6 November 2014
EMA/PRAC/730503/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 6-9 October 2014

Chair: June Raine – Vice-Chair: Almath Spooner

Disclaimers

Some of the information contained in these minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. For orphan medicinal products, the applicant name is published as this information is already publicly available.

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 relate 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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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/

Table of contents

1. Introduction

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

The Chairperson opened the 6-9 October 2014 meeting of the PRAC 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 6-9 October 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 8-11 September 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 9-11 September 2014 were published on the EMA website on 21 October 2014 (EMA/PRAC/608832/2014).

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

None

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

3.1. Newly triggered Procedures

None

3.2. Ongoing Procedures

None

3.3. Procedures for finalisation

3.3.1. Ponatinib - ICLUSIG (CAP)

- Review of the benefit-risk balance following the notification by the European Commission of a referral under Article 20(8) of Regulation (EC) No 726/2004, based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)
PRAC Co-Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/002695/A-20/0003
MAH(s): Ariad Pharma Ltd

Background

A referral procedure under Article 20(8) of Regulation (EC) No 726/2004 for Iclusig (ponatinib) was to be concluded (see Minutes of PRAC July 2014 meeting for background).
A final assessment of the additional data submitted was produced by the Rapporteurs according to the agreed timetable. The review also included the advice of a Scientific Advisory Group.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs and discussed the evidence on the risks of vascular occlusive events associated with Iclusig (ponatinib) in the context of its therapeutic indications as well as possible risk minimisation strategies.

The PRAC considered whether a recommendation for dose reduction in patients with chronic phase chronic myeloid leukaemia (CML) who have achieved major cytogenetic response was justified, even in the absence of an adverse event, since the risk of vascular occlusive events was likely to be dose related. However, data available included a relatively small number of patients, most of whom had been given a reduced dose due to adverse events and follow-up time was limited, and was insufficient to recommend lower doses of Iclusig (ponatinib) in patients who had not experienced an adverse event.

Therefore, the PRAC considered that the recommended starting dose of Iclusig (ponatinib) should remain 45 mg once a day. However, updates to the product information were agreed, to provide healthcare professionals with the latest evidence on safety and efficacy data regarding dose reduction in chronic phase (CP)-CML patients who have achieved major cytogenetic response (MCyR), and to inform physicians of the currently available data on dose reduction. The product information for Iclusig (ponatinib) should also include recommendations to assess the cardiovascular status of patients, consider alternative treatments where appropriate, and consider discontinuation of treatment if haematologic response has not occurred by 3 months as well as additional warnings about hypertension, cardiac failure and risk of bleeding with anti-clotting agents.
Key elements for educational materials that should be provided for healthcare professionals, based on existing data (Annex II) were also agreed.

Finally, the PRAC agreed that conducting a further study aimed at clarifying the dose-efficacy relationship for ponatinib would be key to gaining a better understanding of the benefit risk balance of different starting doses and (potential) down-titration strategies.

Summary of recommendation(s)/conclusions

The PRAC adopted, by consensus, the variation of the marketing authorisations for Iclusig (ponatinib) and adopted a recommendation to be considered by the CHMP – see EMA/615086/2014 'PRAC recommends further measures to minimise risk of blood vessel blockage with Iclusig'.

Post-meeting note: the press release 'European Medicines Agency recommends further measures to minimise risk of blood vessel blockage with Iclusig' representing the opinion provided by the CHMP (EMA/641476/2014) was published on the EMA website on 24 October 2014.

3.3.2. **Testosterone** (NAP)

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

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)
PRAC Co-Rapporteur: Maia Uusküla (EE)

Administrative details:
Procedure number(s): EMEA/H/A-31/1396
MAH(s): various

Background

A referral procedure under Article 31 of Directive 2001/83/EC for testosterone-containing medicines was to be concluded (see Minutes of PRAC July 2014 meeting for background). A final assessment of the additional data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs on the review of potential increased risk of cardiovascular events associated with testosterone-containing medicines - in particular myocardial infarction - in patients treated with testosterone in the context of the authorised indications: as replacement therapy in men with hypogonadism.

The PRAC reviewed all data on the cardiovascular risks associated with testosterone therapy available from clinical trials, observational studies, meta-analyses, post-marketing data and further published data. The PRAC noted that the available evidence did not consistently show an increased risk of cardiovascular events during testosterone therapy.
However in patients suffering from severe cardiac, hepatic, or renal insufficiency or ischaemic heart disease, treatment with testosterone may be associated with serious complications characterised by oedema with or without congestive cardiac failure. The PRAC also recognised that testosterone may have both direct and indirect effects on the cardiovascular system.

Given the knowledge to date, the PRAC considered it justified to reflect in the product information of all testosterone-containing medicinal products approved in the European Union that prescribing testosterone for hypogonadism should be based upon confirmation of both clinical features and biochemical testing. Information on cardiovascular safety and well-documented haematological adverse reactions, which may contribute to an increased cardiovascular risk, should be included in the product information, as well as the fact that there is limited data regarding safety and efficacy in elderly patients above the age of 65.

Lastly, the PRAC recommended that the possible mechanism of the association between cardiovascular/venous thromboembolic events and the level of testosterone will be further investigated by the marketing authorisation holders and reported in the next PSUR.

Summary of recommendation(s)/conclusions

The PRAC adopted, by consensus, the variation of the marketing authorisations for testosterone-containing medicines and adopted a recommendation to be considered by CMDh – see 'PRAC review does not confirm increase in heart problems with testosterone medicines' EMA/611318/2014.

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

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

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

Administrative details:
Procedure number(s): EMEA/H/A-31/1387
MAH(s): Sanofi-aventis GmbH, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC for valproate and related substances (see Minutes of PRAC July 2014 meeting for background) was to be concluded. A final assessment of the additional data submitted was produced by the Rapporteurs, according to the agreed timetable. The review also included the advice of a Scientific Advisory Group (SAG).

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs for the use of valproate and related substances in female children, women of childbearing potential and pregnant women in the authorised indications.

The review highlighted results from recently published studies showing a risk of developmental problems in pre-school children exposed to valproate in utero of up to 30% to 40%, including delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability. The review also confirmed the teratogenic risks associated with the use of valproate in pregnant women. In addition, data showed that children exposed to valproate in utero were at an approximately 11% risk of malformations at birth (such as neural tube defects and cleft palate) compared to a 2 to 3% risk for children in the general population.

Available data also showed that children exposed to valproate in utero were at increased risk of autistic spectrum disorder (around 3 times higher than in the general population) and childhood autism (5 times higher than in the general population). There were also limited data suggesting that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD).

The PRAC confirmed that valproate should not be prescribed to female children, women of childbearing potential or pregnant women for the treatment of epilepsy or manic phase of bipolar disorder, unless other treatments are ineffective or not tolerated. Treatment should be started and supervised by a doctor experienced in treating these conditions. Women for whom valproate is the only option after trying other treatments should use effective contraception.

Furthermore, regarding use in migraine prophylaxis (as indicated in some Member States), the PRAC recommended that valproate treatment should be contraindicated in pregnant women and in women of childbearing potential who do not use effective methods of contraception.

The PRAC agreed that educational material (including a prescriber guide and patient booklet) was needed to improve healthcare professionals' awareness of risk regarding pregnancy outcomes and to ensure that female patients are informed of, and understand, risks associated with valproate use during pregnancy, the need to use effective contraception and the need for regular review of treatment, as well as the need to consult the prescriber if she is planning a pregnancy or becomes pregnant.

A drug utilisation study to assess the effectiveness of these proposed risk minimisation measures and to further characterise the prescribing patterns for valproate should also be conducted.

Summary of recommendation(s)/conclusions

The PRAC adopted, by consensus, the variation of the marketing authorisations for medicines containing valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide and adopted a recommendation to be considered by CMDh – see 'PRAC recommends strengthening the restrictions on the use of valproate in women and girls' EMA/612389/2014. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed as well as educational material for patients and healthcare professionals.

4. Signals assessment and prioritisation[1]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Amiodarone** (NAP)

- Signal of Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH)

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

Administrative details:
EPITT 18091 – New signal
MAH(s): various
Lead MS: NL

Background

Amiodarone is an antiarrhythmic agent used in the treatment of severe rhythm disorders including tachyarrhythmia, atrial flutter and fibrillation. Amiodarone is available in tablets and as an intravenous solution.

The worldwide exposure for medicines containing amiodarone is estimated to have been very wide, since the medicine has been extensively prescribed since its first authorisation in the mid-1960s.

[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

A signal of SIADH was identified by the Netherlands, following a review transmitted by the MAH of one of the marketed generic intravenous products analysing 13 articles corresponding to 15 suspected case reports. NL as the lead member state for signal management activities for amiodarone confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the suspected cases identified and noted that in the majority of them, both oral administration and intravenous (IV) administration in the loading phase were involved. A positive dechallenge was reported for some patients who recovered following discontinuation or dose reduction. The PRAC also noted that some additional cases were retrieved from a further search performed in EudraVigilance.

The PRAC concurred that, even though the biological mechanism remained unclear, the association between occurrence of SIADH and amiodarone was supported by several publications in the scientific literature. The PRAC also noted that SIADH is included in the product information of amiodarone tablets but not for amiodarone intravenous solution and agreed that it was necessary to further investigate the signal. Even if both IV and oral formulations could have been potentially involved in consideration of the presented data, it was considered justified to gather information with a focus on the IV formulation.

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

Summary of recommendation(s)

- The MAH for the nationally authorised reference amiodarone-containing product should submit to the PRAC 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.

4.1.2. Aripiprazole – ABILIFY (CAP)

- Signal of hyperprolactinaemia

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:
EPITT 18086 – New signal
MAH(s): Otsuka Pharmaceutical Europe Ltd
Lead MS: PT

Background

Aripiprazole is an antipsychotic medicine indicated for the treatment of schizophrenia, moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in selected patients.

