13 June 2014
EMA/PRAC/324055/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 5-8 May 2014

Chair: June Raine – Vice-Chair: Almath Spooner

Note on access to documents

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

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Explanatory notes

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

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

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

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

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as reports of adverse events from healthcare professionals or patients (so called spontaneous reports), clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
After evaluation of a safety signal the conclusion could be that the medicine caused the adverse reaction, that a causal relationship with the adverse event was considered unlikely, or that no clear answer could be given and the signal therefore is to be further investigated. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the product information (the summary of product characteristics and the package leaflet).
For completeness the information on signals is complemented, when available, by information on worldwide population exposure.

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

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

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

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

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

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk minimisation activities that have been introduced. The results of a PASS help regulatory agencies to further evaluate the safety and benefit-risk profile of a medicine already in use.

Product-related pharmacovigilance inspections
(Item 9 of the PRAC Minutes)
These are inspections carried out by regulatory agencies to ensure that marketing authorisation holders have systems in place that enable them to comply with their obligations to closely follow the safety of a medicine after authorisation.

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

The use and indications of some of the medicines mentioned as background information in the minutes is described in abbreviated form. We recommend the readers to refer to the EMA website: 'Search for medicines' to find the full product information (Summary of the Product Characteristics and Package Leaflet) of all centrally authorised medicines included.

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1. Introduction

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

The Chairperson opened the meeting, welcoming all participants to the 5-8 May 2014 meeting of the PRAC.

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

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

The PRAC Chair welcomed Leonidas Klironomos and Agni Kapou as the new member and alternate respectively for Greece and Torbjörn Callréus as the new alternate for Denmark.

1.2. Adoption of agenda for the meeting on 5-8 May 2014

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

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

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

Post-meeting note: the PRAC minutes of the meeting held on 7-10 April 2014 EMA/315293/2014 were published on the EMA website on 8 May 2014.

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

2.1. Newly triggered procedures

2.1.1. Ivabradine - **PROCORALAN** (CAP), **CORLENTOR** (CAP)

- Review of the benefit-risk balance following notification by EC of a referral under Article 20 of Reg. 726/2004, based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)
PRAC Co-rapporteur: Kirsti Villikka (FI)

Administrative details:
MAH(s): Servier
Triggering authority: EC

Background

The European Commission initiated a referral procedure on 8 May 2014 under Article 20 of Regulation (EC) No 726/2004 for a benefit-risk review of Procoralan and Corlentor, asking the EMA to give an opinion on whether the MA for Procoralan and Corlentor should be maintained, varied, suspended or withdrawn and if provisional measures were necessary to protect public health. The review was initiated following discussion at the current meeting of the PRAC on the signal of possible increased risk of cardiovascular events (see below Signals 4.1.2.) triggered by the preliminary results of a pre-specified subgroup of patients with symptomatic angina of the SIGNIFY[1] study (see EMA/280865/2014 for details).

Discussion

The PRAC noted the notification letter from the European Commission and discussed a list of questions to be addressed during the procedure as well as a timetable for conducting the review. One oral explanation took place at the meeting and the PRAC noted a proposal for risk minimisation by the MAH including a DHPC.

The PRAC also discussed whether provisional measures to protect public health were needed.
Whilst the Committee broadly supported that provisional measures were needed, the PRAC agreed that their nature should be further clarified, pending receipt of key information from the MAH and related assessment of the Rapporteur, since the current limited availability of data posed strong challenges in elaborating on options for risk minimisation.
Therefore the PRAC agreed that a written procedure would be initiated - following the conclusion of the meeting - to finalise this aspect urgently.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (published on the EMA website EMA/PRAC/281251/2014) and a timetable for the procedure (EMA/PRAC/281252/2014). Provisional measures should be agreed via written procedure following the conclusion of the meeting.

Post-meeting note: on 23/05/2014 the PRAC concluded via written procedure that based on available information, the most effective risk minimisation was targeted communication to healthcare professionals and that, at this stage of the procedure, data was insufficient to support provisional measures.
Therefore a DHPC alerting healthcare professionals to the preliminary results of the SIGNIFY study and reminding them of the existing SmPC warnings and precautions in relation to bradycardia should be distributed promptly according to an agreed communication plan.

2.2. Ongoing Procedures

2.2.1. **Methadone medicinal products for oral use containing povidone** (NAP)

- Review of the benefit-risk balance following notification by Norway of a referral under Article 107i of Directive 2001/83/EC, based on pharmacovigilance data

[1] Study assess InG the morbidity–mortality beNefits of the If inhibitor ivabradine in patients with coronarY artery disease

Regulatory details:
PRAC rapporteur: Qun-Ying Yue (SE)
PRAC Co-rapporteur: Karen Pernille Harg (NO)

Administrative details:
Procedure number: EMEA/H/A-107i/1395
MAH(s): Martindale Pharma, various

Background

A referral procedure under Article 107i of Directive 2001/83/EC is ongoing for methadone medicinal products for oral use containing povidone (see PRAC minutes 7-10 April 2014). An ad-hoc expert meeting is to be organised.

