9 October 2014
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Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 8-11 September 2014

Chair: June Raine – Vice-Chair: Almath Spooner

Disclaimers

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

Note on access to documents

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

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Explanatory notes

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

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

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

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

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

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

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

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

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

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

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

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

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

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

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1. Introduction

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

The Chairperson opened the 8-11 September 2014 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.

1.2. Adoption of agenda of the meeting of 8-11 September 2014

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

1.3. Minutes of the previous PRAC meeting on 7-10 July 2014

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

Post-meeting note: the PRAC minutes of the meeting held on 7-10 July 2014 were published on the EMA website on 22/9/2014 (EMA/PRAC/501208/2014).

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

None

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

3.1. Newly triggered Procedures

None

3.2. Ongoing Procedures

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

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

Regulatory details:

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

Administrative details:

MAH(s): Boehringer Ingelheim, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for ambroxol and bromhexine-containing medicines (see PRAC minutes 5-8 May 2014). Following receipt of further information from the MAHs, the Rapporteurs prepared an assessment report for discussion at the meeting.

Summary of recommendation(s)/conclusions

The PRAC adopted a list of questions to be addressed by the Paediatric Committee (PDCO) on the paediatric use of these products and a list of outstanding issues (LoOI) to be addressed by the MAHs, together with a revised timetable for the procedure (EMA/PRAC/189079/2014 rev1).

Post-meeting note: following the conclusion of the meeting, Boehringer Ingelheim requested an extension of the deadline for providing a reply to the LoOI. The PRAC considered that it was important to proceed as per already established timelines and supported maintaining the agreed timetable.

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

4. Signals assessment and prioritisation[1]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Latanoprost** (NAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

[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

Administrative details:
EPITT 18068 – New signal
MAH(s): Pfizer (Xalatan), various
Leading MS: UK

Background

Latanoprost is a prostaglandin analogue available as eye drops used in adults for the reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension and also in children for the reduction of elevated intraocular pressure and glaucoma.

The exposure for nationally authorised eye drops containing latanoprost, is estimated to have been more than 78 million patient-years worldwide, in the period from first authorisation in 1996 to 2014.

A signal of eye disorders was identified by the German Medicines Agency (BfArM), triggered by an article published by the Drug Commission of German Pharmacists describing an increase in reporting of eye irritation after the formulation of Xalatan, a nationally authorised product containing latanoprost, was changed to allow for storage at room temperature. The UK, reference member state (RMS) for the relevant medicine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted that the recently changed formulation of Xalatan to allow storage at room temperature had been launched in at different time points in the various Member States (MSs). A search conducted in the German database retrieved 35 cases of eye disorders in the 9 months after the switch of formulation, compared with 16 cases in the previous 9 months. The reactions consisted mainly of eye irritation. A similar increase in reporting of cases of eye irritation soon after the launch of the new Xalatan formulation has also been observed in other Member States. The PRAC agreed that the signal should be further investigated, in particular to understand any potential implications for efficacy and safety of the medicine.

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

Summary of recommendation(s)

- The MAH for Xalatan (latanoprost) should submit to the PRAC, within 60 days, a response to a list of questions agreed by the PRAC.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Natalizumab – TYSABRI (CAP)

- Signal of neonatal haematological abnormalities (thrombocytopenia and anaemia)

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

Administrative details:
EPITT 18067 – New signal
MAH(s): Biogen Idec Ltd
Leading MS: DE

Background

Natalizumab is a monoclonal antibody used as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis in selected patients.

The exposure for Tysabri, a centrally authorised medicine containing natalizumab, is estimated to have been more than 120 000 patients worldwide, in the period from first authorisation in 2006 to 2014.

During routine signal detection activities, a signal of neonatal thrombocytopenia associated with natalizumab therapy during the third trimester of pregnancy, was triggered by the UK based on four spontaneously reported cases. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the suspected cases of thrombocytopenia and anaemia reported and noted that mild to severe reductions in neonatal platelet counts and anaemia had been described. Severe neonatal thrombocytopenia can have potentially serious complications that are preventable with supportive care. Some of the case reports have been described in the literature, in clinical case-series[2]; a possible causal association was also suggested by other clinical cases and non-clinical data[3]. Reversible neonatal thrombocytopenia after natalizumab treatment during pregnancy had been observed in cynomolgus monkeys and it is currently reflected in the product information. Based on this information the PRAC agreed that a review of relevant data from all sources, including data from the natalizumab pregnancy register, should be performed.

Summary of recommendation(s)

- The MAH for Tysabri (natalizumab) should submit to the EMA, within the next PSUR (DLP: 7/8/2014), a cumulative review of the signal including a proposal for amending the product information.

4.1.3. Paliperidone – INVEGA (CAP)

- Signal of toxicity following accidental ingestion by children of oral formulations

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

Administrative details:
EPITT 18069 – New signal
MAH(s): Janssen-Cilag International N.V.
Leading MS: SE

Background

Paliperidone is an antipsychotic indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older as well as for the treatment of psychotic or manic symptoms of

[2] Haghikia A, et al. Natalizumab use during the third trimester of pregnancy. JAMA Neurol. doi:10.1001/jamaneurol.2014.209
[3] Wehner NG et al. Embryo/fetal development in cynomolgus monkeys exposed to natalizumab, an α4 integrin inhibitor. Birth Defects Res B Dev Reprod Toxicol 2009a; 86:117-30.
Wehner NG et al. Postnatal development in cynomolgus monkeys following prenatal exposure to natalizumab, an α4 integrin inhibitor. Birth Defects Res B Dev Reprod Toxicol 2009b; 86:144-56.
Wipfler P et al. Adhesion molecules are promising candidates to establish surrogate markers for natalizumab treatment. Mult Scler 2011; 17:16-23.

schizoaffective disorder in adults. Invega, a centrally authorised medicine containing paliperidone is available as a prolonged-release tablets.

The exposure for Invega is estimated to have been more than one million patient-years worldwide, in the period from first authorisation in 2007 to 2013.

During routine signal detection activities, a signal of toxicity following accidental ingestion of paliperidone by children was identified by the EMA, based on 9 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the clinical information on the cases reported and noted that currently tablets of Invega are available either in bottles with induction sealing and child-resistant closure (marketed in one EU country only) and/or in white /clear blisters with push-through layer. The outer packaging carries the special warning that the medicinal product must be stored out of the sight and reach of children. The RMP for Invega states that blisters meet local requirements regarding opacity, such that children cannot see the tablets. Nonetheless the suspected cases of ingestion by children reported, described the expected signs and symptoms suggestive of an exaggeration of paliperidone's known pharmacological effects; some articles were also available in the literature[4]. PRAC noted that from the analysis of the cases, it was not possible to fully explain the reasons why children were exposed. Based on this information the PRAC agreed that a full root cause analysis (RCA) should be performed in order to assess the risk and any aspects of risk minimisation.

Summary of recommendation(s)

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

4.1.4. **Paroxetine** (NAP)

- Signal of aggressive behaviour

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
EPITT 18089 – New signal
MAH(s): GlaxoSmithKline, various
Leading MS: NL

Background

Paroxetine is a selective serotonin re-uptake inhibitor (SSRI) indicated for the treatment of major depressive episode, obsessive compulsive disorder, panic disorder with and without agoraphobia, social anxiety disorders/social phobia, generalised anxiety disorder and post-traumatic stress disorder.

[4] Goossens E, Biarent D, Demarque R, Domken V, Misson J, Mostin M. Accidental ingestion of paliperidone (Invega R) in children: A case series. Clinical Toxicology 2014; 52 (4):416

The exposure for the reference, nationally authorised medicine containing paroxetine is estimated to have been more than 365 million patient-treatments, in the period from first authorisation in 1990 to 2014.

During routine signal detection activities, a signal of aggressive behaviour was identified by the NL, based on periodic analysis of suspected events over the years received by the Netherlands Pharmacovigilance Centre Lareb. NL as reference member state for the originator of paroxetine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of suspected aggressive behaviour reported and commented that a causal association between the use of paroxetine and the occurrence of aggressive behaviour was difficult to assess based on pharmacovigilance data only. This is due to existing confounders like underlying disease and social circumstances. Available scientific literature reports conflicting findings on SSRIs and aggressive behaviour, some showing a beneficial effect and others an increased risk. PRAC also noted that 'aggression' (as an outcome of the review under Article 31 referral procedure in 2005) is currently included as undesirable effect in the product information of all SSRIs for children and adolescents younger than 18 years old and under for some other SSRIs.

Several possible mechanisms that could explain a tendency for aggressive behaviour associated with the use of SSRIs, have been identified. A possible biological explanation could be provided by the pharmacodynamic properties of paroxetine, aggressive behaviour being an expression of the disinhibiting effects induced by treatment with SSRIs.

The PRAC discussed the information on the cases reported and decided that further review of the signal was warranted, taking into consideration spontaneous sources and clinical trial data, as well as data from the scientific literature. Information on time to onset, de- and re-challenge, dose, reporter and outcome should also be taken into account in the review.

The PRAC appointed Sabine Straus (NL) as Rapporteur for the signal.

Summary of recommendation(s)

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

4.1.5. Temozolomide – TEMODAL (CAP)

- Signal of dehydration leading to renal failure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
EPITT 18064 – New signal
MAH(s): Merck Sharp & Dohme Limited
Leading MS: DE

Background

Temozolomide is an antineoplastic agent used in the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment, and in children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

The exposure for Temodal, a centrally authorised medicine containing temozolomide, is estimated to have been more than 500 000 patients worldwide, in the period from first authorisation in 1999 to 2012.

During routine signal detection activities, a signal of dehydration leading to renal failure was identified by EMA, based on 20 cases of renal failure and related terms retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information from the suspected cases of dehydration - leading to renal failure – reported and noted that in a substantial number of cases it was mentioned that the patient's conditions improved after rehydration and administration of anti-emetic therapy. These cases highlighted a potential biological mechanism suggesting temozolomide would cause renal failure indirectly through causing dehydration. In these cases onset of nausea, vomiting and/or diarrhoea were also temporally close to treatment initiation with temozolomide. Further support for a possible causal relationship was provided by the absence of other medication and/or relevant pre-existing disease in some cases, and the documentation of normal renal function prior to temozolomide therapy.

The PRAC took into consideration that temozolomide is taken usually by outpatients. Hence, significant diarrhoea or vomiting, which can potentially lead to renal failure, might remain unrecognized and untreated. Consequently, improved awareness of gastrointestinal adverse reactions that can lead to dehydration and serious complications, such as renal failure, might be a useful tool to manage this risk.

Therefore the PRAC agreed that the signal should be further investigated with a view to minimising the risk of dehydration and its serious complications.

Summary of recommendation(s)

- The MAH for Temodal (temozolomide) should submit to the EMA, within the next PSUR (DLP 12/7/2014) a cumulative review of the signal.

4.1.6. Teriparatide – FORSTEO (CAP)

- Signal of non-uraemic calciphylaxis

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 18056 – New signal
MAH(s): Eli Lilly Nederland B.V.
Leading MS: UK

Background

Teriparatide is the active fragment of endogenous human parathyroid hormone used in the treatment of osteoporosis in postmenopausal women, and in men at increased risk of fracture and for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture.

The exposure for Forsteo, a centrally authorised medicine containing teriparatide, is estimated to have been more than >1.3 million patients worldwide, in the period from first authorisation in 2003 to 2014.

During routine signal detection activities, a signal of non-uraemic calciphylaxis (a rare but serious syndrome of vascular calcification, thrombosis and skin necrosis) was identified by the EMA, based on 9 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of suspected calciphylaxis reported, including cases confirmed by a skin biopsy and cases with a plausible temporal association. The PRAC noted that hypercalcaemia (including calcium greater than 3.25 mmol/L) is a listed adverse reaction in the product information for Forsteo; therefore the reactions seemed to have a biological plausibility. Furthermore according to the analysis performed in EudraVigilance for teriparatide, disproportionally increased reporting of calciphylaxis was considerable. Based on these findings the PRAC recommended that the signal should be further investigated.

Summary of recommendation(s)

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

4.2. New signals detected from other sources

4.2.1. Interferon alfa-2a – ROFERON-A (NAP)
Interferon alfa-2b – INTRONA (CAP)
Interferon beta-1a – AVONEX (CAP), **REBIF** (CAP)
Interferon beta-1b - BETAFERON (CAP), **EXTAVIA** (CAP)
Peginterferon alfa-2a - **PEGASYS** (CAP)
Peginterferon alfa-2b - **PEGINTRON** (CAP)

- Signal of pulmonary arterial hypertension

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

Administrative details:
EPITT 18059 – New signal
MAH(s): Biogen Idec (Avonex), Merck Serono Europe Limited (Rebif), Bayer Pharma AG (Betaferon), Novartis Europharm Ltd (Extavia), Merck Sharp & Dohme Limited (IntronA, PegIntron), Roche Registration Ltd (Pegasys, Roferon A)
Leading MS: SE

Background

Interferons (IFNs) are a group of endogenous glycoproteins with immunomodulatory, antiviral and antiproliferative properties used in a number of therapeutic indications including multiple sclerosis (beta interferons) and several types of cancer and in the treatment of chronic hepatitis B or C (alfa interferons).

The exposure for medicines containing interferons is estimated to be very wide since the medicines have been marketed in the late 90s' and have been widely prescribed worldwide.

During routine signal detection activities, a signal of pulmonary arterial hypertension (PAH) was identified by FR, based on 42 cases reported in France. The Rapporteurs for the medicinal products involved, confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted the outcome of a review conducted in France on PAH and was made aware of an unpublished retrospective study, designed to describe all cases of PAH with a history of interferon exposure. In addition to the French review, other articles were retrieved from the literature, describing cases of PAH in patients receiving IFN. The PRAC also noted that some published non-clinical data suggested a potential biological mechanism.

Based on these findings the PRAC agreed that further exploration of this signal was needed. However, since PAH has been closely monitored and/or cumulatively reviewed in the PSURs in most of the authorised medicines containing IFN alfa and beta, no additional data from MAHs was considered needed at this stage and the review should rather focus on available data. Qun-Ying Yue (SE) was appointed as lead Rapporteur, coordinating further evaluation of the signal.

Summary of recommendation(s)

- The individual Rapporteurs of alfa- and beta-interferon containing medicines should assess available PSUR data and EudraVigilance data, within 60 days.
- The Lead Rapporteur will review the above individual assessments together with published and unpublished clinical and non-clinical data and will circulate an overall assessment report to all PRAC members, for discussion expected at the December 2014 PRAC meeting.

4.2.2. Lithium carbonate, citrate, sulfate, acetate and gluconate (NAP)

- Signal of solid renal tumours

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
EPITT 18090 – New signal
MAH(s): various
Leading MS: DE

Background

Lithium is a chemical element and its salts are used in the treatment of acute episodes of mania or hypomania and for the prophylaxis of recurrent manic-depressive illness.

Medicine containing lithium salts have been very widely used for many years worldwide; however, the exact population exposure is difficult to estimate.

A signal of solid renal tumours in association with lithium was identified by the BfArM, based on a review submitted by the MAH for Hypnorex (lithium carbonate), in the context of a national variation. DE as RMS for this medicine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results of the review presented, consisting of a total of 14 serious cases of renal cell carcinoma, renal oncocytoma and renal cyst, directly reported to the MAH, cases from the literature and cases reported from health authorities. The majority of patients diagnosed with renal neoplasms had been treated with lithium for at least 10 years. All these patients presented chronic renal failure, usually asymptomatic. Histology and immunohistochemistry evaluation performed, showed that these tumours were originated from the collecting duct.
The PRAC commented that the number of cases presented was very small compared to the extensive clinical use of lithium. However, since lithium is known to be nephrotoxic and long-term use of lithium can lead to chronic renal failure through tubular damage with cyst formation, it was considered that the signal should be reviewed in further detail.

The PRAC appointed Martin Huber (DE) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Hypnorex and (in order to follow-up on previous PSUR submissions) the MAH for Quilonum (lithium carbonate) should submit to the PRAC Rapporteur a cumulative review of the signal of solid renal tumours following the administration of lithium, within 60 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3. **Thiotepa – TEPADINA** (CAP)

- Signal of pulmonary arterial hypertension

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
EPITT 18046 – New signal
MAH(s): Adienne S.r.l. S.U.
Leading MS: FR

Background

Tepadina, containing thiotepa, is a centrally authorised medicinal product indicated as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients and when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

The exposure for Tepadina is estimated to have been more than 14 300 patients worldwide, in the period from first authorisation in 2010 to 2014.