The exposure for centrally authorised medicines containing aripiprazole is estimated to have been more than 8.7 million patient-years worldwide, in the period from first authorisation in 2004 to 2013.

During routine signal detection activities, a signal of hyperprolactinaemia was identified by the EMA, based on 8 suspected cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information of the suspected cases of hyperprolactinaemia reported, in the context of common causes and risk factors for hyperprolactinaemia.
Some cases of hyperprolactinaemia and blood prolactin increase, with positive de-challenge to aripiprazole, had been already described in data reviewed in previously assessed regulatory procedures and reported in the literature.

Aripiprazole, at usual therapeutic doses, is a partial agonist of D_2 and $5HT_{1a}$ receptors and an antagonist of $5HT_{2a}$ receptors and a case report published in the literature hypothesized, as one possible biological mechanism, that aripiprazole at higher doses acts as full D_2 receptor antagonist interfering with the physiologic dopamine inhibitory effect on prolactin secretion.

Based on the available data, the PRAC concluded that the signal should be further investigated and that more information was needed on particular aspects such as route of administration, dosage and concomitant antipsychotic therapy.

Summary of recommendation(s)

- The MAH for Abilify/Abilify Maintena (aripiprazole) 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.

4.1.3. Exenatide – BYETTA (CAP)

- Signal of goitre and worsening, enlargement of goitre

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

Administrative details:
EPITT 18077 – New signal
MAH(s): AstraZeneca AB
Lead MS: SE

Background

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination for the treatment of type 2 diabetes mellitus.

The exposure for centrally authorised medicines containing exenatide is estimated to have been more than 3.2 million patient-years worldwide, in the period from first authorisation in 2006 to 2014.

During routine signal detection activities, triggered by two suspected cases reported in the United Kingdom, a signal of thyroid swelling in patients with pre-existing goitre associated with use of exenatide, was identified by the UK. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases available describing, with limited details, a doubling in size of goitre following 3-4 weeks of exenatide treatment. Information regarding thyroid adverse events, including goitre, in particular in patients with pre-existing thyroid disease, had been reported previously in clinical trials for liraglutide, another GLP-1 receptor agonist and this information is included in its product information.

Preclinical safety data, showing a statistically significant increase in thyroid C - cell tumour incidence (adenomas and/or carcinomas) in rats at all doses, is also reflected in the exenatide product information and an effect on thyroid for exenatide is supported by previous data. Based on these considerations, the PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

- The MAH for Byetta (exenatide) should perform a cumulative review of goitre/worsening of goitre in the next PSUR (DLP: 31/3/2015).

4.1.4. Tocilizumab - ROACTEMRA (CAP)

- Signal of cholecystitis

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

Administrative details:
EPITT 18092– New signal
MAH(s): Roche Registration Ltd
Lead MS: DE

Background

Tocilizumab is a humanised IgG1 monoclonal antibody indicated for the treatment of rheumatoid arthritis in adults, systemic juvenile idiopathic arthritis and juvenile idiopathic polyarthritis.

The exposure for RoActemra, a centrally authorised medicine containing tocilizumab, is estimated to have been more than 350,000 patient-years worldwide, in the period from first authorisation in 2009 to 2014.

During routine signal detection activities, a signal of cholecystitis was identified by the EMA, based on 53 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 cholecystitis reported and noted that a few of them had been also described in the scientific literature.

Tocilizumab specifically binds to both soluble and membrane bound interleukin–6 (IL-6) receptors, thereby inhibiting pro-inflammatory and other related processes, such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis.

The inhibition of the effects of IL-6 exerted by tocilizumab could provide a plausible mechanism of action for the development of the reaction. Immune deficiency is one of the risk factors for cholecystitis indicating a possible immune-suppression mediated mechanism of tocilizumab induced cholecystitis. Moreover, according to the profile of the adverse reactions reported so far, tocilizumab seems also to have an effect on the epithelial mucosae.

The PRAC noted that, whereas in many cases there was insufficient information to perform a causality assessment, in some cases there were no reported alternative explanations for the development of cholecystitis. Therefore the PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

- The MAH for RoActemra (tocilizumab) should submit to the EMA a cumulative review of cases of non-chronic cholecystitis and related terms (e.g. cholecystitis acute, cholecystitis infective, cholecystitis emphysematous) reported in association with tocilizumab, with a special focus on acute or recurrent cholecystitis without gallstones, in the next PSUR (DLP: 10/10/2014).

4.2. New signals detected from other sources

4.2.1. **Aflibercept** – **EYLEA** (CAP)

- Signal of higher systemic exposure compared to ranibizumab after intravitreal injection

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
EPITT 18112 – New signal
MAH(s): Bayer Pharma AG
Lead MS: FR

Background

Eylea is a centrally authorised medicine containing aflibercept (a recombinant fusion protein consisting of portions of human vascular endothelial growth factor (VEGF) receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1) indicated for intravitreal injection, for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular oedema secondary to central-retinal-vein occlusion (CRVO), and visual impairment due to diabetic macular oedema (DME).

The exposure to Eylea is estimated to have been about 340,000 patient-years worldwide, in the period from first authorisation in 2012 to 31 May 2014.

A signal of higher systemic exposure of the substance after intravitreal injection of aflibercept compared to ranibizumab was identified by FR, based on a review of several articles[2] investigating

[2] Avery RL, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. Br J Ophthalmol. 2014;0:1-6.
Wang X, et al. Serum and plasma vascular endothelial growth factor concentrations before and after intravitreal injection of aflibercept or ranibizumab for age-related macular degeneration. American Journal of Ophthalmology. 2014; 2014 Oct;158(4):738-744
Yoshida I, et al. Evaluation of plasma vascular endothelial growth factor levels after intravitreal injection of ranibizumab and aflibercept for exudative age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2014 Sep;252(9):1483-9

systemic pharmacokinetics of aflibercept, ranibizumab, bevacizumab following intravitreal injection. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the articles reviewed by France comparing serum and/or plasma VEGF concentration of ranibizumab, aflibercept and bevacizumab and systemic exposure in patients with AMD after intravitreal injection.

Despite limitations observed in each published study individually, the PRAC considered there were converging findings with regard to the impact of intravitreal administration of the various substances on the plasma/serum levels of free VEGF.
However, the clinical significance of the differences in systemic exposure to the VEGF and anti-VEGF drugs is unknown, as no dose/response relationship had been established and no correlation with systemic adverse events was provided in the 3 studies published.

On the other hand, the studies reviewed concerned only a small number of patients and the detection of adverse effects would not have been powerful enough to provide meaningful results.

The PRAC noted that during the clinical development for Eylea (aflibercept), concerns were raised on its potential role in the development of systemic arterial thromboembolic events, especially cerebrovascular events and transient ischemic attack (TIA), and the MAH had committed to conduct a post-authorisation study addressing this risk.

Based on these observations, the PRAC agreed that the signal should be further investigated, particularly to address the potential risk of adverse effects resulting from the potential suppression of systemic VEGF expression by aflibercept.

Summary of recommendation(s)

- The MAH for Eylea (aflibercept) should submit to the EMA, within 60 days, a re-analysis of the data from the VIEW-1 and 2 studies ('VIEW' studies, see 'Eylea: EPAR-Public assessment report' published on the EMA website) which compared aflibercept to ranibizumab, focusing on cerebrovascular events in elderly patients. This analysis should take into account age groups and posology used. A complete review and discussion of all data available on the risks associated with the systemic exposure to anti-vascular-endothelial-growth-factor should be provided, including pharmacokinetic data.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signal follow-up and prioritisation

4.3.1. **Atazanavir – REYATAZ** (CAP)

- Signal of haemolytic anaemia

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
EPITT 17921 - Follow-up May 2014
MAH(s): Bristol-Myers Squibb Pharma EEIG

Background

For background information, see PRAC minutes of 5-8 May 2014.
The MAH replied to the request for information on the signal and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the results of a cumulative review of the risk of haemolytic anaemia described in post-marketing setting and in clinical trials with atazanavir (non-clinical and literature data, study conducted in 3 US claims databases) together with possible mechanisms associated with haemolysis, based on the available in vitro/non-clinical evidence available for atazanavir.

The analysis of these cases, together with other data provided, did not indicate strong evidence of a risk of haemolytic anaemia with atazanavir use. Therefore haemolytic anaemia should continue to be monitored through routine pharmacovigilance and no further regulatory action was deemed necessary at this stage.

Summary of recommendation(s)

- No changes to the product information of atazanavir-containing medicines are required at this point in time. The MAHs should continue to monitor haemolytic anaemia as part of routine pharmacovigilance.

4.3.2. Valproate and related substances (NAP)

- Signal of mitochondrial toxicity

Regulatory details:
PRAC Rapporteur*:* Martin Huber (DE)

Administrative details:
EPITT 17956 – Follow-up May 2014
MAH(s): Neuraxpharm Arzneimittel GmbH, Sanofi-Aventis, various

Background

For background information, see PRAC minutes of 5-8 May 2014.
The MAH replied to the request for information on the signal of mitochondrial toxicity and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the results of the review performed by the MAHs on their global pharmacovigilance database, a literature review and a review of standard pharmacovigilance reference text books.
The analysis focused on liver disorders reported in these patients. Rhabdomyolysis, pancreatitis and convulsions, which appeared more frequently reported in these patients, were also reviewed together with the reported cases of aggravation of mitochondrial disease.

The PRAC concurred that the evidence, cumulatively, was sufficient to support a causal association between valproate use and aggravation of underlying mitochondrial diseases, including risk of

hepatotoxicity, occurring mainly in patients suffering from POLG (polymerase gamma) mutations - *Alpers-Huttenlocher* syndrome.