Summary of recommendation(s)/conclusions

EMA secretariat informed the PRAC of the confirmed date of the ad-hoc expert group which is to be convened on 16 June 2014 in the framework of the procedure. The PRAC agreed on the expertise required at the meeting and on a list of questions for the experts, as well as a revised timetable to take into account this step (EMA/PRAC/186319/2014 rev.1 published on the EMA website). Members were invited to propose candidates from the Member States. EMA clarified that the current provisions in terms of the handling of potential conflict of interest will be applied.

2.3. Procedures for finalisation

None

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

3.1. Newly triggered Procedures

3.1.1. **Hydroxyzine** (NAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)
PRAC Co-Rapporteur: Julia Pallos (HU)

Administrative details:
MAH(s): UCB, various
Triggering MS: HU

Background

Following discussion at the April 2014 meeting of the CMDh (see CMDh Minutes of the 22-24 April 2014 meeting) on the intention of one of the MAHs for hydroxyzine-containing medicines to submit a variation to delete two authorised indications 'preoperative anxiolysis' and 'sleep disorders', and 'anxiety' in paediatric patients and to reduce the highest recommended daily dose, the Hungarian Medicines Agency (GYEMSZI-OGYI) circulated a notification dated 25 April 2014 to initiate a referral procedure under Article 31 of Directive 2001/83/EC to review the benefit-risk of all hydroxyzine-containing medicines in all indications, assessing in particular the pro-arrhythmogenic potential of hydroxyzine.

Discussion

The PRAC noted the notification letter from the Hungarian Medicines Agency and agreed on a list of questions to be addressed during the procedure as well as a timetable for conducting the review. The PRAC also agreed that the PDCO should be consulted during the procedure and that a list of questions to the PDCO will be agreed during the June 2014 PRAC meeting.

The PRAC appointed Isabelle Robine (FR) as Rapporteur and Julia Pallos (HU) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/261900/2014) and a timetable for the procedure (EMA/PRAC/261903/2014), both published on the EMA website.

3.2. Ongoing Procedures

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

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

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

Administrative details:
Procedure number: EMEA/H/A-31/1397
MAH(s): Boehringer Ingelheim, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for ambroxol and bromhexine-containing medicines (see PRAC minutes 7-10 April 2014). A request for extension of the previously agreed timetable for providing a response to the agreed list of questions was requested by one of the MAHs involved.

Summary of recommendation(s)/conclusions

The PRAC, having taken into account the MAH's justification for an extension to the timetable, considered that it was important to proceed in accordance to the already established timelines and supported the decision to maintain the previously agreed timetable.

3.2.2. **Ponatinib - ICLUSIG** (CAP)

- Review of the benefit-risk balance following 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: EMEA/H/C/002695/A-20/0003
MAH(s): Ariad Pharma Ltd

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Iclusig (ponatinib, see PRAC minutes 2-5 December 2013). The PRAC (Co)-Rapporteurs prepared assessment reports on the responses received to the list of questions agreed by the PRAC for discussion at the meeting.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusions reached by the Rapporteurs and agreed that additional data and further analyses were needed in order to conclude on the most effective risk minimisation regarding cardiovascular events that have been noted in clinical trials, and on the overall balance of benefits and risks of use. Therefore the PRAC agreed on a list of outstanding issues to be addressed by the MAH according to a revised timetable (EMA/PRAC/746118/2013 Rev.1).

3.2.3. **Testosterone** (NAP)

- Review of the benefit-risk balance following 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: EMEA/H/A-31/1396
MAH(s): various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for testosterone-containing medicines (see PRAC minutes 7-10 April 2014). A request for extension of the previously agreed timetable for providing a response to the agreed list of questions was requested by one of the MAHs involved.

Summary of recommendation(s)/conclusions

The PRAC, having taken into account the MAH's justification for an extension to the timetable, considered that it was important to proceed in accordance to the already established timelines and supported the decision to maintain the previously agreed timetable.

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

- Review of the benefit-risk balance following notification by the UK 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: EMEA/H/A-31/1387
MAH(s): sanofi-aventis GmbH, various

Background

A referral procedure under Article 31 is ongoing for valproate and related substances (see PRAC minutes 7-10 April 2014). Following the last PRAC discussion an ad-hoc meeting with representatives of patient's organisations is being organised.

Summary of recommendation(s)/conclusions

The PRAC agreed on a list of questions to support the discussion at the meeting with representatives of patient's organisations in particular to discuss additional information from the patients' perspective on the communication, awareness and understanding of the risks of valproate use during pregnancy and in women of child bearing potential.