During routine signal detection activities, a signal of pulmonary arterial hypertension was identified by the EMA, based on 3 cases described in a recently published article[5]. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of severe and biopsy-confirmed pulmonary vasculopathy/pulmonary arterial hypertension reported. The case described in the article consisted of children exposed to thiotepa while undergoing HPCT for CNS malignancies - including two cases resulting in a fatal outcome. The authors concluded that pulmonary arterial vasculopathy and pulmonary arterial hypertension are common and potentially fatal complications in this setting.

PRAC commented that pulmonary toxicity is a known risk of thiotepa and is reflected in the product information and RMP; however, pulmonary arterial hypertension had not been documented so far. Pulmonary hypertension may be a complication of the transplant procedure itself; however the association with thiotepa could not be excluded based on the new information available[6].
Therefore the PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

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

4.3. Signals follow-up and prioritisation

4.3.1. **Androgen Deprivation Therapy (ADT)** (NAP)
Abiraterone – ZYTIGA (CAP); **degarelix – FIRMAGON** (CAP)

- Signal of QT interval prolongation associated with long-term use

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
EPITT 13886 – Follow-up May 2014
MAH(s): Janssen-Cilag International N.V., Ferring Pharmaceuticals A/S, various
Leading MS: DE

Background

For background information, see PRAC minutes of 5-8 May 2014.
The MAH replied to the request for information on the signal of QT interval prolongation associated with long-term use of ADT and the responses were assessed by the Rapporteur.

[5] Schechter T, Leucht S, Bouffet E, Cutz E, Gassas A, Huang A, et al. Pulmonary hypertensive vasculopathy following tandem autologous transplantation in pediatric patients with central nervous system tumors. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2013;19(2):235-9
[6] Dandoy CE, Hirsch R, Chima R, Davies SM, Jodele S. Pulmonary hypertension after hematopoietic stem cell transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2013;19(11):1546-56.
Jodele S, Hirsch R, Laskin B, Davies S, Witte D, Chima R. Pulmonary arterial hypertension in paediatric patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy

Discussion

The PRAC discussed the evidence assessed on long-term androgen deprivation therapy (ADT) and risk of QT interval prolongation.

The analysis of the cases retrieved from EudraVigilance did not provide a clear picture on a potential association of androgen deprivation therapy with QT interval prolongation. However such result was expected taking into account the limitation of spontaneous reporting in investigating this type of ADR. Some cases, based on timelines and a positive de-challenge, showed evidence for a possible causal association.

Analysis of literature data provided some more evidence for QT prolongation linked to androgen deprivation therapy. The publications reviewed[7] revealed a clear trend towards effect of androgen deprivation therapy and a longer QT interval. However, this effect was small in all studies, and its clinical significance was questionable. In conclusion, taking all data on androgen deprivation therapy together, there was sufficient evidence for an effect of androgen deprivation therapy on the QT interval.

However, the PRAC emphasised that a lengthened QT interval is a risk factor for ventricular tachyarrhythmia, and that the average Metastatic Castration Resistant Prostate Cancer (mCRPC) population is older, more prone to pre-existing heart disease and other risk factors than the overall population or the patients investigated in the studies reviewed. Therefore, even a moderate effect on QT interval prolongation might be of clinical relevance for them.

Therefore, further information in the product information and package leaflet could support these patients and their physicians in better assessing the benefit risk ratio of the treatment, including the potential for *torsade de pointes,* prior to initiation.

Summary of recommendation(s)

- The MAHs for the MAHs of the authorised medicines for androgen deprivation (as listed elsewhere – see PRAC recommendations EMA/PRAC/490498/2014) should be requested to submit to the NCAs of the MSs a variation to update the product information to include that androgen deprivation therapy may prolong the QT interval[8], within 60 days.

For the full PRAC recommendations, see EMA/PRAC/490498/2014 published on the EMA website on 30/09/2014.

4.3.2. **Cefepime** (NAP)

- Signal of convulsions

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

[7] Garnick MB, Pratt CM, Campion M, Shipley J. The effect of hormonal therapy for prostate cancer on the electrocardiographic QT interval: phase 3 results following treatment with leuprolide and goserelin, alone or with bicalutamide, and the GnRH antagonist abarelix Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 4578.
Smith MR, Klotz L, Persson BE, Olesen TK, Wilde AA. Cardiovascular safety of degarelix: results from a 12-month, comparative, randomized, open label, parallel group phase III trial in patients with prostate cancer. J Urol. 2010 Dec;184(6):2313-9.
Sağlam H, ÇakarA, Köse O, Kumsar S, Budak S, Beyaz SG, Adsan OE. Changes in Electrocardiogram Findings during Treatment with Gonadotropin-Releasing Hormone Agonist and Surgical Castration for Prostate Carcinoma Open Journal of Urology Vol.2 No.3A, October 2012.
Tolcher AW, Chi KN, Shore ND, et al. Effect of abiraterone acetate plus prednisone on the QT interval in patients with metastatic castration-resistant prostate cancer. Cancer Chemother Pharmacol. 2012;70(2):305–313
[8] SmPC section 4.4, 4.5 and 4.8 and PL

Administrative details:
EPITT 17859 – Follow-up March 2014
MAH(s): various
Lead MS: PT

Background

For background information, see PRAC minutes of 3-6 March 2014.
The MAH replied to the request for information on the signal of convulsions and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the outcome of the signal review performed on data based on post-marketing reports, MAH's studies and published literature.

The analysis submitted supported previous knowledge of the neurological toxicity of cefepime and did not reveal any unexpected finding. The analysis of clinical trial data suggested a low incidence of neurological toxicity (0.036% for convulsions reported as probably related to cefepime therapy). The analysis of reports from the database of the MAH suggested that the frequency of the occurrence of convulsions continued to be rare (affecting ≥1:10,000 to < 1:1,000 patients). Risk factors for the occurrence of convulsions were – as already identified - elderly, reduced renal clearance and concurrent use of drugs with nephrotoxic potential.

Therefore the PRAC agreed that no changes were necessary to the product information of cefepime-containing products.

Summary of recommendation(s)

- No changes to the product information of cefepime containing medicines are required at this point in time. The MAHs should continue to monitor these events as part of routine safety surveillance.

4.3.3. **Chlorhexidine** (NAP)

- Signal of risk of skin injury including chemical burns when used in skin disinfection in premature infants

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 18000 – Follow-up June 2014
Leading MS: UK
MAH(s): various

Background

For background information, see PRAC minutes of 10-13 June 2014. The MAHs replied to the request for information on the signal of skin injury including chemical burns when chlorhexidine is used in skin disinfection in premature infants and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the additional information assessed on the issue and considered the advice provided by the Paediatric Committee (PDCO), as regards the availability of European guidelines and

recommendations regarding skin antisepsis prior to invasive procedure (i.e. central venous catheterisations) in term and preterm newborn infants.

Cases from different sources including published literature confirmed reports of neonates suffering chemical burns, including cases with fatal outcome, following the application of chlorhexidine solutions were also considered.

Data from national surveys highlighted that the majority of Neonatal Intensive Care Units (NICUs) are using chlorhexidine solutions, mostly prior to central vascular access, umbilical catheterisations and peripheral intravenous access. Overall there was considerable variability in the type and concentration of solutions used, as well as in the restriction of their use with regard to weight at birth, gestational or chronological age.

A causal relationship was supported by a clear anatomical and temporal relationship between the application of the product and the occurrence of the adverse event. There was also a positive correlation between extreme prematurity and the risk of skin toxicity given that the skin barrier function is significantly less developed in pre-term neonates compared to older infants.

The PRAC recommended that the safety concerns identified needed to be carefully evaluated against the risks of ineffective skin cleansing, to ensure that any regulatory action would not have a negative impact on the reduction of neonatal sepsis needed in NICUs.

The PRAC nevertheless recognised that changes to the product information of relevant chlorhexidine containing products should be made, to advise of this risk to relevant healthcare professionals (i.e. neonatologists, paediatricians, infectious disease and microbiology specialists and preventive medicine doctors, as well as nursing staff and pharmacists responsible for neonatal/ paediatric intensive care units) and key elements for communication were agreed.

Summary of recommendation(s)

- The MAHs for the nationally authorised[9] chlorhexidine containing cutaneous solutions should be requested to submit to the NCAs of the MSs within 60 days a variation to update the product information[10] informing that skin antisepsis prior to invasive procedures has been associated with chemical burns in neonates.
- Communication of this important safety issue to relevant hospital paediatric physicians, nursing staff and pharmacists responsible for neonatal/ paediatric intensive care units is important and may be best delivered by means of a communication issued by NCAs in accordance with agreed key elements.

For the full PRAC recommendations, see EMA/PRAC/490498/2014 published on the EMA website on 30/09/2014.

4.3.4. **Imatinib – GLIVEC** (CAP), NAP

- Signal of renal impairment associated with long term use (decreased estimated glomerular filtration rate (eGFR))

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

[10] Section 4.4 and 4.8 of the SmPC and PL.

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

Administrative details:
EPITT 17946 – Follow-up April 2014
MAH: Novartis Europharm Ltd

Background

For background information, see PRAC minutes of 7-10 April 2014. The MAH replied to the request for information on the signal of renal impairment associated with long term use of imatinib and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed a review of chronic renal failure associated with imatinib, including an epidemiological review of data on renal function in the population similar in age to that receiving imatinib treatment, a literature review of imatinib, a renal function data review pooled from selected clinical trials and an individual case review based on a previously requested search strategy.

From the analysis of sponsored clinical trials a consistent trend in increase in serum creatinine and decrease in eGFR was observed. The post-marketing data identified cases with decreased or abnormal eGFR or creatinine clearance (CrCl) with a positive de-challenge and some with positive re-challenge. Most of the patients with decreased or abnormal GFR or CrCl and dialysis and/or kidney transplantation had other co-morbidities or were on concomitant medications that could affect the renal function. Although ageing is associated with a decline in renal function, the PRAC agreed, on the basis of the available evidence, that long-term treatment with imatinib can impair renal function.

Therefore, an update of the product information to reflect these findings was considered needed.

Summary of recommendation(s)

- The MAHs for the reference, centrally authorised[11] imatinib containing medicines should be requested to submit to the EMA within 60 days a variation to update the product information to include information that long-term treatment with imatinib may result in a clinically significant decline in renal function[12]. Additionally, the MAH should submit in the next PSUR (DLP 10 May 2015) a response to supplementary information requested by the PRAC.
- The MAHs of generics products should then be requested to submit to the EMA or to the national competent authorities of the MSs, as applicable, a variation to align their product information to that of the originator.

For the full PRAC recommendations, see EMA/PRAC/490498/2014 published on the EMA website on 30/09/2014.

4.3.5. Leuprorelin, suspension for injection (**Eligard** - NAP)

- Signal of lack of efficacy due to medication error - wrong technique in drug usage process

[11] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to
[12] Section 4.4 and 4.8 of the Summary of Product Characteristics and PL

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
EPITT 17753 – Follow-up May 2014
MAH(s): Astellas (Eligard)

Background

For background information, see PRAC minutes of 5-8 May 2014.

The MAH replied to the request for information on the signal of lack of efficacy due to medication error - wrong technique in drug usage process - and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the outcome of the review on the further data received on the signal of medication error described with Eligard (leuprorelin). A further search of the MAH's safety database identified additional cases of medication errors. The cumulative review of cases reporting a medication error event revealed a variety of errors during prescription, preparation, mixing and administration of the product. A number of cases were reported to be associated with a lack of effect.

Therefore the PRAC confirmed the need of risk minimisation measures including changes to the product information. The PRAC also recommended communication to healthcare professionals (DHPC) and a protocol for a study of the effectiveness of risk minimisation, in order to examine the knowledge and awareness of the appropriate reconstitution and administration of Eligard and the reporting rate of medication error cases and cases of lack of efficacy, pre and post the DHPC letter distribution.

Summary of recommendation(s)

- The MAH for Eligard[13] should submit to the NCAs of the MSs within 30 days a variation to update the product information to include that lack of clinical efficacy may occur due to incorrect reconstitution of the product[14]; a room temperature storage variation to allow storage of the product at room temperature for up to 1 month and proposal for a DHPC. Additionally, the MAH should submit within 6 months, a variation to modify the device. Finally, the MAH should within 1 month respond to a request for additional information, which includes a revised protocol for an effectiveness study as well as other clarification requested by the PRAC.

For the full PRAC recommendations, see EMA/PRAC/490498/2014 published on the EMA website on 30/09/2014.

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

- Signal of increased risk of cardiovascular events

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

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

Administrative details:
EPITT 17931 – Follow-up April 2014
MAH: various
Leading MS: UK

Background

For background information, see PRAC minutes of 7-10 April 2014.
Following the request of the PRAC, the EMA Excipients Guideline group had considered whether updates could be made to the product information of sodium-containing medicines.

Discussion

The EMA Excipients Guideline group addressed the PRAC's questions and provided comments including proposal of further changes to the package leaflet wording for sodium containing medicines, acknowledging that some further refinement should be made to existing recommended text in the guideline. The PRAC noted this update and considered that warnings in product information should make it clear that any cardiovascular risk was most relevant for medicines that are used in the long term. Furthermore, PRAC believed it would be helpful to seek input regarding age-related intake thresholds of sodium and most appropriate labelling advice from relevant stakeholders, in particular, the PDCO.

The PRAC commented that potentially this review may be applicable to a wide array of medicinal products for different populations and for different sodium salts (as well as for products where sodium is part of the active ingredients and/or excipient), and therefore requested that further consideration should be given to the scope of the products that would be impacted. This information along with the input of the PDCO should inform the final conclusions and recommendations.

Summary of recommendation(s)

- Aspects of the signal, and in particular the scope of the procedure and the thresholds for paediatric medicines, should be further assessed by the PRAC Rapporteur in consultation with the PRAC secretariat through a continued engagement with the Excipients Guideline group, with the Member States and with input from the Paediatric Committee (PDCO).
- Further PRAC recommendations will be issued at the December 2014 meeting.

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

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

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

5.1.1. Afamelanotide

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

Administrative details:
Product number(s): EMEA/H/C/002548, *Orphan*
Intended indication(s): Treatment of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)
Applicant: Clinuvel (UK) Limited

5.1.2. Apremilast

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

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

5.1.3. Bazedoxifene, estrogens conjugated

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

Administrative details:
Product number(s): EMEA/H/C/002314
Intended indication(s): Treatment of oestrogen deficiency and osteoporosis

5.1.4. Dasabuvir

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

Administrative details:
Product number(s): EMEA/H/C/003837
Intended indication(s): Treatment of chronic hepatitis C

5.1.5. Eliglustat

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

Administrative details:
Product number(s): EMEA/H/C/003724*, Orphan*
Intended indication(s): Treatment of Gaucher disease type 1
Applicant: Genzyme Europe BV

5.1.6. Ketoconazole

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

Administrative details:
Product number(s): EMEA/H/C/003906, *Orphan*
Intended indication(s): Treatment of Cushing's syndrome
Applicant: Laboratoire HRA Pharma

5.1.7. Levofloxacin

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

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

5.1.8. Nintedanib

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

Administrative details:
Product number(s): EMEA/H/C/003821, *Orphan*
Intended indication(s): Treatment of idiopathic pulmonary fibrosis (IPF)
Applicant: Boehringer Ingelheim International GmbH

5.1.9. Ombitasvir, paritaprevir, ritonavir

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

Administrative details:
Product number(s): EMEA/H/C/003839
Intended indication(s): Treatment of chronic hepatitis C

5.1.10. Secukinumab

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

Administrative details:
Product number(s): EMEA/H/C/003729
Intended indication(s): Treatment of plaque of psoriasis

5.2. Medicines already authorised

RMP in the context of a variation[15] – PRAC-led procedure

See under 14.1

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

5.2.1. Collagenase clostridium histolyticum – XIAPEX (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002048/II/0044
Procedure scope: Extension of indication for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity. The PL is updated accordingly
MAH(s): Swedish Orphan Biovitrum AB (publ)

Background

Xiapex is a centrally authorised medicine containing collagenase clostridium histolyticum, used for the treatment of Dupuytren's contracture in adult patients with a palpable cord.

