydrocortisone – PLENADREN (CAP) - PSUSA/09176/201411

Applicant: ViroPharma SPRL

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.18. Insulin aspart – NOVOMIX (CAP), NOVORAPID (CAP) - PSUSA/01749/201409

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.19. Ivabradine – CORLENTOR (CAP), PROCORALAN (CAP) - PSUSA/01799/201410

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

15.1.20. Meningococcal group a, c, w135 and y conjugate vaccine – NIMENRIX (CAP) - PSUSA/10044/201410

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.21. Miglustat – ZAVESCA (CAP) - PSUSA/02062/201410

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.22. Obinutuzumab – GAZYVARO (CAP) - PSUSA/10279/201410

Applicant: Roche Registration Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.23. Ofatumumab – ARZERRA (CAP) - PSUSA/02202/201410

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope of procedure: Evaluation of a PSUSA procedure

15.1.24. Pasireotide – SIGNIFOR (CAP) - PSUSA/09253/201410

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.25. Propranolol – HEMANGIOL (CAP) - PSUSA/10250/201410

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Dolores Montero Corominas

Scope of procedure: Evaluation of a PSUSA procedure

15.1.26. Prucalopride – RESOLOR (CAP) - PSUSA/02568/201410

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.27. Siltuximab – SYLVANT (CAP) - PSUSA/10254/201410

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

15.1.28. Sirolimus – RAPAMUNE (CAP) - PSUSA/02710/201409

Applicant: Pfizer Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope of procedure: Evaluation of a PSUSA procedure

15.1.29. Thalidomide – THALIDOMIDE CELGENE (CAP) - PSUSA/02919/201410

Applicant: Celgene Europe Limited

PRAC Rapporteur: Arnaud Batz

Scope of procedure: Evaluation of a PSUSA procedure

15.1.30. Tocilizumab – ROACTEMRA (CAP) - PSUSA/02980/201410

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

15.1.31. Turoctocog alfa – NOVOEIGHT (CAP) - PSUSA/10138/201410

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

15.1.32. Umeclidinium bromide – INCRUSE (CAP) - PSUSA/10263/201410

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope of procedure: Evaluation of a PSUSA procedure

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

None

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

None

15.4. Follow-up to PSUR procedures

15.4.1. Ambrisentan – VOLIBRIS (CAP) - EMEA/H/C/000839/LEG 026

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to PRAC recommendation on PSUV/0040, as adopted in Jan 2015

15.4.2. Insulin lispro – HUMALOG (CAP) - EMEA/H/C/000088/LEG 026; LIPROLOG (CAP) - EMEA/H/C/000393/LEG 026

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: MAH response to PRAC recommendation on PSUV/0128, as adopted in Dec 2014.

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

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

16.1. Protocols of PASS imposed in the marketing authorisation(s)[42]

16.1.1. Dexamfetamine (NAP) - EMEA/H/N/PSP/021

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Julie Williams

Scope: Protocol for a drug utilisation study of dexamfetamine to follow the use of prescribed dexamfetamine in the European Union using multiple data sources

16.1.2. Ospemifene – SENSHIO (CAP) - EMEA/H/C/PSP/0023

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

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

Scope: Protocol for a post-authorisation safety study to evaluate the incidence of venous thromboembolism and other adverse events, as agreed in the risk management plan, in vulvar and vaginal atrophy (VVA) patients treated with ospemifene as compared to: 1) patients newly prescribed selective oestrogen receptor modulators (SERMs) for oestrogen-deficiency conditions or breast cancer prevention; 2) the incidence in untreated VVA patients

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[43]

16.2.1. Apixaban – ELIQUIS (CAP) - EMEA/H/C/002148/MEA 021.2

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Revised PASS protocol for a study CV185365, in response to MEA 021.1 as adopted in January 2015

16.2.2. Conjugated estrogens, bazedoxifene – DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: PASS protocol for an active surveillance of conjugated estrogens, bazedoxifene (CE/BZA) using US healthcare data (study B2311060)

16.2.3. Conjugated estrogens, bazedoxifene – DUAVIVE (CAP) - EMEA/H/C/002314/MEA 003

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: PASS protocol for a drug utilisation study (study no. B2311061)