However, before concluding on final recommendations, the PRAC concurred that consultation with the Pharmacogenomics Working Party (PgWP) was needed to clarify some aspects on risk minimisation measures and a list of questions was agreed.

Summary of recommendation(s)

- The advice of the PgWP should be requested on a list of questions agreed by the PRAC on the signal of valproate and mitochondrial toxicity. Further PRAC recommendations will be provided after a response is received.

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 medicinal 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. Docetaxel

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

Administrative details:
Product number(s): EMEA/H/C/003925, *Generic*
Intended indication(s): Treatment of breast cancer, non-small cell lung cancer, prostate cancer, metastatic gastric adenocarcinoma and head and neck cancer

5.1.2. Ex vivo expanded autologous human corneal epithelial cells containing stem cells

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

Administrative details:
Product number(s): EMEA/H/C/002450, *ATMP, Orphan*
Intended indication(s): Treatment of limbal stem cell deficiency

5.1.3. Liraglutide

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

Administrative details:
Product number(s): EMEA/H/C/003780
Intended indication(s): Treatment of obesity

5.2. Medicines already authorised

RMP in the context of a variation[3] – PRAC-led procedure

5.2.1. Rivaroxaban – XARELTO (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000944/II/0034
Procedure scope: Proposal to amend Annex II of the marketing authorisation: as an alternative to the study imposed as specific obligation, Bayer proposes to extend and expand the ongoing epidemiological rivaroxaban PASS program to fulfil the CHMP objective on the post approval program for the ACS indication
MAH(s): Bayer Pharma AG

Background

For background, see PRAC minutes 2-5 December 2013. Previously, the PRAC adopted objections on a draft PASS protocol – proposed to fulfil an original obligation in Annex II of the MA, which was included following a previously granted line extension to include indication acute coronary syndrome (ACS). At the time, it was considered that the conduct of this study would have promoted the use of the product, and the design of the study would not fulfil the study objectives.

Following further exploration of possible study designs, the MAH proposed as an alternative to the study imposed as a specific obligation, to extend and expand the ongoing rivaroxaban epidemiological PASS program fulfilling the CHMP objective on the post approval program for the ACS indication. This proposal was assessed by the Rapporteur in the context of a revision of the RMP.

Summary of advice

- The PRAC agreed on a proposal for a post-authorisation study program that addresses the safety of rivaroxaban in the secondary prevention of ACS outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all populations and particularly in patients at increased risk of bleeding'. Some necessary amendments need to be included in the RMP to reflect such changes and should be introduced before finalisation of the procedure at the level of the CHMP. A consequential amendment of the current obligations of the MA should be introduced.

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

5.2.2. Enzalutamide – XTANDI (CAP)

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

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

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

Administrative details:
Procedure number(s): (EMEA/H/C/002639/II/0008
Procedure scope: Extension of indication for the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. Consequently, changes are proposed to SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2. The package leaflet is updated accordingly
MAH(s): Astellas Pharma Europe B.V.

Background

Xtandi is a centrally authorised medicine containing enzalutamide, used for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.
The CHMP is evaluating an extension of the therapeutic indication for Xtandi, to include the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 6 for Xtandi (enzalutamide) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable, provided some minor amendments are introduced to the 'safety concerns' section of the RMP.

5.2.3. **Ustekinumab – STELARA** (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/000958/II/0041
Procedure scope: Update of SmPC section 4.8 to add the adverse reactions of skin exfoliation and erythrodermic psoriasis further to the request of the CHMP to implement the outcome of a PRAC signal recommendation. The Package Leaflet is updated accordingly
MAH(s): Janssen-Cilag International N.V.

Background

Stelara is a centrally authorised medicine containing ustekinumab, indicated in the treatment of plaque psoriasis and psoriatic arthritis. The CHMP is evaluating a type II variation procedure for Stelara, to update the SmPC including information on the adverse reactions of skin exfoliation and erythrodermic psoriasis following previous signal evaluation (see PRAC minutes 3-6 February 2014). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation and the related DHPC.

Summary of advice

- The RMP version 11.1 for Stelara (ustekinumab) in the context of the variation under evaluation by the CHMP was considered acceptable provided that references to routine risk minimisation measures throughout the RMP are updated to reflect the final agreed SmPC

wording. The DHPC and communication plan were supported pending some refinements to be included in the final text.

RMP evaluated in the context of a PSUR procedure

See also Certolizumab pegol – CIMZIA 6.1.1. , Eculizumab – SOLIRIS 15.1.9. , Fingolimod – GILENYA 6.1.6. , Ibritumomab tiuxetan – ZEVALIN 15.1.17. , Mifamurtide – MEPACT 15.1.24.

RMP evaluated in the context of PASS results

See also Human papillomavirus vaccine – GARDASIL, SILGARD 16.1.13. , Eltrombopag – REVOLADE 16.1.13. , Peginterferon alfa-2a – PEGASYS 16.1.15.

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

None

RMP evaluated in the context of a stand-alone RMP procedure

None

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[4]

6.1.1. Certolizumab pegol – CIMZIA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001037/PSUV/0041 (with RMP version 10.0)
MAH(s): UCB Pharma SA

Background

Certolizumab pegol is a tumour necrosis factor alpha (TNFα) inhibitor indicated for the treatment of rheumatoid arthritis, axial spondyloarthritis including ankylosing spondylitis (AS) and axial spondyloarthritis without radiographic evidence of AS as well as for the treatment of psoriatic arthritis under certain conditions.

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

[4] 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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Cimzia (certolizumab pegol) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the warning on tuberculosis to state that rare cases of tuberculosis have been reported with the use of TNF inhibitors despite prophylaxis for tuberculosis. In addition, tuberculosis as an undesirable effect should be refined to explicitly state that this includes miliary, disseminated and extrapulmonary disease. Therefore the current terms of the marketing authorisation(s) should be varied[5].
- The RMP is updated within this PSUR procedure to reflect that hepatitis B reactivation is an important identified risk and concomitant use of disease-modifying antirheumatic drugs (DMARDs) other than methotrexate (MTX) is removed from the safety specifications.
- The MAH should submit to EMA within 60 days a detailed review of cases of autoimmune hepatitis and consider submitting a variation as warranted.
- In the next PSUR, the MAH should provide a detailed analysis of cases of dermatomyositis, a review of cases of glioblastoma and should analyse concomitant medications including DMARDs as part of the review of hepatic events. In addition, the MAH should provide a detailed review relating to the potential relationship between administration of a live vaccine and the development of an infection after vaccination while on certolizumab pegol treatment. As a consequence, the MAH should discuss whether this is missing information, a potential or an identified risk. Finally the MAH should provide a detailed analysis of exposure to certolizumab pegol during pregnancy.

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

6.1.2. Dabigatran – PRADAXA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/PSUV/0069
MAH(s): Boehringer Ingelheim International GmbH

Background

Dabigatran is a direct thrombin inhibitor indicated for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

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

[5] 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

Summary of recommendation(s) and conclusions

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

The PRAC was informed that questions arising from the assessment of latest PSUR were also coordinated by the CHMP as part of an ongoing procedure. Opportunities for further involvement of the PRAC in the aforementioned procedure were discussed and convened to the CHMP.

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. **Dexrazoxane – SAVENE** (CAP), NAP

- Evaluation of a PSUSA[6] procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001001/201402
MAH(s): Clinigen Healthcare Ltd, various

Background

Dexrazoxane is a bisdioxopiperazine indicated in the treatment of anthracycline extravasation in adult and in the prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin use in advanced and/or metastatic adult breast cancer patients under certain conditions.

Based on the assessment of the individual PSURs, part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of dexrazoxane-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 dexrazoxane-containing products in the approved indication(s) remains favourable.
- With regard to dexrazoxane-containing product Savene, the product information should be updated to add a warning on anaphylactic reaction and ensure that previous history of allergy to dexrazoxane is carefully considered prior to administration. In addition, anaphylactic reactions and hypersensitivity should be added as an undesirable effect with an unknown frequency. Finally, the recommendations for safe handling should be revised to ensure that preparation is not handled by pregnant staff. Use of gloves and other protective clothing to prevent skin contact is recommended. Therefore the current terms of the marketing authorisation(s) should be varied[7].
- With regard to dexrazoxane-containing products Cardioxane, Cydranax and Enaxozar, the product information should be updated to add concomitant vaccination with yellow fever

[6] PSUR single assessment, referring to CAP, NAP
[7] Update of SmPC sections 4.4, 4.8 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

vaccine as a contraindication due to the risk of fatal generalised vaccine disease. In addition, liver dysfunction should be added as a warning and a recommendation for routine liver function tests to be conducted before and during administration of dexrazoxane in patients with known liver function disorders. Moreover there should be a recommendation against concomitant use with other live attenuated vaccines due to the risk of systemic and possible fatal disease, as well as against concomitant use with phenytoin due to its reduced absorption that can lead to an exacerbation of convulsions. Finally, concomitant use with ciclosporin and tacrolimus should be assessed carefully due to the risk of excessive immunosuppression with a risk of lymphoproliferative disease. Therefore the current terms of the marketing authorisation(s) should be varied[8].

- In the next PSUR, the MAH for Savene should provide detailed analyses of cases of sepsis/septic shock and cases of medication error. In addition, the MAH for Savene should provide an analysis of differences in patient exposure in the EU.
- In the next PSUR, the MAH for Cardioxane should provide a detailed analysis of cases of drug interaction.