The CHMP is evaluating an extension of the therapeutic indication for Xiapex, to include the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

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

Summary of advice

- The RMP version 10 for Xiapex (collagenase clostridium histolyticum) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable pending amendments and responses to some questions to be reflected in the RMP before finalisation of the procedure.
- The RMP should take into account some additions and clarifications requested by the PRAC with regards to inclusion in Annex II of educational material for healthcare professionals in the treatment of Peyronie's disease, the proposed study protocol for study AUX-CC-810, important potential risks and missing information as well as the summary RMP for the public.

5.2.2. Insulin glargine – OPTISULIN (CAP)

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

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

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

Background

Optisulin is a centrally authorised insulin glargine, a human insulin analogue used in the treatment of diabetes mellitus in adults, adolescents and children aged two years and above.
The CHMP is evaluating a line extension for Optisulin, to add a new strength of 300 U/ml. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation for a line extension.

Summary of advice

- The updated RMP version 4 for Optisulin (insulin glargine) in the context of variation for a line extension under evaluation by the CHMP was considered acceptable provided that an updated version is submitted in response to a request for supplementary information. The request includes aspects relating to the relevance and implications of the increase of basal insulin for the U300 strength compared to U100 regarding the risk of medication errors, as well as some aspects regarding the pharmacovigilance plan and proposed risk minimisation measures.

5.2.3. Nitric oxide – INOMAX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000337/II/0039
Procedure scope: Submission of an updated RMP for INOmax. Consequently, the Annex II conditions are updated. The MAH takes the opportunity to introduce minor changes to the SmPC section 4.8 and PIL in line with the QRD template
MAH(s): Linde Healthcare AB

Background

Inomax is a centrally authorised medicine containing nitric oxide indicated in the treatment of Persistent Pulmonary Hypertension in the Newborn (PPHN) and in the treatment of pulmonary hypertension associated with heart surgery. The CHMP is evaluating a type II variation procedure for Inomax introducing a revised RMP that fully includes both all currently authorised indications. The PRAC is responsible for providing advice to the CHMP on the necessary updates this.

Summary of advice

- The RMP version 4 for Inomax (nitric oxide) in the context of the variation under evaluation by the CHMP was considered acceptable provided that supplementary information is provided before finalisation of the variation procedure by the CHMP. The MAH should comment on feasibility aspects of providing HCPs with a laminated card that details the main safety concerns and risk minimisation measures, as well as some other minor aspects.

RMP evaluated in the context of a PSUR procedure

See Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony stimulating factor (sipuleucel-T) – PROVENGE 15.1.5. , Betaine anhydrous – CYSTADANE 15.1.7. , Brentuximab vedotin – ADCETRIS 15.1.9. , Dexamethasone – OZURDEX 15.1.15. , Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA 15.1.17. , Fampridine – FAMPYRA 15.1.21. Nalmefene – SELINCRO 15.1.35. , Pirfenidone – ESBRIET 15.1.39. , Prasugrel – EFIENT 15.1.41. , Pregabalin – LYRICA 15.1.42. , Tipranavir – APTIVUS 6.1.21. , Velaglucerase alfa – VPRIV 15.1.51.

RMP evaluated in the context of PASS results

Bevacizumab – AVASTIN 16.1.16. , Epoetin zeta – RETACRIT 16.1.17. , Epoetin zeta – SILAPO **Error! Reference source not found.**and 16.1.18. , Golimumab – SIMPONI 16.1.19. , Infliximab – REMICADE 16.1.20. , Mannitol – BRONCHITOL 16.1.21. , Teriparatide – FORSTEO 16.1.24.

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

5.2.4. Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001095/R/0046 (with RMP)
MAH(s): Novartis Vaccines and Diagnostics S.r.l.

Background

Menveo is centrally authorised vaccine indicated for active immunisation of patients at risk of exposure to Neisseria meningitidis groups A, C, W135 and Y, to prevent invasive disease. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in the context of the renewal of the MA.

Summary of advice

- The updated RMP submitted within the renewal procedure was considered acceptable; however, although anaphylaxis and whole limb swelling are adverse events associated with the vaccine, as reflected in the product information, these events did not require inclusion as important risks in the RMP. If in the future, any pharmacovigilance activities would indicate an increase in frequency or severity of anaphylaxis or whole limb swelling, it can be reconsidered to include these ADRs in the RMP.

Others

Bisphosphonates, denosumab and risk of osteonecrosis of the jaw (ONJ): consultation with Scientific Advisory Group (SAG) Oncology, see under 12.13.1.2.

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[16]

6.1.1. Aclidinium – **BRETARIS GENUAIR** (CAP), **EKLIRA GENUAIR** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002211/PSUV/0015, EMEA/H/C/002706/PSUV/0014
MAH(s): Almirall S.A

Background

Aclidinium bromide is an anticholinergic agent indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bretaris Genuair and Eklira Genuair, a centrally authorised medicine containing aclidinium bromide and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bretaris Genuair and Eklira Genuair (aclidinium bromide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add palpitations as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisations should be varied[17].

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

- In the next PSUR, the MAH should provide detailed analyses of cases of oral mucosal disorder, tremor, nausea and vomiting, as well as cases of dizziness, and propose an update of the product information as warranted. In addition, the MAH should also review the number of cases where an oral mucosal sensation of the product's taste or its texture were reported and consider an amendment of the product information as warranted, and consider whether taste disorders may relate to oral mucosal disorders. The MAH should also discuss whether oral mucosal and/or taste disorders should be included as an important potential risk in the RMP. Moreover, the MAH should closely monitor cases of medication error and product quality issues. Finally, the MAH should introduce some minor amendments to the RMP in the framework of the next relevant regulatory procedure, in particular, to expand the information in module SVII.3 relating to the reported undesirable effects of dizziness and palpitations as class effects.

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. Adalimumab – HUMIRA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000481/PSUV/0131
MAH(s): AbbVie Ltd.

Background

Adalimumab is a selective immunosuppressive agent indicated for the treatment of polyarticular juvenile idiopathic arthritis (PJIA) and for the treatment of paediatric Crohn's disease under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Humira, a centrally authorised medicine containing adalimumab, 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 Humira (adalimumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add vasculitis as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should address all important potential risks and missing information. The MAH should also continue to closely monitor cases of malignancies, pregnancy outcomes and cases of infectious adverse events in infants. In addition, the MAH should provide a cumulative review of confirmed Kaposi´s sarcoma and cases of gliobastoma that should be also reviewed in upcoming registry reports.

[18] 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

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. **Aflibercept – ZALTRAP** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002532/PSUV/0009
MAH(s): Sanofi-Aventis Groupe

Background

Aflibercept is an antineoplastic agent indicated in combination in adults with metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zaltrap, a centrally authorised medicine containing aflibercept, 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 Zaltrap (aflibercept) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to provide refined instructions on the use of a filter, including its pore size and material in the sections on method of administration and special precautions for disposal and other handling, following reports of medication error. Therefore the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should present any significant efficacy/safety findings from studies EFC11338, AFLIBC06097 and AFLIBL06266 and should provide a detailed discussion on the magnetic resonance imaging (MRI) findings from study R910-ST-1114, including a discussion on the relevance of these findings for aflibercept monotherapy. In addition, the MAH should discuss if medication errors relating to filter use could have any clinical consequences regarding efficacy or safety. Finally, the MAH should provide a detailed review of the publications by *Qi WX et al*[20] and *Rodriguez et al*[21].

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

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Ingebjørg Buajordet (NO)

[19] Update of SmPC sections 4.2 and 6.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[20] Qi WX, Shen F, Qing Z, Xiao-Mao G. Risk of gastrointestinal perforation in cancer patients treated with aflibercept: a systematic review and meta-analysis. Tumour Biol. 2014 Jul 30
[21] Rodriguez M. Ziv-aflibercept use in metastatic colorectal cancer. J Adv Pract Oncol. 2013 Sep;4(5):348-52. Review

Administrative details:
Procedure number(s): EMEA/H/C/000916/PSUV/0021, EMEA/H/C/000915/PSUV/0023
MAH(s): Servier (Ireland) Industries Ltd., Les Laboratoires Servier

Background

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist indicated in adults for the treatment of major depressive episodes.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Thymanax and Valdoxan, centrally authorised medicines containing agomelatine, 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 PRAC agreed that the risk-benefit balance of Thymanax and Valdoxan (agomelatine) remains favourable provided the terms of the marketing authorisation(s) are varied and that additional risk minimisation measures are imposed. The Committee adopted a recommendation for consideration by the CHMP (meeting highlights from the PRAC 8-11 September 2014 - PRAC PSUR assessment report to be published following EC decision).
- The product information should be updated, taking into account the proposals from the MAH, to clarify the monitoring of the liver function tests in the posology and method of administration section, to amend the warning on liver function monitoring and should also include new contraindications in patients aged 75 years. In addition, the conditions with regard to the safe and effective use of the medicinal products should be amended to require the MAH to ensure that all physicians expected to prescribe or use agomelatine are provided with patient booklets to be distributed to patients emphasising the need for pre-treatment and regular on-treatment monitoring of liver function tests. The educational material for prescribers should be updated accordingly. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- The MAH should inform healthcare professionals of these changes via a Direct Healthcare Professional Communication (DHPC).
- The MAH should submit to EMA within 60 days a detailed review of cases of overdose and consider updating the product information accordingly, additional data for further analysis of signals on palpitations, tachycardia, vertigo, amnesia/memory impairment and delirium. In addition, the MAH should submit narratives for all cases with positive de-challenge or re-challenge, as well as cases resolving despite continued agomelatine treatment. With regard to tachycardia, the MAH should provide a detailed analysis of *Comte et al*[23].
- In the next PSUR, the MAH should provide a re-evaluation of hepatic safety, including a standard categorisation of cases of hepatotoxicity and detailed discussion on the compliance with transaminases monitoring recommendations. The MAH should also provide a new analysis based on data from the prospective cohort study (CLE-20098-068) to reassess the effectiveness of the risk minimisation programme. In addition, the MAH should provide detailed reviews of cases of hypotension, hypertension and QT prolongation. When reviewing events

[22] Update of SmPC sections 4.2, 4.3, 4.4 and Annex II. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[23] Comte H, Auffret M, Lelièvre B, Béné J, Steen P, Gautier S. Tachycardia and precordial pain with agomelatine: a case report. Therapie 2013;68(5):324-325

under close monitoring in future PSURs, the MAH should focus on events with positive de-challenge or re-challenge, as well as cases resolving despite continued treatment with agomelatine. Finally, the MAH should provide a detailed analysis of the recent publication by *Song et al*[24] on the polymorphism on the pharmacokinetics of agomelatine and propose an update of the product information and RMP as warranted.

- The MAH should provide an updated RMP to delete hepatic impairment as missing information, to include information on the patient's booklet as an additional risk minimisation measure and to add a category 3 study to evaluate the adherence to the monitoring regimen, the reasons for non-compliance with liver function monitoring and the compliance to relevant contraindications.

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. Clofarabine – EVOLTRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000613/PSUV/0044
MAH(s): Genzyme Europe BV

Background

Clofarabine is a purine nucleoside anti-metabolite indicated for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Evoltra, a centrally authorised medicine containing clofarabine, 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 Evoltra (clofarabine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to specify that the recommended dose of 52 mg/m^2 should be used in monotherapy and to add a warning regarding a higher toxicity of clofarabine when used in combined regimens rather than alone. In addition, hyponatraemia should be added as an adverse reaction with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should provide detailed reviews of fatal cases, cases of hepatic failure and hepatitis and cases of convulsions and propose an update of the product information as warranted. In addition, the MAH should provide an updated RMP to reflect that caecitis, haemorrhage and off-label use in acute myeloid leukaemia (AML) in paediatric

[24] Song L, Du Q, Jiang X, Wang L. Effect of CYP 1A2 polymorphism on the pharmacokinetics of agomelatine in Chinese healthy male volunteers. J Clin Pharm Ther 2014; 39: 204-9
[25] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

patients, in ALL patients with less than two prior regimens, or in combination with other drugs are important identified risks.

- The MAH should keep the European registry programme ongoing to pursue close monitoring of the use of clofarabine (SOB 014) and the registry protocol should be amended to allow inclusions of any patients treated with clofarabine according to medical practice.

  See also under 8.1.1.

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. Dabrafenib – TAFINLAR (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002604/PSUV/0005
MAH(s): GlaxoSmithKline Trading Services

Background

Dabrafenib is a protein kinase inhibitor indicated in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tafinlar, a centrally authorised medicine containing dabrafenib, 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 Tafinlar (dabrafenib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on RAS-mutation positive non-cutaneous malignancy associated with dabrafenib monotherapy treatment. Therefore careful consideration should be given before administering dabrafenib to patients with a prior or concurrent cancer associated with RAS mutation. Therefore the current terms of the marketing authorisation should be varied[26].
- In the next PSUR, the MAH should provide a detailed discussion on the proportion of patients receiving dabrafenib and radiation therapy concomitantly, together with a description of cases of radiation injury and treatment interruption, the MAH should also consider an update of the product information and study protocols as warranted. In addition, the MAH should provide further analyses of several adverse drug reactions, in particular, cases of pancreatitis, uveitis, atrial fibrillation, colitis, cytokine release syndrome and convulsions/seizures and should propose an update of the product information as warranted.

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

[26] 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

6.1.7. Degarelix – **FIRMAGON** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000986/PSUV/0023
MAH(s): Ferring Pharmaceuticals A/S

Background

Degarelix is a gonadotrophin releasing hormone (GnRH) antagonist indicated for the treatment of adult male patients with advanced hormone-dependent prostate cancer.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Firmagon, a centrally authorised medicine containing degarelix, 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 Firmagon (degarelix) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add clarifications on the drug administration schedule in the posology section to clarify that the recommended starting dose should be administered by two consecutive injections of 120 mg. Therefore the current terms of the marketing authorisation should be varied[27].
- In the next PSUR, the MAH should provide detailed reviews of cases of rhabdomyolysis, hepatic events and interstitial lung disease. The MAH should also provide a detailed review of cerebrovascular disorders and propose to update the product information as warranted. Moreover, the MAH should review the recent publication from *Lapi et al*[28] and *Gandaglia et al*[29] suggesting that the use of androgen deprivation therapy (ADT) was significantly associated with an increased risk of acute kidney injury in non-metastatic prostate cancer patients. Finally the MAH should provide a detailed analysis of suspected cases reported as intentional drug misuse in order to confirm this misuse and should discuss this intentional drug misuse. Finally, the MAH should provide an updated RMP to implement some minor changes in the course of the next regulatory procedure.

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

See also under 8.1.1.

[27] Update of SmPC section 4.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[28] Lapi et al. Androgen deprivation therapy and risk of acute kidney injury in patients with prostate cancer. . 2013 Jul 17;310(3):289-96. doi: 10.1001/jama.2013.8638
[29] Gandaglia et al. Gonadotropin-releasing hormone agonists and acute kidney injury in patients with prostate cancer. Eur Urol. http://dx.doi.org/10.1016/j.eururo.2014.01.026

6.1.8. Docetaxel – **DOCETAXEL ACCORD** (CAP), **DOCETAXEL KABI** (CAP), **DOCETAXEL MYLAN** (CAP), **DOCETAXEL TEVA** (CAP), **DOCETAXEL WINTHROP** (CAP), **TAXOTERE** (CAP), NAP

- Evaluation of a PSUSA[30] procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001152/201311
MAH(s): Accord Healthcare Limited (Docetaxel Accord), Fresenius Kabi Oncology Plc (Docetaxel Kabi), Mylan S.A.S. (Docetaxel Mylan), Teva Pharma B.V. (Docetaxel Teva), Aventis Pharma S.A. (Docetaxel Withrop, Taxotere), various

Background

Docetaxel is an antineoplastic agent indicated for the treatment of breast cancer, non-small cell lung cancer, ovarian cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer. Depending on the indication, docetaxel can be used alone or in combination with doxorubicin and/or cyclophosphamide, or with trastuzumab or capecitabine or cisplatin (with or without 5-fluorouracile) or prednisone/prednisolone.