16.2.4. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope: Protocol for a post-authorisation safety study in patients with type 2 diabetes mellitus to assess the risk of acute liver injury, hospitalisation for acute kidney injury, hospitalisation for urinary tract infection, and the risk of genital infections, among patients treated with empagliflozin compared to patients treated with other sodium-glucose linked transporters (SGLT)2 inhibitors or dipeptidyl peptidase-4 (DPP-4) inhibitors

16.2.5. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/MEA 023

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

[43] 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: Protocol for a PASS study PCYC-PMR-2060-04: enhanced pharmacovigilance to evaluate the risks of haemorrhage with the administration of ibrutinib

16.2.6. Insulin detemir – LEVEMIR (CAP) - EMEA/H/C/000528/MEA 045.3

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Revised PASS protocol for diabetes pregnancy registry (NN304-4016)

16.2.7. Insulin glargine – LANTUS (CAP) - EMEA/H/C/000284/MEA 051.2

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for a differentiation study [UK SoloStar Differentiation Study: Test in patients with Type 1 or Type 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin]

16.2.8. Insulin glulisine – APIDRA (CAP) - EMEA/H/C/000557/MEA 037.2

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for a differentiation study [UK SoloStar Differentiation Study: Test in patients with Type 1 or Type 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin]

16.2.9. Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA 002

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: Protocol for an observational PASS: drug utilisation in selected European populations (study D2288R00081)

16.2.10. Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA 004

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: Protocol for an observational PASS among patients aged 18 years and older diagnosed with cancer pain and treated with opioids chronically (study D2288R00082)

16.2.11. Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: Protocol for an observational PASS among patients aged 18 years and older diagnosed with non-cancer pain and treated with opioids chronically (study D2288R00084)

16.2.12. Tenofovir– VIREAD (CAP) - EMEA/H/C/000419/MEA 265.4

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Arnaud Batz

Scope: MAH's response to MEA 265.3 as adopted in December 2014, including a revised PASS protocol 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

16.3. Results of PASS imposed in the marketing authorisation(s)[44]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[45]

16.4.1. Bivalirudin – ANGIOX (CAP) - EMEA/H/C/000562/II/0058 (without RMP)

Applicant: The Medicines Company UK Ltd

PRAC Rapporteur: Julie Williams

Scope: Study report for the study entitled: 'Exposure and adverse event assessment (EAEA) for protocol TMC-BIV-07-01 bivalirudin (Angiomax) as a procedural anticoagulant in the paediatric population undergoing intravascular procedures for congenital heart disease' to update information on paediatric population

16.4.2. Etanercept – ENBREL (CAP) - EMEA/H/C/000262/II/0182 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Final report of the STORK study, which is a retrospective study to evaluate pregnancy outcomes associated with and without etanercept use among pregnant women with chronic inflammatory arthritis or psoriasis

16.4.3. Raltegravir – ISENTRESS (CAP) - EMEA/H/C/000860/II/0052 (without RMP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Fifth and final report of the five-year EuroSIDA post-authorisation observational study

16.4.4. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/II/0049 (with RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

Scope: Final clinical study report for study WA22762 (SUMACTA) in order to fulfil MEA 044. As a consequence of the analyses of the final study results a revised RMP (version 16.6) has been submitted

16.4.5. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/II/0050 (with RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Final clinical study report for study WA18221 'Tender' in order to address the post-authorisation measure MEA 036. An update RMP version 16.4 was provided as part of the application

16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[46]

16.5.1. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/MEA 046.2

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Annual update for study IM101240: observational registry of abatacept in patients with juvenile idiopathic arthritis (JIA registry)

16.5.2. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.3

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Annual report on the juvenile idiopathic arthritis (JIA) registry, an observational registry of abatacept in patients with juvenile idiopathic arthritis

16.5.3. Belimumab – BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.9

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second interim report on a safety registry evaluating the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus

16.5.4. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 033 Saxagliptin, metformin – KOMBOGLYZE (CAP) – EMEA/H/C/002059/MEA 010

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: First interim analysis of PASS study CV181-099ST: comparison of risk of major cardiovascular events between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

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

16.5.5. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 034 Saxagliptin, metformin – KOMBOGLYZE (CAP) – EMEA/H/C/002059/MEA 011

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: First interim analysis of PASS study CV181-100ST: comparison of risk of hospitalisation with acute liver failure between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