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. Everolimus – AFINITOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/001038/PSUV/0039
MAH(s): Novartis Europharm Ltd

Background

Everolimus is a protein kinase inhibitor indicated for the treatment of hormone receptor-positive advanced breast cancer, for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin and for the treatment of patients with advanced renal cell carcinoma under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Afinitor (everolimus) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on *pneumocystis jirovecii (carinii)* pneumonia to ensure that prophylactic measures are considered when

[8] Update of SmPC sections 4.3, 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

concomitant use of corticosteroids or other immunosuppressive agents is required. In addition, *pneumocystis jirovecii (carinii)* pneumonia should be added as an undesirable effect with a very common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[9].

- In the next PSUR, the MAH should refine its analysis of missing information on patients with central nervous system (CNS) metastases.

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. Everolimus – VOTUBIA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002311/PSUV/0025
MAH(s): Novartis Europharm Ltd

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Votubia (everolimus) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on *pneumocystis jirovecii (carinii)* pneumonia to ensure that prophylactic measures are considered when concomitant use of corticosteroids or other immunosuppressive agents is required. In addition, *pneumocystis jirovecii (carinii)* pneumonia should be added as an undesirable effect with a very common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should provide detailed analyses of cases of status epilepticus/seizures and of male infertility. In addition, the MAH should provide a review of spontaneous reports of suspected lack of therapeutic effect.

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.

[9] Update of SmPC sections 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[10] Update of SmPC sections 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.6. Fingolimod – **GILENYA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002202/PSUV/0029 (with RMP version 8.0)
MAH(s): Novartis Europharm Ltd

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Gilenya (fingolimod) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 60 days a detailed review regarding the proposed switch from the pregnancy registry to the pregnancy outcomes intensive monitoring (PRIM) programme, including a proposal to update the educational materials and RMP accordingly.
- In the next PSUR, the MAH should provide a refined analysis of cases of posterior reversible encephalopathy syndrome (PRES) and of cases of progressive multifocal leukoencephalopathy (PML) including information such as prior immunosuppressant (IS) or immunomodulatory treatment, duration of treatment with fingolimod or time of PML diagnosis. The MAH should also provide detailed reviews of cases of nausea and propose an update of the product information as warranted and a detailed analysis of cases of skin cancers. In addition, a detailed review of maternal and pregnancy histories as well as pregnancy outcomes should be included, together with available data regarding contraception use in women exposed to fingolimod.

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

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

- **Evaluation of a PSUR procedure**

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002691/PSUV/0006, EMEA/H/C/002430/PSUV/0006, EMEA/H/C/002690/PSUV/0007

MAH(s): Novartis Europharm Ltd

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Enurev Breezhaler, Seebri Breezhaler and Tovanor Breezhaler (glycopyrronium bromide) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide detailed reviews from the final results from two clinical studies (CNVA237AAU01 (GLISTEN study) and CQVA149A2107 (comparison of systemic exposure of indacaterol and glycopyrronium alone and in fixed-dose combination)).

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

6.1.8. Glycopyrronium bromide, indacaterol - **ULTIBRO BREEZHALER** (CAP), **ULUNAR BREEZHALER** (CAP), **XOTERNA BREEZHALER** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002679/PSUV/0003, EMEA/H/C/003875/PSUV/0002, EMEA/H/C/003755/PSUV/0005
MAH(s): Novartis Europharm Ltd

Background

Glycopyrronium bromide/indacaterol are used in combination as adrenergic/anticholinergic agents and are 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 Ultibro Breezhaler, Ulunar Breezhaer and Xoterna Breezhaler, centrally authorised medicines containing glycopyrronium bromide/indacaterol, 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 Ultibro Breezhaler, Ulunar Breezhaer and Xoterna Breezhaler (glycopyrronium bromide/indacaterol) in the approved indication(s) remains favourable.

- Nevertheless, the product information should be updated to add angioedema and a warning to discontinue the treatment should this immediate hypersensitivity reaction occur after administration of glycopyrronium bromide/indacaterol. In addition, angioedema should be added as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide a detailed review of cases of syncope and circulatory collapse.

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. Pandemic influenza vaccine (H1N1v) (surface antigen, inactivated, adjuvanted) – FOCETRIA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000710/PSUV/0033
MAH(s): Novartis Vaccines and Diagnostics S.r.l.

Background

Pandemic influenza vaccine (H1N1v) (surface antigen, inactivated, adjuvanted) is indicated for the prophylaxis of influenza caused by A (H1N1v) 2009 virus.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Focetria, a centrally authorised pandemic influenza vaccine, 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 Focetria (pandemic influenza vaccine (H1N1v) (surface antigen, inactivated, adjuvanted)) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to revise the available information on the use of the vaccine during pregnancy. Therefore the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should provide a detailed analysis of any new evidence of a possible association of Focetria and Guillain-Barré syndrome (GBS), regardless of the setting and geographic location.

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.

[11] 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
[12] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.10. Rasburicase – FASTURTEC (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000331/PSUV/0041
MAH(s): Sanofi-Aventis Groupe

Background

Raburicase is a recombinant urate-oxidase enzyme indicated for the treatment and prophylaxis of acute hyperuricaemia to prevent acute renal failure, in adults, children and adolescents with haematological malignancy with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fasturtec, a centrally authorised medicine containing raburicase, 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 Fasturtec (raburicase) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add convulsions as an undesirable effect with an uncommon frequency, as well as muscle contraction involuntary with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[13].
- The MAH should submit to EMA within 60 days detailed reviews of safety data for the ongoing signals of cardiac toxicity, lack of efficacy (including any immunogenicity data) and hepatobiliary disorders.
- The MAH should submit a variation at the next regulatory opportunity to update the undesirable effects section of the SmPC in order to introduce revised frequencies for adverse reactions of nausea and vomiting and to increase the readability of the section.

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. Regorafenib – STIVARGA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002573/PSUV/0004

[13] 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

MAH(s): Bayer Pharma AG

Background

Regorafenib is a protein kinase inhibitor indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies and for the treatment of unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Stivarga, a centrally authorised medicine containing regorafenib, 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 Stivarga (regorafenib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add hypersensitivity reaction as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[14].

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. Tacrolimus – PROTOPIC (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000374/PSUV/0057
MAH(s): Astellas Pharma Europe B.V.

Background

Tacrolimus ointment is indicated for the treatment of moderate to severe atopic dermatitis under certain conditions.

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

[14] 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 MAH should submit to EMA within 90 days detailed reviews of cases of non-cutaneous infection and of cases of more generalised infection secondary to cutaneous infection or infected atopic dermatitis. In addition, the MAH should provide a detailed analysis of cases of lentigo as well as a comprehensive review of cases of skin pigmentation abnormalities with a discussion of this issue in relation to topical calcineurin inhibitor (CNI) use, including potential mechanisms and relevant non-clinical data and data from the scientific literature.
- In the next PSUR, the MAH should provide detailed reviews of cases of off-label use, generalised lymphadenopathy in association with long-term use of tacrolimus ointment, increased creatinine and osteomyelitis. The MAH should also provide a discussion on the use of the targeted lymphoma questionnaire including the gathering of data on such cases and provide the questionnaire responses in its discussion of reported cases. In addition, the MAH should provide further details on the prescription of tacrolimus ointment by non-specialists particularly in children under 2 years and between 2 and 16 years. Finally, the MAH should provide a detailed discussion on first line use of tacrolimus ointment in relation to the European market.

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

6.1.13. Telaprevir – INCIVO (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002313/PSUV/0028
MAH(s): Janssen-Cilag International N.V.

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Incivo (telaprevir) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to reflect that the concentrations of telaprevir are unlikely to be affected when co-adminstered with maraviroc based on historical pharmacokinetic data and the elimination pathway of telaprevir. In addition, pancreatitis

should be added as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[15].

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. Travoprost – TRAVATAN (CAP), NAP

- Evaluation of a PSUSA[16] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00003011/201402
MAH(s): Alcon Laboratories (UK) Ltd, various

Background

Travoprost is a prostaglandin $F_{2\alpha}$ analogue indicated for the treatment of elevated intraocular pressure (IOP) in adult patients with ocular hypertension or open-angle glaucoma.

Based on the assessment of the individual PSURs, part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of travoprost-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 travoprost-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs for travoprost-containing products Travoprost Pharmaproject and Travoprost Polpharma should ensure that the important identified/potential risks and missing information are submitted in line with the summary of safety concerns for the originator product Travatan.

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. Travoprost, timolol – DUOTRAV (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000665/PSUV/0042
MAH(s): Alcon Laboratories (UK) Ltd

[15] Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[16] PSUR single assessment, referring to CAP, NAP

Background

Travoprost/timolol are used in combination and are indicated in adults for the treatment of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Duotrav, a centrally authorised medicine containing travoprost/timolol, 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 Duotrav (travoprost/timolol) 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 prostaglandin-associated periorbitopathy (PAP) and should continue to closely monitor cases of corneal disorders, taste disorders/smell disorders, alopecia and rash in order to detect any increase in the frequency of the occurrence of these cases, as other potential risks not currently categorised as important.

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

6.1.16. Vortioxetine – BRINTELLIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Veerle Verlinden (BE)

Administrative details:
Procedure number(s): EMEA/H/C/002717/PSUV/0003
MAH(s): H. Lundbeck A/S

Background

Vortioxetine is indicated for the treatment of major depressive episodes in adults.

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

- Nevertheless, the product information should be updated to add serotonin syndrome as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- The MAH should also provide an updated RMP to add serotonin syndrome as an identified risk and include nephrolithiasis in the analysis of the potential risk 'precipitation of metabolites in the kidney' in the context of the next regulatory opportunity.
- In the next PSUR, the MAH should include nephrolithiasis in the analysis of the potential risk 'precipitation of metabolites in the kidney'. In addition, the MAH should provide further details on several clinical trial results and a post-authorisation efficacy study (PAES) conducted in the US. Finally, the MAH should provide a review relating to the discontinuation of treatment with vortioxetine and update the product information as warranted.