Based on the assessment of the individual PSURs, part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of docetaxel-containing products[31] 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 docetaxel-containing products in the approved indication(s) remains favourable.
- With regard to docetaxel-containing products with no alcohol in their formulation, the current terms of the marketing authorisations should be maintained.
- With regard to docetaxel-containing products with alcohol in their formulation, the product information should be updated to add a warning on the possible risk of alcohol intoxication in patients with alcoholism, in pregnant or breastfeeding women, in children and in high-risk groups such as patients with liver disease or epilepsy, those who drive or operate machines and those taking medicines that may interact with alcohol. Therefore the current terms of the marketing authorisations should be varied[32].
- With regard to nationally authorised products, MAHs should submit to National Competent Authorities within 60 days variation applications to update their product information in line with the reference product regarding interactions with CYP3A4 inhibitors.
- In the next PSUR, MAHs should provide detailed reviews of fatal cases, cases of abuse and cardiac disorders. In addition, MAHs should discuss the use of docetaxel in elderly patients and consider classifying it as a potential risk (as done for Docetaxel Teva). Moreover, MAHs should propose an update of the product information with regard to the possible occurrence of non-reversible alopecia after docetaxel monotherapy. Finally, MAHs should propose to update their

[30] PSUR single assessment, referring to CAP, NAP
[31] Including products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended, as requested by Competent Authorities [DIR Article 107b (3b)] and reflected in the EURD list for the current PSUSA procedure
[32] 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

product information to reflect the risk of extravasation in line with the reference product (Taxotere) and MAHs should propose risk minimisation measures accordingly.

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

6.1.9. Epoetin beta – NEORECORMON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000116/PSUV/0084
MAH(s): Roche Registration Ltd

Background

Epoetin beta, a human erythropoietin manufactured by recombinant DNA technology, is an antianaemic indicated for the treatment of symptomatic anaemia and indicated for increasing the yield of autologous blood from patients in a pre-donation programme under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of NeoRecormon, a centrally authorised medicine containing epoetin beta, 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 NeoRecormon (epoetin beta) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 90 days a detailed review of cases of acute myocardial infarction, gastrointestinal hemorrhage, pneumonia, Stevens-Johnson syndrome and sudden death. In addition, the MAH should provide a detailed review relating to the potential risk of infantile hemangioma in preterm infants.
- In the next PSUR, the MAH should provide further details on reported cases of medication error. The MAH should also provide an update of the RMP relating to the risks of cardiovascular complications and hypertension.

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. Ivacaftor – KALYDECO (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002494/PSUV/0021
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

Background

Ivacaftor is a selective potentiator of the CFTR[33] protein indicated for the treatment of cystic fibrosis (CF) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Kalydeco, a centrally authorised medicine containing ivacaftor, 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 Kalydeco (ivacaftor) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning following the reports of cases of non-congenital lens opacities without impact on vision in patients aged up to 12 years old and to recommend baseline and follow-up ophthalmological examinations in paediatric patients initiating ivacaftor treatment. Therefore the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAH should closely monitor cases related to bilirubin elevation and the potential risk of effects on liver function tests, particularly in the first weeks of treatment and in patients with a previous history of liver disease. The MAH should also provide a detailed analysis of cases of haemoptysis. In addition, the MAH should provide further information relating to lens opacities, in particular details related to alternative causes as co-administration of corticosteroids, previous x-ray exposure and congenital cause. Finally, the MAH should present further data on genotype and details on exposure of special populations (including pregnant women and patient with co-morbidities) available in the UK CF registry.

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. Lomitapide – LOJUXTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002578/PSUV/0008
MAH(s): Aegerion Pharmaceuticals Limited

Background

Lomitapide is a selective inhibitor of microsomal transfer protein (MTP) indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

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

[33] Cystic fibrosis transmembrane conductance regulator
[34] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Lojuxta (lomitapide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to delete ritonavir and tipranavir from the list of weak CYP3A4 inhibitors listed in the section on the interactions of lomitapide with other medicinal products. Therefore the current terms of the marketing authorisation(s) should be varied[35].
- In the next PSUR, the MAH should provide a detailed review of cases of cardiac disorder and propose to update the product information accordingly.

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

6.1.12. Mercaptopurine – XALUPRINE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002022/PSUV/0008
MAH(s): Nova Laboratories Ltd

Background

Mercaptopurine is an antineoplastic agent indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xaluprine, a centrally authorised medicine containing mercaptopurine, 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 Xaluprine (mercaptopurine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on cases of symptomatic hypoglycaemia reported in children. Photosensitivity reactions and hypoglycaemia should be also added as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[36].
- In the next PSUR, the MAH should provide a detailed review of cases of photosensitivity reactions and propose a further update of the product information under the warning section as warranted.

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

[35] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[36] 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

6.1.13. Mirabegron – BETMIGA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002388/PSUV/0013
MAH(s): Astellas Pharma Europe B.V.

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Betmiga (mirabegron) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add angioedema as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[37].
- In the next PSUR, the MAH should provide detailed reviews of cases of severe cutaneous adverse reactions, cases of medication errors and cases of "drug ineffective". The MAH should also provide further details on all ongoing non-interventional studies. In addition, the MAH should provide a detailed review of serious cases with possible interactions with flecainide and other drugs metabolised by cytochrome CYP2D6.

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.

6.1.14. Nitisinone – ORFADIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000555/PSUV/0044
MAH(s): Swedish Orphan Biovitrum International AB

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

Background

Nitisinone is indicated for the treatment of patients with a confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Orfadin, a centrally authorised medicine containing nitisinone, 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 Orfadin (nitisinone) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a detailed review of cases of suspected respiratory distress syndrome reported and discuss the potential causal relationship with the administration of nitisonine.

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

6.1.15. Paclitaxel – ABRAXANE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000778/PSUV/0066
MAH(s): Celgene Europe Limited

Background

Paclitaxel is an antineoplastic agent indicated for the treatment of metastatic breast cancer in adult patients in monotherapy and for the treatment of adult patients with metastatic adenocarcinoma of the pancreas in combination with gemcitabine under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Abraxane, a centrally authorised medicine containing paclitaxel, 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 Abraxane (paclitaxel) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 60 days a detailed analysis of the potential underdosage of paclitaxel due to residual liquid in the infusion system after completion of the intravenous administration as described in the 'special precautions for disposal and other handling' section of the product information. The MAH should propose a substantiated comprehensive instruction to prevent paclitaxel remaining in infusion lines. As a consequence, the MAH should propose to

update the product information as warranted, and discuss the need to take precautionary measures, including an update to the RMP and the possibility to use risk communication materials.

- In the next PSUR, the MAH should provide a detailed review of cases of cross-hypersensitivity with solvent-based taxanes. Finally, in the course of the next regulatory procedure with an RMP update, the MAH should discuss the relevance of deleting the use of paclitaxel in patients with renal impairment as missing information.

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

6.1.16. Pomalidomide – IMNOVID (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002682/PSUV/0006
MAH(s): Celgene Europe Limited

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Imnovid (pomalidomide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add epistaxis under all adverse drug reactions as an undesirable effect with a common frequency and epistaxis under grade 3-4 adverse reactions with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[38].
- In the next PSUR, the MAH should provide detailed analyses of cases of upper and lower gastrointestinal haemorrhage, cases of heart failure and discuss if the RMP should be updated to reflect it as an important identified risk instead of a potential risk. The MAH should also discuss the evidence for reversibility of abnormal liver function tests with treatment interruption or dose reduction. In addition, the MAH should provide detailed reviews of cases of atrial fibrillation, interstitial lung disease, gastrointestinal perforation and angioedema. The MAH should propose to update the product information accordingly as warranted. Finally, the MAH should provide an updated RMP to add hepatotoxicity as an important potential risk in the course of the next regulatory procedure.

[38] 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

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.

6.1.17. **Rotigotine – LEGANTO** (CAP), **NEUPRO** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Maria Alexandra Pêgo (PT)

Administrative details:
Procedure number(s): EMEA/H/C/002380/PSUV/0013, EMEA/H/C/000626/PSUV/0063
MAH(s): UCB Manufacturing Ireland Ltd.

Background

Rotigotine is a dopamine agonist indicated for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Leganto and Leupro, centrally authorised medicines containing rotigotine, 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 Leganto and Leupro (rotigotine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add delusion and delirium as undesirable effects with a rare frequency and creatinine phosphokinase (CPK) increase with a common frequency in special populations. Therefore the current terms of the marketing authorisations should be varied[39].
- In the next PSUR, the MAH should provide detailed reviews of cases of tinnitus, diarrhoea, dysphagia, cases of reported wrong technique in drug usage process and cases of overdose.

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

6.1.18. **Sildenafil – VIAGRA** (CAP), NAP

- Evaluation of a PSUSA[40] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002699/201312
MAH(s): Pfizer Limited, various

[39] 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
[40] PSUR single assessment, referring to CAP, NAP

Background

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) and is indicated in adult men with erectile dysfunction (ED).

Based on the assessment of the individual PSURs, part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of sildenafil-containing products 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 sildenafil-containing products in the approved indication(s) remains favourable.
- For all sildenafil-containing products, the current terms of the marketing authorisations should be maintained as part of this PSUSA procedure.
- With regard to Sildenafil Sandoz, Sildenafil AbZ, Sildenafil ratiopharm and Valedonis, relevant MAHs should submit separately variation applications to update their product information in line with the reference product (Viagra).
- In the next PSURs, MAHs should closely monitor cases of chorioretinopathy and cases of off label use.

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

6.1.19. Sorafenib – NEXAVAR (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000690/PSUV/0037
MAH(s): Bayer Pharma AG

Background

Sorafenib is a multikinase inhibitor indicated for the treatment of hepatocellular carcinoma, for the treatment of patients with advanced renal cell carcinoma under certain conditions and for the treatment of patients with progressive, locally advanced or metastatic differentiated thyroid carcinoma, refractory to radioactive iodine.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nexavar, a centrally authorised medicine containing sorafenib, 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 Nexavar (sorafenib) in the approved indication(s) remains favourable.

- Nevertheless, the product information should be updated to add encephalopathy as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[41].
- In the next PSUR, the MAH should provide a detailed review of cases of myositis and of osteonecrosis of the jaw.

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

6.1.20. Teriflunomide – AUBAGIO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002514/PSUV/0005
MAH(s): Sanofi-Aventis Groupe

Background

Teriflunomide is an immunomodulatory agent indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aubagio, a centrally authorised medicine containing teriflunomide, 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 Aubagio (teriflunomide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on the occurrence of drug reaction of eosinophilia and systemic symptoms (DRESS). Therefore the current terms of the marketing authorisation(s) should be varied[42].
- In the next PSUR, the MAH should provide a detailed analysis of fatal cases as well as cases of renal failure, myocardial infarction and peripheral neuropathy. In addition, the MAH should provide detailed reviews of several adverse events, including depression, fatigue and associated events, headache, upper abdominal pain, arthralgia and increased blood creatine phosphokinase and propose an update of the product information as warranted. Finally, the MAH should provide an updated RMP to add long-term safety as missing information and to consider peripheral neuropathy as an important identified risk.

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

[41] 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
[42] 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

6.1.21. **Tipranavir – APTIVUS** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000631/PSUV/0067 (with RMP version 5.0)
MAH(s): Boehringer Ingelheim International GmbH

Background

Tipranavir is a protease inhibitor co-administered with low dose ritonavir for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adults and adolescents 12 years of age or older with virus resistant to multiple protease inhibitors.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aptivus, a centrally authorised medicine containing tipranavir, 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 Aptivus (tipranavir) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 90 days an updated review of the use of tipranavir during pregnancy.

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

6.2. Follow-up to PSUR procedures[43]

6.2.1. **Buprenorphine, naloxone – SUBOXONE** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000697/LEG 027
Procedure scope: MAH's response to the request for additional information as concluded in the evaluation of PSUR#7 [PSUV/0023] as adopted in May 2014
MAH(s): RB Pharmaceuticals Ltd.

Background

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine, the PRAC requested the MAH to submit further data (see PRAC Minutes May 2014). The responses were assessed by the Rapporteur for further PRAC advice.

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

Summary of advice/conclusions

- The MAH should submit to EMA within 60 days a variation to update the product information to add a contraindication to avoid concomitant administration of buprenorphine/naloxone with opioid receptor antagonists (naltrexone, nalmefene).

6.2.2. Vernakalant – BRINAVESS (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001215/LEG 021
Procedure scope: MAH's response to the request for additional information as concluded in the evaluation of PSUV/0019 (PSUR #5 [PSU-008]) as adopted in April 2014
MAH(s): Cardiome UK Limited

Background

Following the evaluation of the most recent PSUR for the above mentioned medicine, the PRAC requested the MAH to submit further data (see PRAC Minutes April 2014). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusions

- The MAH should submit to EMA within 60 days supplementary information to further examine the use and impact of the risk minimisation tools, and aspects relating to the dissemination and communication strategy of the risk minimisation materials.

6.2.3. Voriconazole – VFEND (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000387/LEG 085.2
Procedure scope: MAH's response to the request for additional information as concluded in the evaluation of PSUR#13 as adopted at PRAC in October 2013
MAH(s): Pfizer Limited

Background

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

Summary of advice/conclusions

- The MAH should submit to EMA within 60 days a variation to update the product information to clarify the instructions for the preparation of the liquid oral dosage.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[44]

7.1.1. Cyproterone, ethinylestradiol – DIANE 35 & other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms (NAP)

- Evaluation of an imposed PASS protocol

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

Administrative details:
Procedure number(s): NL/H/xxxx/WS/073
Procedure scope: Evaluation of a protocol for a PASS to evaluate physician knowledge of safety and safe use supporting information for Diane-35 and its generics in Europe, as per the conclusions of the Article 107i concluded in May 2013
MAH(s): Bayer

Background

For background, see PRAC minutes 9-11 April 2014. Following the advice provided in April 2014, final protocols had been submitted for a PASS and a DUS (see below 7.1.2.) that had been assessed by the NL (Medicines Evaluation Board of the Netherlands (MEB) acting as Reference Authority).

Endorsement/Refusal of the protocol

The PRAC, having considered the draft non-interventional drug utilisation study (DUS) protocol (i.e. survey) version ZEG2014_04 and the non-interventional PASS protocol version 01 for Diane 35 (cyproterone, ethinylestradiol) and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms, endorsed the draft protocols provided that some modifications, as outlined in the respective assessment report, are implemented. A satisfactory data analysis plan should be submitted before the studies start.

7.1.2. Cyproterone, ethinylestradiol – DIANE 35 & other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms (NAP)

- Evaluation of an imposed PASS protocol

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

Administrative details:
Procedure number(s): NL/H/xxxx/WS/073
Procedure scope: Evaluation of a protocol for a drug utilisation study on the prescribing indications for cyproterone, ethinylestradiol (CPA/EE) in five European countries, as per the conclusions of the Article 107i concluded in May 2013
MAH(s): Bayer

See above 7.1.1.

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

- Evaluation of an imposed PASS protocol

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

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

Administrative details:
Procedure number(s): EMEA/H/C/00560/ANX 034, EMEA/H/C/00561/ANX 034
Procedure scope: Non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice
MAH(s): Les Laboratoires Servier

Background

The requirement for the conduct of a non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice, patterns of use and cardiovascular risk, was introduced as an obligation of the Annex II of the marketing authorisation for Protelos and Osseor following the conclusion of the review conducted under referral Article 20 of Regulation (EC) No 726/2004 (see EMA/112925/2014).

A draft protocol for such study was submitted and assessed by the rapporteur for review by the PRAC.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC objected to the draft protocol as the Committee considered that the design of the study does not fulfil the study objectives. In particular changes in the therapeutic indication should be taken into consideration in the analyses of utilisation patterns as well as relevant timing regarding implementation of the revised product information and distribution of the related DHPC.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 30 days-assessment timetable will be applied.

7.1.4. **Teicoplanin** (NAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): DE/H/3916/001-003/MR ; DE/H/3918/001-003/MR ; DK/H/2336/001-003/MR
Procedure scope: Evaluation of a revised protocol for a prospective, observational cohort, non-comparative study describing the safety profile of the higher recommended teicoplanin loading dose of 12 mg/kg twice a day
MAH(s): Sanofi-Aventis (Targocid)

Background

Teicoplanin is a glycopeptide antibiotic used for parenteral treatment of infections. Targocid is a nationally authorised medicine containing teicoplanin (MRP procedures with DE and DK acting as RMSs). Following the conclusion of a referral under Directive 2001/83/EC to conduct of a PASS to evaluate the safety of Targocid in adults with Gram-positive infections who are exposed to the higher loading dose of 12mg/kg twice a day (24 mg/kg/day) was included as obligation of the marketing authorisation (Annex IV of the EC decision). A draft protocol for such study was submitted and assessed by DE for review by the PRAC (see also PRAC minutes 9-11 April 2014).