16.5.6. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 035 Saxagliptin, metformin – KOMBOGLYZE (CAP) – EMEA/H/C/002059/MEA 014

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: First interim analysis of PASS study CV181-103ST: comparison of risk of hospitalisation with severe hypersensitivity (including severe cutaneous reactions) between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

16.5.7. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 036 Saxagliptin, metformin – KOMBOGLYZE (CAP) – EMEA/H/C/002059/MEA 012

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: First interim analysis of PASS study CV181-101ST: comparison of risk of hospitalisation with infection between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

16.5.8. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA 037 Saxagliptin, metformin – KOMBOGLYZE (CAP) – EMEA/H/C/002059/MEA 013

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: First interim analysis of PASS study CV181-157ST: comparison of risk of hospitalisation with acute kidney injury between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

16.5.9. Ulipristal – ESMYA (CAP) - EMEA/H/C/002041/MEA 004.4

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim study results on a retrospective drug utilisation chart review study on Esmya prescription patterns (PGL11-020)

16.6. Others

16.6.1. Interferon beta-1a – REBIF (CAP) - EMEA/H/C/000136/MEA 039.2

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to MEA-039.1 [Feasibility study report, EPID multiple sclerosis pregnancy study / ER12-9430] following the adoption of a request for supplementary information (RSI) as adopted in September 2014

16.6.2. Interferon beta-1b – EXTAVIA (CAP) - EMEA/H/C/000933/MEA 019.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA-019.1 [Feasibility study report, EPID multiple sclerosis pregnancy study / ER12-9430] request for supplementary information (RSI) as adopted in September 2014

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

17.1.1. Agalsidase alfa – REPLAGAL (CAP) - EMEA/H/C/000369/S/0086 (without RMP)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Sabine Straus

Scope: Annual reassessment of the marketing authorisation

17.1.2. Amifampridine – FIRDAPSE (CAP) - EMEA/H/C/001032/S/0036 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

17.2. Conditional renewals of the marketing authorisation

17.2.1. Crizotinib – XALKORI (CAP) - EMEA/H/C/002489/R/0026 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Arnaud Batz

Scope: Conditional 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 4-7 May 2015 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
Harald Herkner	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement
Yuliyan Eftimov	Alternate	Bulgaria	No interests declared	Full involvement
Viola Macolić Šarinić	Member	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
Jana Mladá	Member	Czech Republic	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
Terhi Lehtinen	Alternate - via telephone	Finland	No interests declared	Full involvement
Arnaud Batz	Member	France	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	
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Ruchika Sharma	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Alternate	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Artūras Kažemekaitis	Alternate	Lithuania	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Ingebjørg Buajordet	Member	Norway	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Magda Pedro	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
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
Qun-Ying Yue	Member	Sweden	No interests declared	Full involvement
Ulla Wändel Liminga	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 restrictions applicable to this meeting	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Hervé Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Filip Babylon	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Marco Greco	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Kenneth Skov	Expert - in person*	Denmark	No interests declared	Full involvement
Tiina Jaakkola	Expert - in person*	Finland	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
Corinne Fechant	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Isabelle Robine	Expert - in person*	France	No interests declared	Full involvement
Rhea Fitzgerald	Expert - via telephone *	Ireland	No restrictions applicable to this meeting	Full involvement
Giuseppe Rosano	Expert - in person*	Italy	No interests declared	Full involvement
Zane Stade	Expert - in person*	Latvia	No interests declared	Full involvement
Maria Vanenburg	Expert - in person*	Netherlands	No interests declared	Full involvement
Steven Teerenstra	Expert - via telephone *	Netherlands	No interests declared	Full involvement
Karsten Bruins Slots	Expert - via telephone *	Norway	No interests declared	Full involvement
Soňa Fundarková	Expert - in person*	Slovakia	No interests declared	Full involvement
Ernesto Vera Sanchez	Expert - in person*	Spain	No interests declared	Full involvement
Eva Segovia	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Patrick Batty	Expert - in person*	United Kingdom	No interests declared	Full involvement
Nicola Parkinson	Expert -	United Kingdom	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	via telephone *		declared	
Andrew Ruddick	Expert - via telephone *	United Kingdom	No restrictions applicable to this meeting	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 product(s) they have been invited to talk about.

Explanatory notes

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

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