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

6.2. Follow-up to PSUR procedures[18]

See Annex 15

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[19]

7.1.1. **Aprotinin** (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Veerle Verlinden (BE)

Administrative details:
Procedure number(s): EMEA/H/N/PSP/0004
Procedure scope: Evaluation of a protocol for a non-interventional post-authorisation safety study of pattern of use of Nordic aprotinin
MAH(s): Disphar International B.V (Nordic Group)

Background

According to the conclusion of a referral under Article 31 of Directive 2001/83/EC for antifibrinolytics (see EMA/673031/2013 rev1 and ANNEX IV) marketing authorisation holders were supposed to conduct a registry study, in order to monitor the pattern of use of aprotinin in the EU. The registry was to be designed to record utilisation information on patients at cardiac surgery centres exposed to aprotinin in the participating countries.
Nordic Group BV submitted a draft protocol for such registry PASS to be reviewed by the PRAC.

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

Conclusion

The PRAC appointed Veerle Verlinden (BE) as PRAC Rapporteur for the assessment of the protocol and agreed a timetable for the procedure.

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/065
Procedure scope: Evaluation of a protocol for a drug utilisation study as per the conclusions of the Article 107i referral procedure
MAH(s): Bayer

Background

For background, see PRAC minutes 8-11 September 2014 and April 2014. Following the protocol for a survey drug utilisation study (DUS) which had already been submitted, a protocol for a database DUS was submitted by one of the MAHs for review by the PRAC.

Conclusion

The PRAC appointed Menno van der Elst (NL) as PRAC Rapporteur for the assessment of the protocol and agreed a timetable for the procedure.

7.1.3. Hydroxyethyl starch (HES) (NAP)

- Evaluation of an imposed PASS protocol

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

Administrative details:
Procedure scope: Evaluation of a PASS protocol (drug utilisation study) to assess the effectiveness of the risk minimisation taken following the European Commission decision dated 19 December 2013 for the referral procedure EMEA/H/A-107I/1376
MAH(s): B. Braun Melsungen AG (Tetraspan, Venofundin), Fresenius Kabi Deutschland GmbH (Volulyte, Voluven Fresenius, Voluven, HyperHAES, HAES-steril), Serumwerk Bernburg AG (VitaHES, Vitafusal, Plasma Volume Redibag, PlasmaHES Redibag, Hesra, Hesra infuusioneste)

Background

For background, see PRAC minutes July 2014. The Rapporteur assessed the draft protocol submitted in accordance with the agreed timetable.

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 submitted, as the Committee considered that the design of the study did not fulfil the study objective in line with the European Commission decision.

The stated objective was considered to adequately reflect the safety issues to be addressed with such a study, but the PRAC considered there were issues identified in the protocol regarding the design and conduct of the study that could threaten the validity of the results. 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.

In the context of the discussion, the PRAC was updated on the Scientific Advice Working Party (SAWP) advice to CHMP on other conditions of the marketing authorisations (i.e. draft protocol for an interventional study) following the completion of the referral procedure for HES solutions and at the request of the CMDh.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[20]

7.2.1. **Ruxolitinib – JAKAVI** (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002464/MEA 012
Procedure scope: Final study protocol v1.0 for study CINC424A2408 - Jakavi utilisation in major EU markets
MAH(s): Novartis Europharm Ltd

Background

Jakavi is a centrally authorised medicine containing ruxolitinib, an antineplastic agent indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia-vera myelofibrosis or post-essential-thrombocythaemia myelofibrosis.

As part of the RMP for Jakavi, there was a requirement to conduct a drug utilisation study to collect data to quantify and describe the off-label use of Jakavi in routine clinical practice in Europe. The MAH submitted a protocol for a study which was assessed by the Rapporteur.

Summary of advice

- The PRAC noted that based on the evolution of the product lifecycle to gather information on off-label use was no longer considered a public health concern. Moreover the original recommendation to perform a DUS was not driven by specific safety concerns or due to risk minimisation activities. Therefore the need for the DUS was reappraised and the PRAC concluded that a DUS should no longer be a request within the RMP and thus no further detailed comments on the protocol were pursued.
- The RMP should, at the next suitable occasion, be revised by removing this study from the pharmacovigilance plan section.

[20] 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

Post meeting note: the updated assessment report was adopted by written procedure on 29/10/2014.

7.3. Results of PASS imposed in the marketing authorisation(s)[21]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[22]

See Annex 16

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[23]

See Annex 16

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

See Annex 17

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

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.

9.2. On-going or concluded pharmacovigilance inspection

None

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

None

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

11.1. Safety related variations of the marketing authorisation

None

[21] In accordance with Article 107p-q of Directive 2001/83/EC
[22] 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
[23] In line with the revised variations regulation for any submission before 4 August 2013

11.2. Renewals of the Marketing Authorisation

None

11.3. Other requests

11.3.1. **Cabergoline** (NAP)

- PRAC consultation on PASS study results, upon Italy's request

Regulatory details:
Lead member: Jelena Ivanovic (IT)

Administrative details:
Procedure scope: Final report for the study on utilisation of cabergoline for compliance with risk minimisation activities (SUCRE) measuring
MAH(s): Pfizer Limited

Background

Cabergoline is a long-acting dopamine agonist, an ergot-derivative, indicated for the treatment of signs and symptoms of Parkinson's disease, treatment of hyperprolactinemic disorders and the inhibition of physiological lactation soon after delivery and for suppression of already established lactation.

As part of the outcome of the Article 31 referral procedure on the review of ergot-derived dopamine agonists concluded in 2008 (See EMEA/CHMP/319054/2008), an obligation for cabergoline-containing medicines to perform a study for the long term follow-up on the adherence to and effectiveness of the changes to the product information, was included as a condition of the MA for cabergoline-containing medicines. Changes to prescribing information included a warning stating that patients must be monitored for signs of cardiac valve fibrosis with echocardiography before treatment is started and regularly (every 6 months) during treatment, a reduction of the maximum recommended dose to 3 mg per day and a statement that cardiac valve fibrosis is 'a very common' side effect.

A final study report for the 'SUCRE' study, a study designed with this purpose, was submitted for assessment to the NCAs and Italy requested the PRAC to provide advice on such assessment.

Summary of advice

The PRAC concluded that the study report should address a number of clarifications on the results including the reasons for exclusion of data concerning hyperprolactinemic patients from the analysis of the study objectives, the reasons for the extension of recruitment and the centres selected, data concerning echocardiograms and the adopted statistical approach. A revised version should be provided to the NCA within 3 months. Further PRAC advice will be provided as requested.

11.3.2. **Isotretinoin** (NAP)

- PRAC consultation on risk minimisation measures, upon Netherland's request

Regulatory details:
Lead member: Sabine Straus (NL)

Administrative details:
Procedure scope: Evaluation of the results of a population-based study
MAH(s): various

Background

Isotretinoin is indicated for severe forms of acne which are resistant to adequate courses of standard therapy with systemic antibacterial and topical therapy. Isotretinoin is teratogenic and it is contraindicated in women who are pregnant. In women of childbearing potential, pregnancy should be excluded prior to start of treatment and effective contraception should be taken during therapy and 30 days after stopping treatment in order to prevent pregnancy. The need for an extensive pregnancy prevention plan (PPP) was established following an Article 29 referral procedure that received a positive Commission Decision in October 2003 (Decision (2003)3928 of 17/10/2003).

Following the presentation from the Netherlands of the results of a study accepted for publication the PRAC discussed the need to review the currently approved additional risk minimisation measures.

Summary of advice

Based on the data presented, the PRAC considered that there is a need to explore whether the awareness of the current requirements of the PPP at the level of healthcare professionals and patients could be expanded. This will be evaluated during the assessment of the effectiveness of the risk minimisation measures in the next isotretinoin PSUSA planned for submission in August 2015.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Pharmacovigilance audits and inspections

None

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

12.3.1. Union Reference Date List

- Consultation on the draft List, version October 2014

The PRAC endorsed the draft revised EURD list version October 2014 reflecting the PRAC comments impacting the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC Minutes April 2013).
Post-meeting note: following the PRAC meeting in October 2014, the updated EURD list was adopted by the CHMP at its October 2014 meeting and published on the EMA website on 4/11/2014 (see:

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

12.4. Signal Management

12.4.1. Signal Management

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

The PRAC heard a progress report of the activity of the SMART working group. The group discussed updates needed to the European pharmacovigilance issues tracking tool (EPITT) to reflect changes of the new signal assessment report template and, in the framework of the discussion of the need to develop guidance on signal detection methods and signal management aspects for medication errors, agreed to investigate which validated techniques of signal detection of medication errors are currently applied in EU Member States. Based on this feedback, the scope for guidance will be further discussed taking into account both methodological and signal management aspects relevant to the EU regulatory network.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. List of Product under Additional Monitoring

- Consultation on the draft list, version October 2014

Status: *for information*

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 29/10/2014 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.6. EudraVigilance Database

12.6.1. Activities related to the confirmation of full functionality

- Update on collaboration with WHO regarding ICSR provision

As part of the EudraVigilance (EV) functionalities adopted by the EMA Management Board in December 2013, the PRAC was updated on the current status of developing the functionality for providing ICSRs occurring in the EU to VigiBase, the database of the WHO Collaborating Centre Uppsala Monitoring Centre (UMC), in accordance with legal requirements. The EMA works with WHO and the UMC on a transfer agreement in line with the revised EV Access Policy and respecting the EU personal data protection regulation. In parallel, the technical development of the functionality is ongoing. It is aimed to sign the transfer agreement early 2015 prior to the audit of all functionalities.