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 2 - in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s). The PRAC noted the challenges associated with the study design's ability to address concerns about the safety of the higher loading dose and, therefore, recommended some modifications to the proposed draft protocol.

The PRAC recommended that:

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

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

7.2.1. **Apixaban - ELIQUIS** (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002148/MEA/021
Procedure scope: PASS protocol for a non-interventional study to assess the effectiveness of the additional risk minimisation measures for Eliquis (apixaban) for PRAC assessment (No. CV185365). The draft study protocol includes the evaluation of the effectiveness of the HCP educational materials and patient alert card for the indication on prevention of stroke in patients with non-valvular atrial fibrillation
MAH(s): Bristol-Myers Squibb / Pfizer EEIG

Background

Eliquis is a centrally authorised medicine containing apixaban, indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery and for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).
As part of the RMP for Eliquis, the MAH was required to conduct a non-interventional study to assess the effectiveness of the additional risk minimisation measures for the medicine. The MAH submitted a protocol for a study evaluating the effectiveness of the HCP educational materials and patient alert card for the indication of prevention of stroke in patients with non-valvular atrial fibrillation, which was assessed by the Rapporteur for review by the PRAC.

Summary of advice

- The study protocol for Eliquis (apixaban) could be acceptable provided an updated protocol addressing a number of points raised by the PRAC is submitted within 30 days. The MAH should update the PASS protocol assessing the effectiveness or risk minimisation measures for all the Eliquis indications, and provide clarification on the primary and secondary end-points, the targeted population and the sample size.

[45] 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

7.3. Results of PASS imposed in the marketing authorisation(s)[46]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[47]

7.4.1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study

- PRAC evaluation of D:A:D data merger results

Regulatory details:
PRAC Representatives: Filip Josephson (SE), Deborah Ashby (UK)

Administrative details:
Procedure number(s): N/A
Procedure scope: Evaluation of the 14th data merger
MAH(s): various
The PRAC discussed the assessment of the D:A:D study's 14th data merger - relating mainly to the relative safety of antiretroviral therapy – performed by the EMA representative on the Highly Active Antiretroviral Therapy (HAART) Oversight Committee.

The PRAC discussed various findings relating to the risks under investigation in the cohort and concluded that the 14th data merger does not contain any data that would require further questions to be put to the D:A:D study investigators, or any other regulatory action.

7.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS submitted before the entry into force of the revised variations regulation[48]

7.5.1. Mannitol - BRONCHITOL (CAP)

- Evaluation of interim (interventional) PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001252/ANX 002.3
Procedure scope: MAH's response to MEA-002.2 (second interim report) questions, as adopted in February 2014
MAH(s): Pharmaxis Pharmaceuticals Limited

Background

Bronchitol is a centrally authorised medicine containing mannitol, indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.
The MAH had committed to perform an interventional PASS to be conducted over 5 years in the UK Cystic Fibrosis Registry according to the conditions included in the Annex II of the MA.
Interim results of a PASS examining the rates of identified and potential risks of Bronchitol in CF by comparing mannitol exposed vs. unexposed patients in a matched cohort from the CF registry, were assessed by the Rapporteur for PRAC review.

[46] In accordance with Article 107p-q of Directive 2001/83/EC
[47] 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
[48] In line with the revised variations regulation for any submission before 4 August 2013

Summary of advice

- The PRAC noted that for the secondary outcome of acquisition of new microbial infections, more new infections had been observed in mannitol-treated patients. Given the small number of mannitol-treated patients and the limited duration of exposure and that it was not clear whether certain events/infections were present at baseline, the PRAC agreed that these findings should be further evaluated before taking any regulatory action.
- The next planned interim analysis should take this into consideration, in order to verify whether such observation is repeated in a larger number of patients. Further clarifications on the analysis already performed should be provided in the meantime by the MAH.

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

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

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

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

Background

Clofarabine is a purine nucleoside anti-metabolite indicated for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients under certain conditions.
Evoltra, a centrally authorised product containing clofarabine, was authorised under exceptional circumstances in 2006. The benefit-risk is reviewed on a yearly basis by the CHMP - based on the additional post-authorisation data (i.e. specific obligations). The PRAC is responsible for providing advice to the CHMP on this annual re-assessment with regard to safety and risk management aspects.

Summary of advice

Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, the PRAC considered that the annual re-assessment procedure for Evoltra could be finalised provided that the MAH undertakes to amend the inclusion criteria of the registry protocol for SOB 014 (clofarabine registry to set up a voluntary adverse event reporting system) to allow inclusion of any patients treated with clofarabine, according to medical practice. Moreover, in the next registry progress report to be submitted to EMA yearly, the MAH is requested to provide a detailed analysis of cases reporting use of clofarabine in a combined regimen. The registry protocol should be amended accordingly.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. On-going or concluded pharmacovigilance inspection

None

9.3. Others

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

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

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

10.1.1. Colistimethate sodium - COLOBREATHE (CAP)

- PRAC consultation on a variation procedure, upon CHMP request

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number: EMEA/H/C/001225/II/0015
Procedure scope: Consultation of the PRAC on a DHPC in the framework of a variation of SmPC sections 4.2 and 6.6 to update the information on the administration of the product. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template
MAH(s): Forest Laboratories UK Limited

Background

For background see PRAC minutes March 2014. Following the assessment of a PSUR the PRAC recommended investigating the root cause of breakage of the capsules which occurred – according to some reports - during administration. A review was performed and the MAH had been exploring long-term solutions to minimise the risk of capsule breakage (including a possible change of capsule shell) but has proposed changes to the instructions for administration as an interim measure. A variation of the product information to update the information on the administration of the product is being assessed by the CHMP and a DHPC was proposed to communicate such changes.

Summary of advice

The PRAC supported the changes in the product information highlighting the importance of inserting the capsule into the chamber of the inhaler with the widest end of the capsule first, in addition to including more detailed information on how to pierce the capsule before inhalation.

The PRAC noted that copies of the updated product information were already being prepared and packaged by the MAH to be distributed to all relevant prescribers, as soon as the variation is concluded. The PRAC concluded that this mechanism would be appropriate for prompt communication and recommended that this should be used in preference to a DHPC.

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

11.1. Safety related variations of the marketing authorisation

11.1.1. **Ethinylestradiol, dienogest** (NAP)

- PRAC consultation on a variation procedure, upon Germany's request

Regulatory details:
Lead member: Valerie Strassmann (DE)

Administrative details:
Procedure scope: Consultation on the evaluation of a variation relating to a meta-analysis of 4 observational studies LASS, INAS-OC, TASC and INAS-SCORE (interim results)
MAH(s): Jenapharm GmbH & Co. KG (Celimona/ Celimone)

Background

Celimona (Celimone) is a monophasic progestogen-estrogen combination for oral hormonal contraception containing ethinylestradiol and dienogest.

Several large prospective cohort studies have been conducted on the risk of venous thromboembolic events (VTE) associated with the use of hormonal contraceptive. This was the subject of a review concluded in 2013 by the PRAC EMA/607314/2013.

In four[49] of these studies combined oral contraceptives (COCs) with a combination of 2 mg of dienogest (DNG) and 30 µg of ethinylestradiol (EE) were included.

The MAH presented results of a meta-analysis of these post-authorisation safety studies to analyse the VTE risk of DNG/EE versus levonorgestrel/EE-containing COCs (LNG/EE) which are generally used as a reference for the VTE risk associated with combined hormonal contraceptives. An overview of these meta-analysis methods and preliminary findings as well as a list of considerations and outstanding issues was assessed and proposed by the RMS (DE) who requested PRAC advice on the issue.

Summary of advice

Based on the review of the preliminary findings of the meta-analysis and pending the full results of the INAS-SCORE study the PRAC agreed that at present, no changes to the product information for Celimona are warranted and that the MAH should address some aspects first by responding to an agreed list of questions. The MAH should also submit to the RMS an updated meta-analysis comprising data from the finalised INAS-SCORE[50] study.

Further PRAC advice will be provided upon request of the MS as appropriate.

11.2. Renewals of the Marketing Authorisation

None

[49] "Long-term Active Surveillance Study for Oral Contraceptives" (LASS)
"International Active Surveillance Study of Women Taking Oral Contraceptives" (INAS-OC)
"Transatlantic Active Surveillance on Cardiovascular Safety of Nuvaring" (TASC)
"International Active Surveillance Study – Safety of Contraceptives: Role of Estrogens" (INAS-SCORE)
[50] International Active Surveillance Study - Safety of Contraceptives: Role of Estrogens

11.3. Other requests

11.3.1. **Acetylsalicylic acid** (NAP)

- PRAC consultation on a review of safety in pregnancy, upon France's request

Regulatory details:
Lead member: Arnaud Batz (FR)

Administrative details:
Procedure scope: Safety in pregnancy
MAH(s): Bayer (Asproflash)

Background

Following a procedure discussed by the Member States during the assessment of an initial marketing authorisation for a medicine containing acetyl salicylic acid (ASA) through a decentralised procedure, questions arose on the most appropriate wording regarding the contraindication for use during pregnancy and the most appropriate gestational time from which this contraindication should apply – use of acetyl salicylic acid is currently contraindicated in the last trimester of pregnancy according to a previous recommendation of the former CHMP Pharmacovigilance Working Party (PhVWP) (EMEA/12148/04/Final).

FR requested PRAC advice on whether there was a need to amend the PhVWP recommendation regarding class labelling contraindication in pregnancy for the ASA (at doses ≥ 100 mg/day) and nonsteroidal anti-inflammatory drugs (NSAIDs) based on some evidence recently evaluated.

Summary of advice

Based on the review presented PRAC concluded that before any changes are made to the SmPC of ASA ≥ 100 mg/day or other NSAIDs, more robust evidence is required. Further evaluation should focus on ASA ≥ 100 mg/day and on all NSAIDs, on pharmacological considerations such as dose-response assessments, and on any new information that had become available beyond the thorough evaluation that was the basis for the PhVWP recommendation.

Post-meeting note: this PRAC advice was finalised on 11 October 2014 following further written consultation.

11.3.2. **Fentanyl**, transdermal patch (NAP)

- PRAC consultation on risk of accidental exposure, upon Netherlands' request

Regulatory details:
Lead member: Sabine Straus (NL)

Administrative details:
Procedure scope: Consultation on MAH's proposal to improve patch visibility and timelines for implementation
MAH(s): Janssen-Cilag (Durogesic)

Background

For background see PRAC minutes 7-10 July 2014. The brand leader MAH was requested to provide revised proposals that were assessed by the RMS for review by the PRAC. The MAH presented also their position at an oral explanation at the meeting.

Summary of advice

The PRAC noted a proposal from the MAH to gather further evidence to fully address the issue by performing Human Factor Studies. The MAH's proposal to keep unique colours for all strengths in the EU and improve visibility by darkening the current ink tone and add new graphics at this point in time was considered justified. Depending on the outcomes of the HFS studies including the paediatric population– performed in EU and in North America – measures put in place to improve visibility of the patches might need to be reconsidered.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. European Pharmacovigilance legislation

- Measuring the impact of the new pharmacovigilance legislation

At the organisational matters teleconference on 17 September 2014, the PRAC heard a high level proposal to develop a programme for studying the public health impact of the new pharmacovigilance legislation including monitoring the effectiveness of targeted risk minimisation measures which was supported. Suggested deliverables for demonstrating impact were discussed and the EMA secretariat clarified governance and planned consultation flow for impact measurement with identified partners and stakeholders. The PRAC welcomed this important initiative and a progress update will be given at future meetings.

12.1.2. PRAC Plenary activities

- Figures over 2 years

At the organisational matters teleconference on 17 September 2014, in which EMA secretariat presented some metrics of procedures evaluated by PRAC at their meeting upon completion of 2 years of activity.

12.1.3. PRAC Work Plan

- Draft PRAC Work Programme 2014-2015

At the organisational matters teleconference on 17 September 2014, the PRAC adopted a work plan covering the remaining period of 2014 and 2015 recommending final refinements.

12.2. Pharmacovigilance audits and inspections

12.2.1.1. Pharmacovigilance Audit Facilitation Group (PAFG)

- Risk ratings of pharmacovigilance process areas

The PRAC endorsed the guidance on network risk ratings of pharmacovigilance process areas. Hungary, in the lead for producing the guidance, clarified that risk assessments should be reviewed annually.

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

12.3.1. Periodic Safety Update Reports

12.3.1.1. PSUR single Assessment for Nationally Approved Products only

At the organisational matters teleconference on 17 September 2014, the PRAC discussed a preliminary proposal for the process to perform the PSUR single assessment for nationally approved products. The proposal is jointly developed with the CMDh and will be further discussed at the October 2014 meeting.

12.3.2. Union Reference Date List

12.3.2.1. Consultation on the draft List, version September 2014

The PRAC endorsed the draft revised EURD list version September 2014 reflecting the PRAC comments impacting DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC Minutes April 2013).

Post-meeting note: following the PRAC meeting in September 2014, the updated EURD list was adopted by the CHMP at its September 2014 meeting and published on the EMA website on 6/10/2014 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission)

12.4. Signal Management

12.4.1. Signal Management

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

At the organisational matters teleconference on 17 September 2014, the PRAC heard a progress report of the activity of the SMART group. The group discussed process related aspects on handling of signals for vaccines and for products with several rapporteurs for CAPs, a new assessment report template (to be used as of November 2014) and a training that will be provided at the planned pharmacovigilance assessors' training in October 2014. PRAC enquired about progression of the work based on the outcome of the 'Methods for signal detection' developed by PROTECT WP3. Discussion will be planned at next group meetings.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Additional Monitoring

- Measuring the impact of additional monitoring elements – proposal for EMA procured ENCePP study on qualitative aspects

EMA presented a proposal for an EMA procured ENCePP study on qualitative aspects to measure the impact of additional monitoring elements. The study will investigate knowledge, attitudes and practices and awareness of additional monitoring status by patients and healthcare professionals arising from either publication of the Agency's list or through product information. The study is expected to have two components: a survey of a representative sample of prescribing physicians (GPs and specialists) and pharmacists to be conducted in at least 8 EU Member States; and a survey of patients in at least three EU Member States. PRAC supported the initiative but recommended before progressing in the

work, further interaction with MSs to identify any areas of overlap that might exist or research that is being carried out under other framework.

12.5.1. European database of suspected adverse drug reaction reports

- Extension of the website to additional substances

The EMA secretariat informed PRAC on the planned launch of the extension of the 'adverse drug reactions (ADR) website' (http://www.adrreports.eu/) which will provide access to information on suspected adverse drug reactions of an additional 1,700 nationally approved active substances. This further step in the development of the 'ADR website' is in line with the planned phased implementation described in the 'Eudravigilance access policy', which started providing information on centrally authorised products and is being extended gradually to all products authorised in the EU. A poster to promote ADR reporting by patients was also presented.

12.5.2. List of Products under Additional Monitoring

12.5.2.1. Consultation on the draft List, version September 2014

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

Post-meeting note: The updated additional monitoring list was published on 30/09/2014 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of risk Minimisations

None

12.8. Post-authorisation Safety Studies

None

12.9. Community Procedures

None

12.10. Renewals, conditional renewals, annual reassessments

None

12.11. Risk communication and Transparency

None

12.12. Continuous pharmacovigilance

None

12.13. Interaction with EMA Committees and Working Parties

None

12.13.1. Working Parties

12.13.1.1. Feedback from EMA/EDQM Joint Workshop on Characterisation of new clotting factor concentrates (FVIII, FIX)

At the organisational matters teleconference on 17 September 2014, the PRAC was presented with a report from the EMA/EDQM Joint Workshop on characterisation of new clotting factor concentrates (factors VIII and IX) with respect to potency assays used for labelling and testing of post infusion samples. The PRAC noted that the EMA 'blood cluster' will be used as a platform to exchange information with other national competent authorities for products which will be globally marketed. PRAC emphasised that assessors will need to consider the most appropriate assay for potency labelling and the adequacy of measures proposed in the product information and risk management plan, to avoid misleading results when monitoring plasma levels. Therefore PRAC supported the suggestion to develop a 'points to consider for assessors' document on this topic.

12.13.1.2. Scientific Advisory Group (SAG) Oncology

- Effectiveness of risk minimisation measures: consultation on risk of osteonecrosis of the jaw

The PRAC agreed a list of questions for a SAG oncology meeting on bisphosphonates /denosumab and effectiveness of risk minimisation for osteonecrosis of the jaw (ONJ). This is being organised to gather feed-back on current awareness about the risk for ONJ among prescribers and among dental specialists; feed-back on the extent of implementation of the current recommendations for risk minimisation; possible additional measures be recommended for the prescriber and/or patients in order to reduce the occurrence; awareness of ongoing research in this area which can contribute to increased knowledge. The PRAC will be presented with the outcome of the SAG at the November 2014 meeting.

12.14. Interaction within the EU regulatory network

None

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

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

None

12.15.2. PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium)

- VISUALizE study (VISualizing Uncertainty Among Laypersons and Experts): proposal for pharmacovigilance assessors involvement

At the organisational matters teleconference on 17 September 2014, the PRAC heard a presentation from researchers involved in the conduct of the VISUALizE study describing the aims and objectives of the study. A call for assessors to volunteer to participate in a survey was launched. Results will be presented to PRAC once the study is concluded.

12.15.3. World Health Organisation (WHO)

- EMA comments on proposal for a biological qualifier (BQ) from WHO INN committee

The EMA secretariat presented for discussion the EMA comments on the draft response to the proposal for the WHO Biological Qualifier - An INN Proposal (INN Working Doc. 14.342 Revised draft July 2014). PRAC commented on the draft response to the proposal which will be revised accordingly.

13. Any other business

13.1. New organisational model: Harmonisation of timetables for post-authorisation measures

The PRAC was informed that the EMA is currently reviewing the current procedural timetables existing for post-authorisation Measures (PAM). The proposal will be presented to the PRAC for agreement in due course.

13.2. Procedural Advice on CAT-CHMP-PRAC Rapporteur Appointments

At the organisational matters teleconference on 17 September 2014, the PRAC adopted a revised version of the 'Procedural Advice on CHMP/CAT/PRAC Rapporteur/Co-Rapporteur appointment principles, objective criteria and methodology in accordance with Article 62 (1) of Regulation (EC) No 726/2004'. The document will then be transmitted to CHMP for adoption and then published on the EMA website for immediate applicability.

14. ANNEX I Risk Management Plans

Medicines in the pre-authorisation phase

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

14.1.1. Aclidinium, formoterol

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

Administrative details:
Product number(s): EMEA/H/C/003969, EMEA/H/C/003745
Intended indication(s): Maintenance bronchodilator treatment for airflow obstruction and relief of symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

14.1.2. Balugrastim

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

Administrative details:
Product number(s): EMEA/H/C/002637
Intended indication(s): Treatment of chemotherapy-induced neutropenia

14.1.3. Cangrelor

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

Administrative details:
Product number(s): EMEA/H/C/003773
Intended indication(s): Percutaneous coronary intervention (PCI)

14.1.4. Ciclosporin

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

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

14.1.5. Clopidogrel

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

Administrative details:
Product number(s): EMEA/H/C/004006, *Generic*
Intended indication(s): Prevention of myocardial infarction and acute coronary syndrome, ischaemic stroke, peripheral arterial disease, acute coronary syndrome, prevention of atherothrombotic and thromboembolic events in atrial fibrillation

14.1.6. Dalbavancin

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

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

14.1.7. Darunavir, cobicistat

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

Administrative details:
Product number(s): EMEA/H/C/002819
Intended indication(s): Treatment of patients with human immunodeficiency virus (HIV-1)

14.1.8. Dulaglutide

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

Administrative details:
Product number(s): EMEA/H/C/002825
Intended indication(s): Treatment of adults with type 2 diabetes mellitus

14.1.9. Idebenone

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

Administrative details:
Product number(s): EMEA/H/C/003834, *Orphan, Hybrid*
Intended indication(s): Treatment of Leber hereditary optic neuropathy (LHON)
Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

14.1.10. Naloxegol

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

Administrative details:
Product number(s): EMEA/H/C/002810
Intended indication(s): Treatment of adult patients 18 years and older with opioid-induced constipation (OIC) including patients with inadequate response to laxatives

14.1.11. Nintedanib

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

Administrative details:
Product number(s): EMEA/H/C/002569
Intended indication(s): Treatment of non-small cell lung cancer (NSCLC)

14.1.12. Nonacog gamma

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

Administrative details:
Product number(s): EMEA/H/C/003771
Intended indication(s): Treatment of haemophilia B

14.1.13. Olaparib

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

Administrative details:
Product number(s): EMEA/H/C/003726, *Orphan*

Intended indication(s): Treatment of ovarian cancer
Applicant: AstraZeneca AB

14.1.14. Panobinostat

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

Administrative details:
Product number(s): EMEA/H/C/003725*, Orphan*
Intended indication(s): Treatment of patients with multiple myeloma
Applicant: Novartis Pharmaceuticals UK Limited

14.1.15. Phenylephrine, ketorolac trometamol

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

Administrative details:
Product number(s): EMEA/H/C/003702
Intended indication(s): Maintenance of intraoperative mydriasis, prevention of intraoperative miosis and reduction of acute postoperative ocular pain in intraocular lens replacement (ILR) in adults

14.1.16. Pitolisant

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

Administrative details:
Product number(s): EMEA/H/C/002616*, Orphan*
Intended indication(s): Treatment of narcolepsy treatment of narcolepsy
Applicant: Bioprojet Pharma

14.1.17. Ramucirumab

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

Administrative details:
Product number(s): EMEA/H/C/002829, *Orphan*
Intended indication(s): Treatment of gastric cancer
Applicant: Eli Lilly Nederland B.V.

14.1.18. Safinamide

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

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

14.1.19. Sofosbuvir, ledipasvir

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

Administrative details:
Product number(s): EMEA/H/C/003850
Intended indication: Treatment of chronic hepatitis C

14.1.20. Sonidegib

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

Administrative details:
Product number(s): EMEA/H/C/002839
Intended indication(s): Treatment of advanced basal cell carcinoma (BCC)

14.1.21. Tadalafil

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

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

14.1.22. Tasimelteon

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

Administrative details:
Product number(s): EMEA/H/C/003870*, Orphan*
Intended indication(s): Treatment of non-24-hour sleep-wake disorder (non-24) in the totally blind
Applicant: Vanda Pharmaceuticals Ltd.

14.1.23. Vorapaxar

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

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

Medicines already authorised

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

RMP in the context of a variation[51] – PRAC-led procedure

14.1.24. Aclidinium bromide – BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002706/II/0012, EMEA/H/C/002211/II/0012
Procedure scope: Update of the RMP to version 4.0
MAH(s): Almirall S.A

14.1.25. Adalimumab – HUMIRA (CAP)

- Evaluation of an RMP in the context of a variation

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000481/II/0130
Procedure scope: Update of RMP to version 11.1
MAH(s): AbbVie Ltd

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

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/WS0588/0094, EMEA/H/C/002073/WS0588/0095, EMEA/H/C/000964/WS0588/0064
Procedure scope: Update of the RMP to amend the timelines for initiation, completion and submission of study reports of ongoing or planned studies together with update to some of objectives of the planned long-term safety and efficacy study
MAH(s): Novartis Europharm Ltd

14.1.27. Capecitabine – XELODA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000316/II/0060
Procedure scope: Update of RMP to version 7 further to a request of PRAC/CHMP in assessment of variations, including an update on dihydropyrimidine dehydrogenase deficiency (MEA 029)
MAH(s): Roche Registration Ltd

14.1.28. Dabigatran – PRADAXA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/II/0058
Procedure scope: Changes in the agreed study protocol for 1160.136 (SPAF MEA 025), a global registry programme GLORIA-AF investigating patients with newly diagnosed non-valvular AF at risk for stroke receiving dabigatran. The consequent changes were done to the RMP that was also submitted within this variation
MAH(s): Boehringer Ingelheim International GmbH

14.1.29. Pioglitazone – ACTOS (CAP), **GLUSTIN** (CAP)
Pioglitazone, glimepiride – TANDEMACT (CAP)
Pioglitazone, metformin – **COMPETACT** (CAP), **GLUBRAVA** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000285/WS0609/0063, EMEA/H/C/000286/WS0609/0061, EMEA/H/C/000680/WS0609/0038, EMEA/H/C/000655/WS0609/0048, EMEA/H/C/000893/WS0609/0034
Procedure scope: Update of the RMP to version 19 (for Actos, Glustin, Competact and Glubrava) and version 17 (for Tandemact) in order to change the due date for reporting of the Pan-European multiple database bladder cancer risk characterisation study ER 12-9433 (previously listed as AD4833-410) from 30 September 2014 to 30 December 2014
MAH(s): Takeda Pharma A/S

14.1.30. **Riociguat - ADEMPAS** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002737/II/0001 (with RMP version 3.0)
Procedure scope: Submission of non-clinical study reports ph-37417 and ph-37435; in vitro studies undertaken to determine the M-1 potential to inhibit renal efflux transporters MATE1 and MATE2K. A revised RMP version 3.0 was provided as part of the application. No changes to the product information are proposed
MAH(s): Bayer Pharma AG

14.1.31. **Sildenafil – REVATIO** (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000638/II/0061
Procedure scope: Update of the RMP and consequential update of the annex II
MAH(s): Pfizer Limited

14.1.32. **Tenofovir disoproxil, emtricitabine, rilpivirine, – EVIPLERA** (CAP) **Tenofovir disoproxil, emtricitabine – TRUVADA** (CAP) **Tenofovir disoproxil – VIREAD** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002312/WS0598/0048/G, EMEA/H/C/000594/WS0598/0107/G, EMEA/H/C/000419/WS0598/0141/G
Procedure scope: Worksharing variations to: 1) update of the RMP to remove FUM 234 (study 174-0127 on renal safety); to add references to studies previously submitted, to add intermediate results for APR and MITOC studies and to correct the classification from category 3 to 4 of the 7 studies (in the RMP for Eviplera and Truvada); 2) update the deadline for the final submission of study 104-0423 in the RMP
MAH(s): Gilead Sciences International Ltd

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

14.1.33. Abatacept – ORENCIA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000701/II/0081/G
Procedure scope: Grouped variations to: 1) update of SmPC sections 4.4 and 4.8 regarding systemic injection reactions with the use of subcutaneous abatacept to harmonize the SmPC for SC abatacept with the SmPC for intravenous (IV) abatacept. The RMP is updated accordingly; 2) change to the milestones for the core subcutaneous study protocols IM101063, IM101167, IM101173, IM101174 and IM101185 study timelines
MAH(s): Bristol-Myers Squibb Pharma EEIG

14.1.34. Aflibercept – EYLEA (CAP)

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

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

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

14.1.35. Bevacizumab – AVASTIN (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000582/II/0072
Procedure scope: Extension of indication for the use of Avastin in combination with paclitaxel and cisplatin or paclitaxel and topotecan in patient with persistent, recurrent, or metastatic carcinoma of the cervix. Consequently, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 and the Package Leaflet are updated
MAH(s): Roche Registration Ltd

14.1.36. Bortezomib – VELCADE (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000539/II/0072
Procedure scope: Extension of indication for the use of Velcade in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma. Consequently, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 and the Package Leaflet are updated

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

14.1.37. Cabozantinib – COMETRIQ (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002640/II/0006
Procedure scope: Update of SmPC section 4.4 to delete the warning on concomitant use with proton pump inhibitors further to the results of a drug-drug Interaction Study XL184-018 with medicinal products affecting gastric pH (esomeprazole and Famotidine) (MEA 004). The Package leaflet is updated accordingly. The MAH also took the opportunity to make a correction in section 4.5 and the PL
MAH(s): TMC Pharma Services Ltd

14.1.38. Caffeine – PEYONA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Jan Neuhauser (AT)

Administrative details:
Procedure number(s): EMEA/H/C/001014/II/0013
Procedure scope: Update of SmPC section 4.8 to reflect the results of an European Non-Interventional Post-Authorisation Study to assess drug utilisation and safety of caffeine citrate in the treatment of premature infants affected by apnoea. This study addresses a post-authorisation measure in the RMP. Section 4 of the package leaflet is updated accordingly
MAH(s): Chiesi Farmaceutici S.p.A.

14.1.39. Darunavir – PREZISTA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000707/II/0063
Procedure scope: Update of SmPC section 4.1 for the 100mg/ml oral suspension and the 400mg, 800mg film-coated tablets with information on the use of darunavir with cobicistat as pharmacokinetic enhancer
MAH(s): Janssen-Cilag International N.V.

14.1.40. Darunavir – PREZISTA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000707/II/0064
Procedure scope: Update of the SmPC with an extension of indication in treatment naïve children aged 3 to 12 years and changes in the posology of the treatment experienced children aged 3 to 12 years with no DRV RAMs based on the data from a 2 week qd substudy of the Phase 2 study TMC114 C228 and results from model-based pharmacokinetic simulations. The PL has been updated accordingly
MAH(s): Janssen-Cilag International N.V.

14.1.41. Darunavir – PREZISTA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000707/II/0067/G
Procedure scope: Grouped variations to: 1) update SmPC sections 4.3 and 4.5 with information of CYP3A mechanism based interactions, 2) update SmPC sections 4.3 and 4.5 with information of CYP2D6 mechanism based interactions. The PL is updated accordingly. In addition editorial changes are implemented in SmPC sections 4.3, 4.4, 4.5 and 9 and list of local representatives in PL is revised
MAH(s): Janssen-Cilag International N.V.

14.1.42. Dolutegravir –TIVICAY (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002753/II/0005/G
Procedure scope: Grouped variations: 1) update of SmPC section 4.5 to revise information concerning the interaction between dolutegravir and boceprevir based on a drug-drug interaction study; 2) inclusion of information concerning the hepatic uptake transporters OATP1B1 and OATP1B3 based on an in vitro study requested to address a post-authorisation measure
MAH(s): ViiV Healthcare

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

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002574/II/0022
Procedure scope: Update of SmPC sections 4.2, 4.4 and 4.8 to revise recommendations to initiate/discontinue treatment based on creatinine levels and to update safety data as a result of the interim 48 weeks data from the GS-US-236-0118 study. Consequently Annex II.D 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated. The MAH included additional analyses using the pooled Week 144 safety analysis set from theGS-US-236-0102 and GS-US-236-0103 studies to support this variation. The RMP has been updated accordingly and is provided in this submission
MAH(s): Gilead Sciences International Ltd

14.1.44. Eslicarbazepine – ZEBINIX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000988/II/0044
Procedure scope: Update of SmPC sections 4.2 and 5.1 with the information from concluded safety and efficacy study in the elderly
MAH(s): Bial - Portela & Cª, S.A.