At the same time, the PRAC was informed of the EMA's work on clarifying the EU reporting requirements in order to avoid interruption of donation of medicines against neglected tropical diseases used in public health programmes outside the EU.

12.7. Risk Management Plans and Effectiveness of risk Minimisations

None

12.8. Post-authorisation Safety Studies

12.8.1. Post-Authorisation Safety Studies

- Non-imposed PASS protocols – proposal for a revised process

The EMA secretariat presented a draft proposal for a revision of the assessment process for non-imposed PASS protocols. The PRAC provided comments, including elements on feasibility aspects that will be taken into account in a revised proposal to be further discussed at the level of the PRAC.

12.9. Community Procedures

None

12.10. Risk communication and Transparency

None

12.11. Continuous pharmacovigilance

None

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Blood Products Working Party

- Guideline on core SmPC for human plasma derived recombinant coagulation Factor IX products

The topic was deferred to the 3-6 November 2014 meeting.

12.13. Interaction within the EU regulatory network

None

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

None

12.15. Others

None

13. Any other business

13.1. Update on EMA Medical Literature Monitoring Service project

The EMA secretariat provided an update regarding the plans for development of the medical literature monitoring (MLM) service based on key concepts developed in partnership with stakeholders. The MLM guide (EMA/161530/2014) following release for public consultation in June 2014 is being revised based on comments received. Current discussion focuses on defining substance groups, related revisions of EudraVigilance functionalities and practical implementation for putting in place the MLM service. A pilot phase will take place in the first quarter of 2015.

13.2. New organisational model: Review of the Initial marketing authorisation applications (MAA) process

The PRAC heard a progress report on the revised process for the evaluation of initial marketing authorisation applications (MAA) conducted in the framework of the internal reorganisation of the EMA exercise 'Review and Reconnect'. Expected timelines for implementation were provided.

13.3. Marketing Authorisation Application: planned submissions for the remainder of 2014

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

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(s).

14.1.1. 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: Treatment of phototoxicity

14.1.2. Bortezomib

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

Administrative details:
Product number(s): EMEA/H/C/003984, *Generic*
Intended indication(s): Treatment of multiple myeloma

14.1.3. Duloxetine

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

Administrative details:
Product number(s): EMEA/H/C/004000, *informed consent*
Intended indication(s): Treatment of major depressive disorder, diabetic peripheral neuropathic pain, generalised anxiety disorder

14.1.4. Glycerol phenylbutyrate

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

Administrative details:
Product number(s): EMEA/H/C/003822, *Orphan*
Intended indication(s): Treatment of patients with urea cycle disorders

14.1.5. Insulin human

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

Administrative details:
Product number(s): EMEA/H/C/003858
Intended indication(s): Treatment of diabetes

14.1.6. Naltrexone, bupropion

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

Administrative details:
Product number(s): EMEA/H/C/003687
Intended indication(s): Management of obesity

14.1.7. Olaparib

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

Administrative details:
Product number(s): EMEA/H/C/003726
Intended indication: Treatment of ovarian cancer

14.1.8. Paliperidone

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

Administrative details:
Product number(s): EMEA/H/C/004066, *informed consent*
Intended indication(s): Treatment of schizophrenia in adult patients

14.1.9. Pembrolizumab

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

Administrative details:
Product number(s): EMEA/H/C/003820
Intended indication(s): Treatment of unresectable or metastatic melanoma in adults

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[24] – PRAC-led procedure

14.1.10. Desloratadine – AERIUS (CAP), AZOMYR (CAP), NEOCLARITYN (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/000313/WS0641/0077, EMEA/H/C/000310/WS0641/0080, EMEA/H/C/000314/WS0641/0075
Procedure scope: Update of the RMP (version 1.0)
MAH(s): Merck Sharp & Dohme Limited

14.1.11. Elvitegravir, cobicistat, emtricitabine, tenofovir – STRIBILD (CAP)

- Evaluation of an RMP in the context of a variation

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002574/II/0036/G
Procedure scope: Grouped variations to 1) update the RMP with information on applications recently finalised and studies recently concluded, 2) update the due date for a category 3 study (GS-US-236-0140), 3) implement the agreed change in due date for a category 3 study (GS-US-236-0141)
MAH(s): Gilead Sciences International Ltd

14.1.12. Everolimus – VOTUBIA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002311/II/0021
Procedure scope: Update of the RMP (version 8)
MAH(s): Novartis Europharm Ltd

14.1.13. Fentanyl – INSTANYL (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000959/II/0028
Procedure scope: Updated RMP to add a planned study to evaluate the effectiveness of the educational material approved in July 2013 as requested by PRAC and addition of new potential risks as requested by PRAC following the assessment of the latest PSUR and RMP
MAH(s): Takeda Pharma A/S

14.1.14. Imiglucerase – CEREZYME (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/000157/II/0087
Procedure scope: Update of the RMP to reflect the results of the THEME survey, which tested the effectiveness of the educational materials for home infusion, evaluated as PAM 40.7 and to reflect the results of the sixth annual report on the pregnancy and lactation Registry in Gaucher patients, submitted in parallel of the variation as PAM 40.8
MAH(s): Genzyme Europe BV

14.1.15. Influenza vaccine (split viron, inactivated) – IDFLU (CAP), INTANZA (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/000966/WS0638/0028, EMEA/H/C/000957/WS0638/0031
Procedure scope: Update of the RMP (version 8)
MAH(s): Sanofi Pasteur MSD SNC

14.1.16. Insulin human – INSUMAN (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/000201/II/0102
Procedure scope: Update of the RMP for Insuman implantable 400 IU/ml version 2.0
MAH(s): Sanofi-aventis Deutschland GmbH

14.1.17. Romiplostim – NPLATE (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/000942/II/0045
Procedure scope: Type II variation to remove the existing education programme (both the physician education booklet and dosing calculator) as a condition of the Nplate marketing authorisation. An updated EU RMP (version 14, dated 01 July 2014) is submitted with this variation in Module 1.8.2, in which, distribution of the education material is removed where it is specified as an additional risk minimisation activity, and is replaced by routine risk minimisation only
MAH(s): Amgen Europe B.V.

14.1.18. Teduglutide – REVESTIVE (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/002345/II/0009, *Orphan*
Procedure scope: Update of the RMP (version 6.0)
MAH(s): NPS Pharma Holdings Limited

14.1.19. Temoporfin – FOSCAN (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/000318/II/0036
Procedure scope: Submission of a new RMP (version 1.0)
MAH(s): Biolitec Pharma Ltd

14.1.20. Ulipristal – ELLAONE (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/001027/II/0033
Procedure scope: Submission of the final clinical study report (HRA 2914-012):prospective, multicentre observational study to assess clinical follow-up and outcomes of pregnancies exposed to ulipristal
MAH(s): Laboratoire HRA Pharma, SA

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

14.1.21. Adalimumab – HUMIRA (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/000481/II/0134
Procedure scope: Extension of indication to add the treatment of chronic plaque psoriasis in children and adolescents from 4 years of age, based on data from study M04-717: multicentre, randomised, double-dummy, double-blind study evaluating two doses of adalimumab versus methotrexate in paediatric subjects with chronic plaque psoriasis. As a consequence SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 of have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH proposed minor editorial changes in the SmPC and Package Leaflet. A revised RMP version 11.2 was included as part of this application
MAH(s): AbbVie Ltd.

14.1.22. Ambrisentan – VOLIBRIS (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/000839/II/0039, *Orphan*
Procedure scope: Update of SmPC section 4.4 in relation to the current recommendations for liver function and SmPC section 5.1 with data on aminotransferase abnormalities from an analysis of the CSR for PASS 'AMB110094 (VOLT)'. The current 'Health care Professional information' in Annex II has been updated accordingly as well as the Package Leaflet and RMP (revised version 6 provided)
MAH(s): Glaxo Group Ltd

14.1.23. Bedaquiline – SIRTURO (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002614/II/0002/G

Procedure scope: Grouping of 8 variations for the submission of the final report for non-clinical studies listed as category 3 in the RMP. Update of section 5.3 of the SmPC with the data from the final study report for rat carcinogenicity (TMC207-TOX9596). Submission of the final study reports for the studies 1692-0049281 (FK 10493), 1692-0049280 (FK 10497), 1692-0055447 (FK 10603), 1692-0054807 (FK 10542), 1692-0055364 (FK 10608), 1692-0055365 (FK 10641) and 1692-0055366 (FK 10604) relating to drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters. No changes to the product information are proposed based on these data
MAH(s): Janssen-Cilag International N.V.

14.1.24. Empagliflozin – JARDIANCE (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/002677/II/0002
Procedure scope: Update of SmPC section 4.5 in order to reflect the results of an in vitro study investigating the inhibition of UGT2B7, UGT1A3, UGT1A8, and UGT1A9 by empagliflozin. The RMP was updated to reflect the finalisation of the study and results
MAH(s): Boehringer Ingelheim International GmbH

14.1.25. Human fibrinogen, human thrombin – EVICEL (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/000898/II/0026
Procedure scope: RMP update
MAH(s): Omrix Biopharmaceuticals N. V.