14.1.45. Fluticasone furoate, vilanterol – RELVAR ELLIPTA (CAP)
Fluticasone furoate, vilanterol trifenatate – REVINTY ELLIPTA (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002673/WS0602/0005/G, EMEA/H/C/002745/WS0602/0001/G
Procedure scope: Grouped variations: 1) addition of hypersensitivity to SmPC section 4.8. The Package Leaflet has been updated accordingly; 2) amendment of the due date in Annex II and the RMP for the provision of the clinical study report (CSR) for study HZC115151. The application included a revised RMP version 7.0
MAH(s): Gilead Sciences International Ltd

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

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000721/II/0061
Procedure scope: Update of SmPC section 4.6 on pregnancy outcomes in women exposed to the vaccine during pregnancy to reflect the outcome of study EPI-HPV-018 (an observational cohort) and other available data on safety during pregnancy. The Package Leaflet is amended accordingly
MAH(s): GlaxoSmithKline Biologicals

14.1.47. Insulin degludec – TRESIBA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002498/II/0011
Procedure scope: Extension of indication in children aged from 1 to 18 years. Update to SmPC sections 4.1, 4.2, 4.8 and 5.1. The PL is updated accordingly. In addition, update of the Section 2 of the PL in line with the existing information in SmPC section 4.2
MAH(s): Novo Nordisk A/S

14.1.48. Ipilimumab – YERVOY (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002213/II/0026/G
Procedure scope: Update of SmPC sections 4.8 and 5.1 further to the one-year interim results of two observational studies CA184332 and CA184338 (MEA 029 and MEA 030) and survival data from the chemotherapy-naive patients pooled across Phase 2 and 3 clinical trials. The RMP is updated accordingly to change also the timelines of two category 3 studies CA184143 (MEA 017) and CA184242 (MEA 027)
MAH(s): Bristol-Myers Squibb Pharma EEIG

14.1.49. Leflunomide – **ARAVA** (CAP), **LEFLUNOMIDE WINTHROP** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000235/WS0560/0062/G, EMEA/H/C/001129/WS0560/0019/G
Procedure scope: Worksharing variations: 1) update of SmPC sections 4.3 and 4.4 of contraindicating and adding a warning on teriflunamide (active metabolite of leflunomide); 2) update of SmPC section 4.5 for leflunomide related to the study reports HWA486/1032/001 (interaction cimetidine) and - HWA486/2F0.1 (interaction with methotrexate); 3) update of SmPC section 4.5 for teriflunomide related to the following Study reports INT11697-INT11720-INT12503-INT12500-INT10564-INT6040. Furthermore the MAH took the opportunity of this worksharing to include drug reaction with eosinophilia and systemic symptoms (DRESS) in the RMP as requested by PRAC
MAH(s): Sanofi-aventis Deutschland GmbH

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

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

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

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

14.1.51. Lipegfilgrastim – **LONQUEX** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002556/II/0004
Procedure scope: Update of SmPC sections 4.4 and 4.8 upon PRAC‘s request to include information regarding capillary leakage syndrome (CLS); a class effect of G-CSFs. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC, Annex II and the Package Leaflet, and to update the contact details for the local representative in Malta in the Package Leaflet. An updated RMP version 7.1 is included in this submission
MAH(s): Sicor Biotech UAB

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

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/001026/II/0027
Procedure scope: Implementation of the conclusions of the Art 5(3) referral procedure on GLP-1 based products and pancreatic issues. The MAH proposes an update to SmPC section 4.4 with the PL updated accordingly. The submission includes an update of the RMP

MAH(s): Novo Nordisk A/S

14.1.53. Loxapine – ADASUVE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002400/II/0010/G
Procedure scope: Update of Section 4.5 of the SmPC with the results of the Lorazepam Drug-Drug Interaction Study (m5.3.5.4, CSR 204-402) and the CYP Induction study (DM-103).
MAH(s): Alexza UK Ltd.

14.1.54. Paclitaxel – ABRAXANE (CAP)

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

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000778/II/0067
Procedure scope: Addition of a new indication for Abraxane in combination with carboplatin for the first-line treatment of non-small cell lung cancer (NSCLC) in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. Consequently the MAH proposes to update SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 and to update the Package Leaflet accordingly. An updated RMP version 14.0 has been provided accordingly
MAH(s): Celgene Europe Limited

14.1.55. Palonosetron – ALOXI (CAP)

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

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000563/II/0038
Procedure scope: Extension of the indication for paediatric patients 1 month of age and older for the prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy for the IV formulation, based on the paediatric studies PALO-10-14 and PALO-10-20 and update of sections 5.1 and 5.2 of the Aloxi Oral formulation to reflect those studies
MAH(s): Helsinn Birex Pharmaceuticals Ltd.

14.1.56. Pegvisomant – SOMAVERT (CAP)

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

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000409/X/0072
Procedure scope: Addition of 25 mg and 30 mg powder and solvent for solution for injection
MAH(s): Pfizer Limited

14.1.57. Pneumococcal polysaccharide conjugate vaccine (adsorbed) – SYNFLORIX (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000973/II/0083
Procedure scope: Re-analysis of the convulsions reported in Synflorix clinical studies and those reported during post marketing surveillance as a result of a commitment made in the context of variations II/0069 & II/0070. An updated version of the Synflorix RMP (version 11.0) including the convulsion re-analyses is submitted within this application as well as the amended clinical study report of study 10PN-PD-DIT-028
MAH(s): GlaxoSmithKline Biologicals

14.1.58. Pramipexole – OPRYMEA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000941/X/0017
Procedure scope: Addition of new strengths 2.62 mg and 3.15 mg prolonged-release tablets
MAH(s): Krka d.d. Novo mesto

14.1.59. Propanolol – HEMANGIOL (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002621/II/0002
Procedure scope: Update of SmPC section 4.8 to reflect the number of studies and the number of patients included in the safety database analysed, following completion of 2 safety studies one of which to investigate long term effects including effect on growth
MAH(s): Pierre Fabre Dermatologie

14.1.60. Ruxolitinib – JAKAVI (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002464/II/0016
Procedure scope: Extension of indication to add treatment of adult patients with polycythaemia very resistant to or intolerant of hydroxyurea. As a result, the MAH proposes to update SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2. The Package Leaflet is proposed to be updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. An updated RMP version 4.0 has been provided as part of the application
MAH(s): Novartis Europharm Ltd

14.1.61. Ruxolitinib – JAKAVI (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002464//II/0017/G
Procedure scope: Grouping of two type II variations to update SmPC sections 4.5 and 5.2 based on the drug-drug interaction studies CINC424A2102, undertaken to evaluate the effects of ruxolitinib on the pharmacokinetics of a monophasic oral contraceptive, and CINC424A2103, undertaken to evaluate the intestinal CYP3A4 inhibitory effect of ruxolitinib on the pharmacokinetics of orally administered midazolam. The application addresses MEA 003 and MEA 004. A revised RMP version 3.1 has been included as part of the application
MAH(s): Novartis Europharm Ltd

14.1.62. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000674/II/0077
Procedure scope: Update of SmPC sections 4.3, 4.4, 4.8 and 5.1 to reflect the results of a double blind placebo controlled study to investigate the immunogenicity, and safety of Zostavax in subjects with HIV infection to address a post-authorisation measure in the RMP. The MAH took the opportunity to perform other updates of the RMP: to classify Herpes zoster/herpes zoster like rash and varicella/varicella-like rash as an Important Identified Risk and to reflect in the RMP the results of 2 other clinical studies with Implications for Safety Concerns (Protocol 029 a booster dose study and Protocol 016)
MAH(s): Sanofi Pasteur MSD SNC

14.1.63. Sitagliptin – JANUVIA (CAP), RISTABEN (CAP), TESAVEL (CAP), XELEVIA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000722/WS0534/0039, EMEA/H/C/001234/WS0534/0029, EMEA/H/C/000910/WS0534/0039, EMEA/H/C/000762/WS0534/0043
Procedure scope: Update to SmPC section 4.4 and submission of an updated RMP to implement the CHMP recommendations of the Art 5(3) referral procedure on GLP-1-based therapies and pancreatic safety. The PL is proposed to be updated accordingly. The RMP is also updated to include rhabdomyolysis as a potential risk as outcome of post-authorisation measure LEG 006.2
MAH(s): Merck Sharp & Dohme Limited

14.1.64. Sitagliptin, metformin – EFFICIB (CAP), JANUMET (CAP), RISTFOL (CAP), VELMETIA (CAP)

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

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

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

14.1.65. Temsirolimus – TORISEL (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000799/II/0058
Procedure scope: Update of SmPC sections 4.5 and 5.2 following the pharmacokinetic (PK) analysis from an in vivo drug-drug interaction (DDI) study between temsirolimus 175mg or 75mg and desipramine
MAH(s): Pfizer Limited

14.1.66. Trastuzumab emtansine – KADCYLA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002389/II/0006/G
Procedure scope: Grouped variations: 1) Update of SmPC section 4.6 and section 2 of the Package Leaflet in order to change the duration of contraception to be used after Kadcyla (trastuzumab emtansine) treatment from 6 to 7 months in line with the Herceptin (trastuzumab) product information. Furthermore the MAH took the opportunity to make minor editorial changes in the Package Leaflet; 2) Update of the due dates concerning the submission of the overall survival outcome data from the pivotal study BO21977 (EMILIA) in Annex II of the product information and the RMP; 3) Update the due date in the RMP concerning the submission of data from the study BO25499; 4) Update of the due date in the RMP concerning the submission of data for the study BO28407 (KAITLIN). A revised RMP version 4.0 has been provided as part of this application
MAH(s): Roche Registration Limited

14.1.67. Travoprost – TRAVATAN (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000390/II/0046
Procedure scope: Extension of the indication for decrease of elevated intraocular pressure in paediatric patients with ocular hypertension or paediatric glaucoma
MAH(s): Alcon Laboratories (UK) Ltd

14.1.68. Vinflunine – JAVLOR (CAP)

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

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

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

14.1.69. Eltrombopag – REVOLADE (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/001110/R/0018 (with RMP)
MAH(s): GlaxoSmithKline Trading Services

14.1.70. Leflunomide – LEFLUNOMIDE WITHTROP (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001129/R/0018 (with RMP)
MAH(s): Sanofi-aventis Deutschland GmbH

14.1.71. Sevelamer – RENAGEL (CAP)

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

Regulatory details:
PRAC Rapporteur: Terhi Lehtinen (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000254/R/0100 (with RMP)
MAH(s): Genzyme Europe BV

14.1.72. Thiotepa – TEPADINA (CAP)

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

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/001046/R/0017 (with RMP)
MAH(s): Adienne S.r.l. S.U.

14.1.73. Zoledronic acid – ACLASTA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000595/R/0051 (with RMP)
MAH(s): Novartis Europharm Ltd

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

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

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

Evaluation of PSUR procedures

15.1.1. Abacavir –ZIAGEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUV/0079
MAH(s): ViiV Healthcare UK Limited

15.1.2. Abacavir, lamivudine – KIVEXA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000581/PSUV/0053
MAH(s): ViiV Healthcare UK Limited

15.1.3. Abacavir, lamivudine, zidovudine – TRIZIVIR (CAP), NAP

- Evaluation of a PSUSA[52] procedure

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

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00003144/201312
MAH(s): ViiV Healthcare UK Limited

15.1.4. Anidulafungin – ECALTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000788/PSUV/0027
MAH(s): Pfizer Limited

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002513/PSUV/0001 (with RMP version 7.0)
MAH(s): Dendreon UK LTD

15.1.6. Axitinib – INLYTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Ingebjørg Buajordet (NO)

Administrative details:
Procedure number(s): EMEA/H/C/002406/PSUV/0009
MAH(s): Pfizer Limited

15.1.7. Betaine anhydrous – CYSTADANE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000678/PSUV/0015 (with RMP version 5.0)
MAH(s): Orphan Europe S.A.R.L.

15.1.8. Bevacizumab – AVASTIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000582/PSUV/0070
MAH(s): Roche Registration Ltd

15.1.9. Brentuximab vedotin – ADCETRIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002455/PSUV/0019 (with RMP version 4.0)
MAH(s): Takeda Pharma A/S

15.1.10. Catridecacog – NOVOTHIRTEEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002284/PSUV/0004
MAH(s): Novo Nordisk A/S

15.1.11. Cobicistat – TYBOST (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002572/PSUV/0007
MAH(s): Gilead Sciences International Ltd

15.1.12. Colistimethate sodium – COLOBREATHE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001225/PSUV/0014
MAH(s): Forest Laboratories UK Limited

15.1.13. Copper (^{64}Cu) chloride – CUPRYMINA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002136/PSUV/0002
MAH(s): Sparkle Srl

15.1.14. Crizotinib – XALKORI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002489/PSUV/0017
MAH(s): Pfizer Limited

15.1.15. Dexamethasone – OZURDEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001140/PSUV/0017 (with RMP version 4.0)
MAH(s): Allergan Pharmaceuticals Ireland

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002577/PSUV/0006, EMEA/H/C/002574/PSUV/0029
MAH(s): Gilead Sciences International Ltd

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002312/PSUV/0041 (with RMP version 7.0)
MAH(s): Gilead Sciences International Ltd

15.1.18. Eptifibatide – INTEGRILIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000230/PSUV/0070
MAH(s): Glaxo Group Ltd

15.1.19. Estradiol, nomegestrol acetate – IOA (CAP), ZOELY (CAP), NAP

- Evaluation of a PSUSA[53] procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002182/201401
MAH(s): Merck Sharp & Dohme Limited (Ioa), Theramex S.r.l. (Zoely) various

15.1.20. Etanercept – ENBREL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000262/PSUV/0172
MAH(s): Pfizer Limited

15.1.21. Fampridine – FAMPYRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002097/PSUV/0017 (with RMP version 9.0)
MAH(s): Biogen Idec Ltd.

15.1.22. Fenofibrate, simvastatin – CHOLIB (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002559/PSUV/0005
MAH(s): Abbott Healthcare Products Ltd.

15.1.23. Fondaparinux– ARIXTRA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000403/PSUV/0062
MAH(s): Glaxo Group Ltd

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

15.1.24. Gadoversetamide – OPTIMARK (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000745/PSUV/0022
MAH(s): Mallinckrodt Deutschland GmbH

15.1.25. Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed) – FENDRIX (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000550/PSUV/0037
MAH(s): GlaxoSmithKline Biologicals

15.1.26. Human coagulation factor VIII, human von Willebrand factor – VONCENTO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002493/PSUV/0007
MAH(s): CSL Behring GmbH

15.1.27. Imiquimod – ALDARA (CAP), ZYCLARA (CAP), NAP

- Evaluation of a PSUSA[54] procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001729/201401
MAH(s): Meda AB, various

15.1.28. Ingenol mebutate – PICATO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002275/PSUV/0005
MAH(s): Leo Pharma A/S

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

15.1.29. Linaclotide – CONSTELLA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002490/PSUV/0016
MAH(s): Almirall S.A

15.1.30. Lipegfilgrastim – LONQUEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002556/PSUV/0002
MAH(s): Sicor Biotech UAB

15.1.31. Lixisenatide – LYXUMIA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002445/PSUV/0005
MAH(s): Sanofi-Aventis Groupe

15.1.32. Loxapine – ADASUVE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002400/PSUV/0007
MAH(s): Alexza UK Ltd.

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002522/PSUV/0002
MAH(s): Genzyme Europe BV

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002333/PSUV/0019
MAH(s): Novartis Vaccines and Diagnostics S.r.l.

15.1.35. Nalmefene – SELINCRO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002583/PSUV/0009 (with RMP version 3.0)
MAH(s): H. Lundbeck A/S

15.1.36. Nilotinib – TASIGNA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000798/PSUV/0069
MAH(s): Novartis Europharm Ltd

15.1.37. Orlistat – ALLI (CAP), **XENICAL** (CAP), NAP

- Evaluation of a PSUSA[55] procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002220/201402
MAH(s): Glaxo Group Ltd (Alli), Roche Registration Ltd (Xenical), various

15.1.38. Perampanel – FYCOMPA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002434/PSUV/0014
MAH(s): Eisai Europe Ltd.

15.1.39. Pirfenidone – ESBRIET (CAP)

- Evaluation of a PSUR procedure

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002154/PSUV/0020 (with RMP version 6.0)
MAH(s): InterMune UK Ltd.

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001104/PSUV/0107
MAH(s): Pfizer Limited

15.1.41. Prasugrel – EFIENT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000984/PSUV/0016 (with RMP version 10.0)
MAH(s): Eli Lilly Nederland B.V.

15.1.42. Pregabalin – LYRICA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000546/PSUV/0069 (with RMP version 11.0)
MAH(s): Pfizer Limited

15.1.43. Raloxifene – EVISTA (CAP), **OPTRUMA** (CAP), **RALOXIFENE TEVA** (CAP), NAP

- Evaluation of a PSUSA[56] procedure

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002603/201312
MAH(s): Daiichi Sankyo Europe GmbH (Evista), Eli Lilly Nederland B.V. (Optruma), Teva Pharma B.V. (Raloxifene Teva), various

15.1.44. Riluzole – RILUTEK (CAP), **RILUZOLE ZENTIVA** (CAP), NAP

- Evaluation of a PSUSA[57] procedure

[56] PSUR single assessment, referring to CAP, NAP
[57] PSUR single assessment, referring to CAP, NAP

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002645/201312
MAH(s): Aventis Pharma S.A., various

15.1.45. Rivastigmine – EXELON (CAP), **PROMETAX** (CAP), **RIVASTIGMINE 1A PHARMA** (CAP), **RIVASTIGMINE HEXAL** (CAP), **RIVASTIGMINE SANDOZ** (CAP), NAP

- Evaluation of a PSUSA[58] procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002654/201401
MAH(s): 1 A Pharma GmbH (Rivastigmine 1A Pharma), Hexal AG (Rivastigmine Hexal), Novartis Europharm Ltd (Exelon, Prometax), Sandoz Pharmaceuticals GmbH (Rivastigmine Sandoz), various

15.1.46. Rufinamide – INOVELON (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000660/PSUV/0030
MAH(s): Eisai Ltd

15.1.47. Ruxolitinib – JAKAVI (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002464/PSUV/0015
MAH(s): Novartis Europharm Ltd

15.1.48. Silodosin – SILODYX (CAP), **UROREC** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001209/PSUV/0017, EMEA/H/C/001092/PSUV/0017
MAH(s): Recordati Ireland Ltd.