14.1.26. Human protein C – CEPROTIN (CAP)

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000334/II/0079
Procedure scope: Update of SmPC sections 4.1, 4.2 and 5.1 in order to extend the indication to treatment of patients with Purpura fulminans due to severe acquired protein C deficiency with consequential updates of sections 4.8 and 5.2. Additionally, section 4.6 information has been revised. The PL is updated accordingly
MAH(s): Baxter AG

14.1.27. Ivacaftor – KALYDECO (CAP)

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

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:
Procedure number(s): EMEA/H/C/002494/II/0027
Procedure scope: Extension of indication to include the treatment of cystic fibrosis in patients aged 18 years and older who have a R117H mutation in the CFTR gene. Consequently, changes are proposed to SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 and to the Package Leaflet
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

14.1.28. Lamivudine, abacavir – EPIVIR (CAP), LAMIVUDINE VIIV (CAP), ZIAGEN (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000107/WS0578/0092, EMEA/H/W/000673/WS0578/0027, EMEA/H/C/000252/WS0578/0078
Procedure scope: Update of SmPC sections 4.2, 4.8, 5.1 and 5.2 to update the information related to the extension of the once-daily oral administration of abacavir, 3TC and Lamivudine ViiV to HIV-1–infected paediatric patients aged 3 months and older, according to amended weight-band ranges, based on the final clinical study report of the ARROW study. In addition, the safety, pharmacokinetic (PK) and efficacy data support harmonisation with the World Health Organization (WHO) Treatment Guidelines for dosing of ABC scored tablet and 3TC scored tablet in subjects $\geqslant$ 14 kg. The Package Leaflet is updated accordingly
MAH(s): ViiV Healthcare UK Limited

14.1.29. Nitisinone – ORFADIN (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000555/X/0041
Procedure scope: Addition of an oral suspension 4 mg/ml as additional pharmaceutical form
MAH(s): Swedish Orphan Biovitrum International AB

14.1.30. Oseltamivir – TAMIFLU (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/000402/II/0107
Procedure scope: Change of study NV20234 objectives post-authorisation measure in immunocompromised patients. Study NV20234 is a double blinded, randomized, stratified, multicentre trial evaluating conventional and double dose oseltamivir in the treatment of immunocompromised patients with influenza
MAH(s): Roche Registration Ltd

14.1.31. Pazopanib – VOTRIENT (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/001141/II/0027/G
Procedure scope: Update of SmPC sections 4.4 and 4.8 in order to update the safety information. The Package Leaflet is updated accordingly
MAH(s): Glaxo Group Ltd

14.1.32. Peginterferon alfa-2a – PEGASYS (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000395/II/0075
Procedure scope: Update of SmPC sections 4.1, 4.4 and 4.8 based on data from the long term follow up study to the paediatric study NV17424. The package leaflet is updated accordingly
MAH(s): Roche Registration Ltd

14.1.33. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) – PREVENAR 13 (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/001104/II/0111
Procedure scope: Extension of indication to add pneumonia to the authorised indication for adults (≥18 years of age), based on data from the recently completed community–acquired pneumonia immunisation trial in adults (CAPiTA), which studied the efficacy of Prevenar 13 in preventing vaccine-serotype pneumococcal community-acquired pneumonia (CAP) and vaccine-serotype invasive pneumococcal disease (IPD) in adults aged 65 years and older. As a consequence the MAH proposes to update SmPC sections 4.1, 4.8 and 5.1 and to update the Package Leaflet accordingly
MAH(s): Pfizer Limited

14.1.34. 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
Procedure scope: Evaluation 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

14.1.35. Ritonavir – NORVIR (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000127/X/0127
Procedure scope: Line extension for a new oral powder formulation as a replacement for the currently marketed oral solution for a more suitable ritonavir formulation for the paediatric population
MAH(s): AbbVie Ltd.

14.1.36. Tegafur, gimeracil, oteracil – TEYSUNO (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/001242/II/0018
Procedure scope: Update of SmPC sections 4.1, 4.2 and 5.1 in order to add the use in combination therapy of Teysuno with oxaliplatin (with or without epirubicin) with consequential updates to sections 4.3, 4.4, 4.5, 4.6, 4.8
MAH(s): Nordic Group B.V.

14.1.37. Trastuzumab – KADCYLA (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/002389/II/0006/G
Procedure scope: Grouped variation application to update 1) SmPC section 4.6 of and section 2 of the Package Leaflet in order to change the duration of contraception to be used after trastuzumab emtansine treatment from 6 to 7 months in line with the trastuzumab product information; 2) 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) due date in the RMP concerning the submission of data from the study BO25499; 4) due date in the RMP concerning the submission of data for study BO28407 (KAITLIN). A revised RMP version 4.0 has been provided as part of this application
MAH(s): Roche Registration Limited

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. Afatinib – GIOTRIF (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002280/PSUV/0004
MAH(s): Boehringer Ingelheim International GmbH

15.1.2. Alemtuzumab – LEMTRADA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/003718/PSUV/0005
MAH(s): Genzyme Therapeutics Ltd

15.1.3. Aprepitant – EMEND (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000527/PSUV/0044
MAH(s): Merck Sharp & Dohme Limited

15.1.4. Belimumab – BENLYSTA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002015/PSUV/0026
MAH(s): Glaxo Group Ltd

15.1.5. Bosutinib – BOSULIF (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002373/PSUV/0007
MAH(s): Pfizer Limited

15.1.6. Cholic acid – ORPHACOL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001250/PSUV/0004
MAH(s): Laboratoires CTRS – Boulogne-Billancourt

15.1.7. Dexmedetomidine – DEXDOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002268/PSUV/0008
MAH(s): Orion Corporation

15.1.8. Dimethyl fumarate – TECFIDERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002601/PSUV/0005
MAH(s): Biogen Idec Ltd

15.1.9. Eculizumab – SOLIRIS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000791/PSUV/0069 (with RMP version 11.0)
MAH(s): Alexion Europe SAS

15.1.10. Emtricitabine – EMTRIVA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000533/PSUV/0096
MAH(s): Gilead Sciences International Ltd

15.1.11. Enfuvirtide – FUZEON (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000514/PSUV/0042
MAH(s): Roche Registration Ltd

15.1.12. Etravirine – INTELENCE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Patrick Maison (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000900/PSUV/0038
MAH(s): Janssen-Cilag International N.V.

15.1.13. Florbetapir (^{18}F) – AMYVID (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002422/PSUV/0009
MAH(s): Eli Lilly Nederland B.V.

15.1.14. Fosaprepitant – IVEMEND (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000743/PSUV/0025
MAH(s): Merck Sharp & Dohme Limited

15.1.15. Hepatitis B vaccine (rDNA) – HBVAXPRO (CAP), NAP

- Evaluation of a PSUSA[25] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001597/201402
MAH(s): Sanofi Pasteur MSD SNC, various

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

15.1.16. Human fibrinogen, human thrombin – EVARREST (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002515/PSUV/0004
MAH(s): Omrix Biopharmaceuticals N. V.

15.1.17. Ibritumomab tiuxetan – ZEVALIN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000547/PSUV/0040 (with RMP version 4.0)
MAH(s): Spectrum Pharmaceuticals B.V.

15.1.18. Infliximab – INFLECTRA (CAP), REMSIMA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002778/PSUV/0012, EMEA/H/C/002576/PSUV/0010
MAH(s): Hospira UK Limited, Celltrion Healthcare Hungary Kft.

15.1.19. Insulin degludec – TRESIBA (CAP)
Insulin degludec, insulin aspart – RYZODEG (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002498/PSUV/0010, EMEA/H/C/002499/PSUV/0011
MAH(s): Novo Nordisk A/S

15.1.20. Ipilimumab – YERVOY (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002213/PSUV/0025
MAH(s): Bristol-Myers Squibb Pharma EEIG

15.1.21. Lapatinib – TYVERB (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000795/PSUV/0035
MAH(s): Glaxo Group Ltd

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001095/PSUV/0045
MAH(s): Novartis Vaccines and Diagnostics S.r.l.

15.1.23. Methylnaltrexone – RELISTOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000870/PSUV/0032
MAH(s): TMC Pharma Services Ltd

15.1.24. Mifamurtide – MEPACT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000802/PSUV/0037 (with RMP version9.0)
MAH(s): Takeda France SAS

15.1.25. Octocog alfa – ADVATE (CAP), NAP

- Evaluation of a PSUSA[26] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002200/201402
MAH(s): Baxter AG, various

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

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

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/001200/PSUV/0019
MAH(s): Baxter AG

15.1.27. Pegloticase – KRYSTEXXA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Administrative details:

Procedure number(s): EMEA/H/C/002208/PSUV/0004
MAH(s): Savient Pharma Ireland Ltd.

15.1.28. Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture) – VEPACEL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Administrative details:

Procedure number(s): EMEA/H/C/002089/PSUV/0010
MAH(s): Baxter Innovations GmbH

15.1.29. Raltegravir – ISENTRESS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000860/PSUV/0049
MAH(s): Merck Sharp & Dohme Limited

15.1.30. Retigabine – TROBALT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Administrative details:

Procedure number(s): EMEA/H/C/001245/PSUV/0029
MAH(s): Glaxo Group Ltd

15.1.31. Riociguat – ADEMPAS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002737/PSUV/0002
MAH(s): Bayer Pharma AG

15.1.32. Rivaroxaban – XARELTO (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000944/PSUV/0032
MAH(s): Bayer Pharma AG

15.1.33. Teduglutide – REVESTIVE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002345/PSUV/0008
MAH(s): NPS Pharma Holdings Limited

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001242/PSUV/0017
MAH(s): Nordic Group B.V.