15.1.49. Trastuzumab emtansine – KADCYLA (CAP)

- Evaluation of a PSUR procedure

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002389/PSUV/0004
MAH(s): Roche Registration Limited

15.1.50. Ulipristal – ESMYA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002041/PSUV/0025
MAH(s): Gedeon Richter Plc.

15.1.51. Velaglucerase alfa – VPRIV (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/001249/PSUV/0018 (with RMP version 8.1)
MAH(s): Shire Pharmaceuticals Ireland Ltd.

15.1.52. Vemurafenib – ZELBORAF (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002409/PSUV/0016
MAH(s): Roche Registration Ltd

15.1.53. Vismodegib – ERIVEDGE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002602/PSUV/0007
MAH(s): Roche Registration Ltd

Follow-up to PSUR procedures[59]

15.1.54. Aclidinium bromide – BRETARIS GENUAIR (CAP), **EKLIRA GENUAIR** (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002706/LEG 006.2, EMEA/H/C/002211/LEG 006.2
Procedure scope: MAH's response to LEG 006.1 (LEG006/PSU-004/PSUR#1) as adopted in June 2014
MAH(s): Almirall S.A

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

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

16.1.1. Glycopyrronium bromide, indacaterol – ULTIBRO BREEZHALER (CAP), ULUNAR BREEZHALER (CAP), XOTERNA BREEZHALER (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002679/ANX 002.1, EMEA/H/C/003875/ANX 003, EMEA/H/C/003755/ANX 002.1
Procedure scope: Evaluation of the updated PASS protocol for a multinational database cohort study to assess RMP specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe
MAH(s): Novartis Europharm Ltd

16.1.2. Modified vaccinia Ankara virus – IMVANEX (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002596/SOB 002
Procedure scope: PASS protocol for 1) POX-MVA-038: observational, non-interventional post-authorisation safety study for the prophylactic vaccination with IMVANEX in adults; 2) POX-MVA-039: An observational, non-interventional post-authorisation safety and efficacy study for the prophylactic vaccination with IMVANEX following re-emergence of circulating smallpox infections
MAH(s): Bavarian Nordic A/S

16.1.3. Canakinumab - ILARIS (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/001109/MEA/037.1
Procedure scope: Revised PASS protocol for a non-interventional study collecting safety and efficacy data from SJIA patients enrolled in Pharmachild registry (Study CACZ885G2401)
MAH(s): Novartis Europharm Ltd

16.1.4. Dabigatran – PRADAXA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/MEA 041.1
Procedure scope: MAH's response to MEA-041 including a revised PASS protocol of Study No. 1160.149, as adopted at PRAC in May 2014
MAH(s): Boehringer Ingelheim International GmbH

16.1.5. Delamanid - DELTYBA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002552/MEA 002
Procedure scope: PASS protocol for study 242-120402: multicentre EU-wide observational non-interventional post-authorisation study to assess the safety and drug usage of delamanid (OPC-67683) in routine medical practice in multidrug-resistant tuberculosis patients (Delamanid registry)
MAH(s): Otsuka Novel Products GmbH

16.1.6. Dextromethorphan, quinidine – NUEDEXTA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002560/MEA 001.1, EMEA/H/C/002560/MEA 001.2
Procedure scope: Evaluation of the MAH's responses to the list of questions on a revised PASS protocol for an observational study to collect information on utilisation patterns of Nuedexta when used in routine medical practice (protocol number: 13-AVR-403), as adopted in December 2013
MAH(s): Jenson Pharmaceutical Services Ltd

16.1.7. Fenofibrate, pravastatin - PRAVAFENIX (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/001243/MEA 007.4
Procedure scope: Evaluation of the MAH's responses to the list of questions for a revised PASS protocol: European, observational, three-year cohort study on the safety of the fixed-dose combination pravastatin 40 mg/fenofibrate 160 mg in real clinical practice (FENOPRA-IV-14-1), as adopted by PRAC in April 2014
MAH(s): Laboratoires SMB S.A.

16.1.8. Follitropin alfa - OVALEAP (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002608/MEA 002
Procedure scope: PASS protocol of a prospective observational study to assess the safety of Ovaleap compared to Gonal-f in one treatment cycle with respect to the incidence rates of OHSS in infertile women undergoing superovulation for assisted reproductive technologies (ART)
MAH(s): Teva Pharma B.V.

16.1.9. Glycopyrronium bromide, indacaterol – ULTIBRO BREEZHALER (CAP)**, ULUNAR BREEZHALER** (CAP), **XOTERNA BREEZHALER** (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002679/MEA 003.1, EMEA/H/C/003875/MEA 004, EMEA/H/C/003755/MEA 003.1
Procedure scope: Evaluation of the updated protocol for a drug utilisation study (DUS) (QVA 149A2401) to determine the proportion of patients who do not meet the criteria specified in the product information and the proportion of patients who have missing information as per RMP or pre-defined high risk treatment conditions
MAH(s): Novartis Europharm Ltd

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

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002617/MEA 004
Procedure scope: PASS protocol of a non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2-17 years of age (D2560C00008)
MAH(s): MedImmune LLC

16.1.11. Tenofovir disoproxil - VIREAD (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000419/MEA 265.2
Procedure scope: Evaluation of the MAH's responses to the list of questions for a revised PASS protocol to explore the long term safety profile of tenofovir disoproxil fumarate and describe the management of tenofovir-associated renal and bone toxicity in chronic hepatitis B-infected adolescents in Europe (GS-EU-174-1403), as adopted by PRAC in June 2014
MAH(s): Gilead Sciences International Ltd

16.1.12. Tocilizumab - ROACTEMRA (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/000955/MEA 045.1
Procedure scope: Revised PASS protocol for BSR register of tocilizumab treated patients and prospective surveillance study for adverse events
MAH(s): Roche Registration Ltd

16.1.13. Tocilizumab - ROACTEMRA (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/000955/MEA 041.2
Procedure scope: Revised registry protocol collecting long term efficacy and safety data in polyarticular juvenile idiopathic arthritis (pJIA) treatment
MAH(s): Roche Registration Ltd

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

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/WS0561/0092, EMEA/H/C/002073/WS0561/0093, EMEA/H/C/000964/WS0561/0062
Procedure scope: Submission of the final study report for the non-interventional study CSPP100A2415 – a cohort study including a nested case-control analysis using data from the United States IMS PharMetrics Plus health plan claims database – assessing the prevalence and incidence of angioedema among patients with hypertension treated with aliskiren or other antihypertensive medications in the US
MAH(s): Novartis Europharm Ltd

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

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/WS/0581, EMEA/H/C/002073/WS/0581, EMEA/H/C/000964/WS/0581
Procedure scope: Submission of the final study report for the non- interventional study CSPP100A2414 – A cohort study to assess various safety outcomes in aliskiren initiators using US claims data.
MAH(s): Novartis Europharm Ltd

16.1.16. Bevacizumab – AVASTIN (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000582/II/0073/G (with RMP 17.0)
Procedure scope: Submission of two final clinical study reports (CSR) (MO18725 and ML21823), both listed in Section III.4 details of outstanding additional pharmacovigilance activities of the RMP. Consequentially the RMP has been updated to version 17.0
MAH(s): Roche Registration Ltd

16.1.17. Epoetin zeta – RETACRIT (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000872/0053/G (with RMP version 13.0)
Procedure scope: Final reports for the following two studies in order to fulfil post-authorisation measures: 1) MEA 044: PASCO (PMS-830-07-0043): post-authorisation safety cohort observation of Silapo (epoetin zeta) administered for the treatment of renal anaemia 2) MEA 045: REG-830-10-0098 and REG-830-10-0097 (Pilot Study): epidemiological study based on health care insurance data to determine the risk of venous thromboembolism and all-cause mortality in cancer patients treated with epoetins either with or without transfusions versus cancer patients treated with transfusions alone
MAH(s): Hospira UK Limited

16.1.18. Epoetin zeta – SILAPO (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000760/II/0031/G (with RMP version 10.0)
Procedure scope: Final reports for the following two studies in order to fulfil post-authorisation measures: 1) MEA 036: post-authorisation safety cohort observation of Silapo (epoetin zeta) administered intravenously for the treatment of renal anaemia (PASCO); 2) LEG 038: risk of venous thromboembolism and all-cause mortality in cancer patients treated with epoetins either with or without transfusion versus cancer patients treated with transfusion alone. This submission includes an updated RMP to reflect the outcome of the two studies
MAH(s): Stada Arzneimittel AG

16.1.19. Golimumab – SIMPONI (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000992/II/0060 (with RMP version 10.1)
Procedure scope: Submission of the final report of educational programme on the risk of serious infection, congestive heart failure, maladministration and the potential for hypersensitivity reactions (as requested in MEA 010.1). A revised RMP is included to reflect the final report of the educational programme survey and to include the latest version of mock-up of proposed additional risk minimization measures, to add synopses of the completed studies C0524T08 and C0524T09 (related to procedure II/55), and to update the unknowns related to treatment benefits section of the public summary (related to procedure X/47)
MAH(s): Janssen Biologics B.V.

16.1.20. Infliximab – REMICADE (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000240/II/0182/G (with RMP version 9.1)
Procedure scope: Submission of the final reports from the rheumatoid arthritis (RA) registries BIOBADASER, BSRBR, and RABBIT cohort 1. An updated RMP is submitted in order to delete lack of efficacy and hypersensitivity from the missing information and add acute hypersensitivity reaction (including anaphylactic shock) as important identified risk
MAH(s): Janssen Biologics B.V.

16.1.21. Mannitol – BRONCHITOL (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001252/II/0011 (with RMP version 5)
Procedure scope: Provision of further qualitative sputum microbiology data from study DPM-B-305 in relation to the safety concern of microbial infection via a contaminated inhaler device (MEA 003)
MAH(s): Pharmaxis Pharmaceuticals Limited

16.1.22. Palivizumab – SYNAGIS (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000257/II/0098 (without RMP)
Procedure scope: Submission of the final study report for study A11-632, an observational study carried out to assess the risk of autoimmune and allergic diseases in high risk children exposed to palivizumab, in fulfilment of the Post Authorisation Measure (REC) FU2 032
MAH(s): AbbVie Ltd.

16.1.23. Pioglitazone – ACTOS (CAP), GLUSTIN (CAP)
pioglitazone, metformin – COMPETACT (CAP), GLUBRAVA (CAP)
pioglitazone, glimepiride – TANDEMACT (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000285/WS0541/0061, EMEA/H/C/000286/WS0541/0059, EMEA/H/C/000655/WS0541/0046, EMEA/H/C/000893/WS0541/0032, EMEA/H/C/000680/WS0541/0036
Procedure scope: Submission of final analysis report (post approval commitment) for the KPNC non-bladder malignancy study extension (AD4833-403)
MAH(s): Takeda Pharma A/S

16.1.24. Teriparatide – FORSTEO (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000425/II/0039/G (with RMP version 3.0)
Procedure scope: Submission of the concluding report of the European Union component of the post-authorisation safety study (PASS), Study B3D-MC-GHBX(1) and the update to the RMP of Forsteo. Proposal to remove 'limited clinical trial experience in pre-menopausal women' as important missing information
MAH(s): Eli Lilly Nederland B.V.

16.1.25. Abatacept - ORENCIA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000701/MEA/048.2
Procedure scope: Annual updates of the juvenile idiopathic arthritis (JIA) registry
MAH(s): Bristol-Myers Squibb Pharma EEIG

16.1.26. Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000797/MEA/039
Procedure scope: Annual periodic update report for malignant events [ATR-14-022]
MAH(s): Bristol-Myers Squibb and Gilead Sciences Ltd

16.1.27. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000758/MEA 041.2
Procedure scope: Yearly interim clinical study report (V58_30OB*) for a post-marketing observational cohort study to replace study V58P14 (prematurely terminated)
MAH(s): Novartis Vaccines and Diagnostics GmbH

16.1.28. Vernakalant - BRINAVESS (CAP)

- See procedure scope below

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

Administrative details:
Procedure number(s): EMEA/H/C/001215/LEG 022
Procedure scope: Evaluation of a serious case of hypotension together with causality assessment
MAH(s): Cardiome UK Limited

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

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

17.1.1. **Amifampridine – FIRDAPSE** (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001032/S/0027 (without RMP)
MAH(s): BioMarin Europe Ltd

17.1.2. **Nelarabine – ATRIANCE** (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000752/S/0025 (without RMP)
MAH(s): Glaxo Group Ltd

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 8 - 11 September 2014 meeting.

PRAC member PRAC alternate	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting***	***Topics on the current Committee Agenda for which restriction applies*** ***Product/ substance***
Harald Herkner	Austria	Full involvement	
Jan Neuhauser	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer Reviewer for:	interferon alfa-2b , interferon beta-1a, interferon beta-1b , peginterferon alfa-2a , peginterferon alfa-2b, aflibercept, sorafenib , riociguat, cyproterone, ethinylestradiol, ethinylestradiol, dienogest, acetylsalicylic acid
Veerle Verlinden	Belgium	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Nectaroula Cooper	Cyprus	Full involvement	
Eva Jirsová	Czech Republic	Full involvement	
Torbjörn Callreus	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Terhi Lehtinen	Finland	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Patrick Maison	France	Full involvement	
Arnaud Batz	France	Cannot act as Rapporteur or Peer Reviewer for:	paliperidone, androgen deprivation therapy (ADT), abiraterone; degarelix, darunavir, cobicistat, bortezomib, golimumab, infliximab, fentanyl
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
Julia Pallos	Hungary	Cannot act as Rapporteur or Peer Reviewer for:	riluzole
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Jelena Ivanovic	Italy	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Cannot act as	fenofibrate, simvastatin

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product/ substance
		Rapporteur or Peer Reviewer for:	
Jolanta Gulbinovic	Lithuania	Full involvement	
Nadine Petitpain	Luxembourg	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Karen Pernille Harg	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
June Munro Raine (Chair)	United Kingdom	Full involvement	
Julie Williams	United Kingdom	Full involvement	
Rafe Suvarna	United Kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting:**	**Topics on the current Committee Agenda for which restriction applies** ***Product/ substance***
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer reviewer for:	paroxetine, human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed), pneumococcal polysaccharide conjugate vaccine (adsorbed), eltrombopag, dabrafenib, eptifibatide, fondaparinux, hepatitis B (rDNA) vaccine (adjuvanted, adsorbed), orlistat, nelarabine
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Full involvement	

Health care professionals and patients members	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting:**	**Topics on the current Committee Agenda for which restriction applies** **Product/substance**
Filip Babylon		Full involvement	
Marco Greco		Full involvement	
Kristen Myhr		Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (16-05-2014) http://www.ema.europa.eu/docs/en_GB/document_library/contacts/avanderzeijden_DI.pdf	

Additional European experts participating at the meeting for specific Agenda items	Country	
Christelle Bizimungu	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Cédric Gigot	Belgium	
Fabrice Moore	Belgium	
Miranda Vroenhove	Belgium	
Nikica Mirošević Skvrce	Croatia	
Kimmo Jaakkola	Finland	
Florence Cardona	France	
Cyndie Picot	France	
Caitriona Fisher	Ireland	
Maria Vanenburg	Netherlands	
Jessica van Montfoort	Netherlands	
Marco van Teijlingen	Netherlands	
Natividad Galiana	Spain	
Charlotte Backman	Sweden	
Filip Josephson	Sweden	
Anna Lundberg	Sweden	
Elina Rönnemaa	Sweden	
Cecilia Chisholm	United Kingdom	
Claire Doe	United Kingdom	
Eleni Gaki	United Kingdom	
Angeliki Siapkara	United Kingdom	
Jane Woolley	United Kingdom	

ANNEX III – List of abbreviations

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

www.ema.europa.eu

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