15.1.35. Telavancin – VIBATIV (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001240/PSUV/0014
MAH(s): Clinigen Healthcare Ltd

15.1.36. Trastuzumab – HERCEPTIN (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000278/PSUV/0082
MAH(s): Roche Registration Ltd

15.1.37. Voriconazole – VFEND (CAP), VORICONAZOLE ACCORD (CAP), NAP

- Evaluation of a PSUSA[27] procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00003127/201402
MAH(s): Pfizer Limited, Accord Healthcare Limited

15.1.38. Zonisamide – ZONEGRAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000577/PSUV/0073
MAH(s): Eisai Ltd

Follow-up to PSUR procedures28

15.1.39. Aliskiren – RASILEZ (CAP)
aliskiren, amlodopine – RASILAMLO (CAP)
aliskiren, hydrochlorothiazide – RASILECT HTC (CAP

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/LEG 038, EMEA/H/C/002073/LEG 014, EMEA/H/C/000964/LEG 033
Procedure scope: MAH's response to PSUV/0090 and PSUV/0060 as adopted in April 2014
MAH(s): Novartis Europharm Ltd

[27] PSUR single assessment, referring to CAP, NAP
[28] Follow up as per the conclusions of the previous PSUR procedure, assessed outside next PSUR procedure

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

- Evaluation of an imposed PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002513/ANX 001
Procedure scope: PASS protocol P13-1 for an observational EU-based registry of men with mCRPC (therapy in men with metastatic castrate-resistant prostate cancer) to evaluate overall survival, the risk of ischemic stroke or myocardial infarction following treatment with Provenge and other identified and potential risks
MAH(s): Dendreon UK Ltd

16.1.2. Ethinylestradiol, gestodene transdermal patch (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure scope: Evaluation of a revised PASS protocol on the European active surveillance study comparing regimens of application in combined hormonal contraception (EURAS-CORA)
MAH(s): Bayer (Apleek)

16.1.3. Aliskiren – RASILEZ (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/MEA 036.1
Procedure scope: Revised PASS protocol for a non-interventional study CSPP100A2417: multi-database cohort study to assess the incidence rates of colorectal hyperplasia among hypertensive patients
MAH(s): Novartis Europharm Ltd

16.1.4. Darunavir – PREZISTA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000707/MEA 069.1

Procedure scope: Revised PASS protocol for a study to assess growth abnormalities (height) in children using Prezista in which data will be compared with data from the European pregnancy and paediatric HIV cohort collaboration (EPPICC) or other data in children on other antiretroviral(s) (ARV)
MAH(s): Janssen-Cilag International N.V.

16.1.5. 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 002.1
Procedure scope: MAH's response to the list of questions for an EU registry study to assess the safety, tolerability and effectiveness of dextromethorphan/quinidine in the treatment of pseudobulbar affect (PBA) (protocol: 13-AVR-402)
MAH(s): Jenson Pharmaceutical Services Ltd

16.1.6. Etanercept – ENBREL (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000262/MEA 156
Procedure scope: Evaluation of the proposed changes in the target number of recruited paediatric psoriasis patients for the PASS study (0081X1-4654): PURPOSE Study: long-Term, prospective, observational cohort study of the safety and effectiveness of etanercept in the treatment of paediatric psoriasis patients in a naturalistic setting
MAH(s): Pfizer Limited

16.1.7. Fenofibrate, simvastatin – CHOLIB (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002559/MEA 002.1
Procedure scope: Revised protocol for a drug utilisation research (DUR) study on the use of fenofibrate and simvastatin fixed combination: a European multinational study using secondary health records databases
MAH(s): Abbott Healthcare Products Ltd.

16.1.8. Fingolimod – GILENYA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002202/MEA 031
Procedure scope: MAH's response to CHMP's request for the update of the long term safety study CFTY720D2406, as detailed in the final assessment report of variation II/21

MAH(s): Novartis Europharm Ltd

16.1.9. Florbetapir (^{18}F) – AMYVID (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002422/MEA 002.2
Procedure scope: MAH's response to MEA-002.1 [European drug usage survey for Amyvid] as adopted in December 2013 including a revised PASS protocol (Study I6E-MC-AVBF)
MAH(s): Eli Lilly Nederland B.V.

16.1.10. Telavancin – VIBATIV (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001240/MEA 017.1
Procedure scope: Revised PASS protocol as MAH's response to MEA-017 [audit of the effectiveness of educational materials for telavancin / study CLIN_2014_TLV_003] RSI as adopted in June 2014
MAH(s): Clinigen Healthcare Ltd

16.1.11. Telavancin – VIBATIV (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number: EMEA/H/C/001240/ANX 007.2
Procedure scope: MAH's response to MEA-007.1 (pregnancy exposure registry 9809-CL-1409) as adopted in June 2014, including updated PASS protocol (9809-CL-2404)
MAH(s): Clinigen Healthcare Ltd

16.1.12. 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 256.3
Procedure scope: Revised PASS protocol as MAH's response to MEA 256.3 [HIV drug utilisation study protocol GS-EU-104-0433] following a request for supplementary information adopted at CHMP in January 2014
MAH(s): Gilead Sciences International Ltd

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

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000703/WS0643/0053 (with RMP version 8.0), EMEA/H/C/000732/WS0643/0049 (with RMP)
Procedure scope: Submission of the final pregnancy registry report in order to address PAMs MEA 65 (Gardasil) and MEA 64 (Silgard) on submission of annual pregnancy registry reports. The RMP is updated accordingly
MAH(s): Sanofi Pasteur MSD SNC (Gardasil), Merck Sharp & Dohme Limited (Silgard)

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

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/001110/II/0014/G (with RMP version 23.0)
Procedure scope: Submission of four final study reports for the fulfilment of RMP commitments and a proposal for changes in the RMP (replacement of a study and date extensions for RMP commitments listed in section III 4.3)
MAH(s): GlaxoSmithKline Trading Services

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

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000395/II/0076 (with RMP version 7.0)
Procedure scope: Submission of the final clinical study report for study MV22255 (GUARD-C) (MEA 43.1) to add safety analysis of serious adverse events (SAEs) from an international observational cohort PASS on the prediction of unwanted adverse effects in individuals infected with chronic hepatits C receiving a long acting interferon plus ribavarin. The RMP is updated accordingly
MAH(s): Roche Registration Ltd

16.1.16. Ponatinib – **ICLUSIG** (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002695/II/0012 (without RMP)
Procedure scope: Submission of a study as part of the pharmacovigilance plan to evaluate whether ponatinib is an effective treatment in patients with newly diagnosed chronic myeloid leukaemia (CML) in chronic phase
MAH(s): Ariad Pharma Ltd

16.1.17. Adalimumab - HUMIRA (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000481/MEA/046.4
Procedure scope: Fifth year interim report from a registry in Juvenile Idiopathic Arthritis (JIA) patients
MAH(s): AbbVie Ltd.

16.1.18. Adalimumab – HUMIRA (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000481/MEA 080.2
Procedure scope: First annual registry report 2014 from a long-term non-interventional registry to assess safety and effectiveness of adalimumab in paediatric patients with moderately to severely active Crohn's disease (CD) (P11-292)
MAH(s): AbbVie Ltd.

16.1.19. Canagliflozin – INVOKANA (CAP)
canagliflozin, metformin - VOKANAMET (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002649/MEA 005, EMEA/H/C/002656/MEA 004
Procedure scope: Independent data monitoring committee (IDMC) status report for the DIA3008 CANVAS study
MAH(s): Janssen-Cilag International N.V.

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 level of the PRAC without further plenary discussion.

17.1.1. Galsulfase – NAGLAZYME (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000640/S/0053 (without RMP)
MAH(s): BioMarin Europe Ltd

17.1.2. Lomitapide – LOJUXTA (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002578/S/0011 (without RMP)
MAH(s): Aegerion Pharmaceuticals Limited

17.1.3. Modified vaccinia Ankara virus – IMVANEX (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002596/S/0010 (without RMP)
MAH(s): Bavarian Nordic A/S

17.1.4. Vandetanib – CAPRELSA (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002315/R/0009 (without RMP)
MAH(s): AstraZeneca AB

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 6 - 9 October 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***
June Munro Raine	Chair	Full involvement	
Jan Neuhauser	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer Reviewer for:	aflibercept; rivaroxaban; riociguat; regorafenib; cyproterone, ethinylestradiol; ethinylestradiol, gestodene
Veerle Verlinden	Belgium	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Jana Mladá	Czech Republic	Full involvement	
Torbjörn Callreus	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Patrick Maison	France	Full involvement	
Arnaud Batz	France	Cannot act as Rapporteur or Peer Reviewer for:	paliperidone; bedaquiline; ustekinumab; etravirine; telaprevir; darunavir; canagliflozin, metformin
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
Julia Pallos	Hungary	Full involvement	
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Ruchika Sharma	Ireland	Full involvement	
Jelena Ivanovic	Italy	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Cannot act as Rapporteur or Peer Reviewer for:	fenofibrate, simvastatin
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	

PRAC member PRAC alternate	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product/substance
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Karen Pernille Harg	Norway	Full involvement	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Roxana Stroe	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Milena Radoha-Bergoč	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Julie Williams	UK	Full involvement	
Rafe Suvarna	UK	Full involvement	

Independent scientific experts nominated by the European Commission	Country	Outcome restriction following evaluation of e-DoI for the meeting:	Topics on the current Committee Agenda for which restriction applies Product/substance
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer reviewer for:	ambrisentan; pazopanib; belimumab; lapatinib; tetigabine; eltrombopag
Birgitte Keller-Stanislawski		Full involvement	
Hervé 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	
Michala Oron Lexner	Denmark	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Carine Condy	France	
Serge Bakchine	France	
Corinne Fechant	France	
Cyndie Picot	France	
Annette Viktoria Hinze	Germany	
Ineke Crijns	Netherlands	
Jan Schellens	Netherlands	
Maria Willemen	Netherlands	
Tamar Wohlfarth	Netherlands	
Charlotte Backman	Sweden	
Rebecca Chandler	Sweden	
Bertil Jonsson	Sweden	
Filip Josephson	Sweden	
Rolf Gedeborg	Sweden	
Lotta Lindqvist	Sweden	
Anna Skogh Andrén	Sweden	
Inga Bellahn	United Kingdom	
Julia Double	United Kingdom	
Sarah Mee	United Kingdom	
Karen Slevin	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

Home>About Us>Committees>PRAC Agendas, minutes and highlights