3.3. Procedures for finalisation

None

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

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Androgen Deprivation Therapy (ADT)** (NAPs)
Abiraterone - **ZYTIGA** (CAP); **degarelix** - **FIRMAGON** (CAP)

- Signal of QT interval prolongation due to long-term use

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

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

Background

Following discussion at the PRAC upon request of the MSs in April 2014 (see PRAC minutes April 2014), DE raised a signal concerning androgen deprivation therapy and QT interval prolongation due to long-term use concerning the whole class of GnRH analogues as well as other medicines acting on the same pharmacological pathway such as abiraterone and degarelix.

Discussion

The PRAC confirmed that published literature suggested a potential association between the use of medicinal products used for androgen deprivation therapy and QT interval prolongation, as a

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

consequence of low testosterone levels. Therefore it was agreed that the issue should be further evaluated taking into account information concerning all active substances from the same therapeutic class.

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

Summary of recommendation(s)

- The PRAC Rapporteur, with support of the EMA secretariat, should perform further analysis of the signal in order to assess whether the pharmacological mechanism - decreased testosterone and other androgens serum levels - shared by all medicinal products of the class, that could be associated with QT interval prolongation. This further analysis should include products from the ATC codes L02AE Gonadotropin releasing hormone analogues, L02BX other hormone antagonists and related agents and L02BB Anti-androgens.
- A 4 month timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. **Atazanavir – REYATAZ** (CAP)

- Signal of haemolytic anaemia

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
EPITT 17921 – New signal
MAH(s): Bristol-Myers Squibb Pharma EEIG

Background

Atazanavir is a protease inhibitor co-administered with low-dose ritonavir, which is indicated for the treatment of HIV-1-infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products.

The exposure for Reyataz, a centrally authorised medicine containing atazanavir, is estimated to have been more than 1.200.000 patients worldwide, in the period from 2003 to 2012.

During routine signal detection activities, a signal of haemolytic anaemia was identified by the EMA, based on 20 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 suspected cases of haemolytic anaemia reported and noted that the number of cases in consideration of wide population exposure of the product was low in absolute terms, however the reactions reported were serious since some patients required transfusion and in some other cases, for which information is available, patients experienced severe anaemia. Therefore the PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

- The MAH for Reyataz (atazanavir) should submit to the EMA, within 60 days, a comprehensive and detailed cumulative review of the risk of haemolytic anaemia reported in post-marketing and in clinical trials.

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

4.1.3. **Quetiapine** (NAP)

- Signal of possible misuse and abuse

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
EPITT 17960 – New signal
MAH(s): AstraZeneca, various
Leading MS: NL

Background

Quetiapine is an atypical antipsychotic agent used in the treatment of schizophrenia and bipolar disorder (both manic and depressive episodes). A pharmaceutical form of extended release quetiapine is also indicated as add-on treatment of major depressive episodes in major depressive disorder (MDD).

The exposure for nationally authorised medicines containing quetiapine is estimated to have been more than 36 million patients worldwide, in the period from first authorisation in 1997 until 2013.

A signal of possible misuse and abuse was identified by the EMA following communication with the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and an analysis conducted on EudraVigilance. NL, the Reference Member State for nationally authorised medicines containing quetiapine (originator) confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the suspected cases reported and noted that literature data suggested there might be a divergent risk between abuse in poly-drug users - who may use quetiapine to counteract the effect of other substances that are used and drug-seeking behaviour – and in psychiatric patients seeking a higher dose for its sedative effects to counteract symptoms of insomnia and agitation (misuse). The PRAC agreed that it was useful to further review the evidence available and to require more information.

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

Summary of recommendation(s)

- The MAH for Seroquel (quetiapine) should provide to the PRAC Rapporteur in the next PSUR (DLP 31/07/2014) answers to a list of questions including a cumulative review of the reports of misuse and abuse and exposure data for both the immediate release (IR) and the extended release (XR) formulations.
- The PRAC Rapporteur will inform the PRAC of the conclusion of this review.

4.1.4. **Temozolomide – TEMODAL** (CAP)

- Signal of diabetes insipidus

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
EPITT 17951 – New signal
MAH(s): Merck Sharp & Dohme Limited

Background

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

The exposure for Temodal a centrally authorised medicine containing temozolomide, is estimated to have been more than 530,000 patients worldwide, in the period from first authorisation until 2012.

During routine signal detection activities, a signal of diabetes insipidus was identified by the EMA, based on 13 cases retrieved from EudraVigilance reporting diabetes insipidus and related terms. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported and noted a recently published article on the subject[3] describing a case series showing, from the first administration to the onset of signs and symptoms, a mean time of 2-3 months. Some cases reported information on positive dechallenge and the suggestion for an association was provided by the alleviation of symptoms after treatment with a diabetes insipidus medication, exclusion of alternative aetiologies in some cases, the absence of confounding medication in some other cases and close temporal relationship. Therefore PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

- The MAH for temozolomide (Temodal) should submit to the EMA, a cumulative review of all potential cases of this ADR within the next PSUR (DLP 12/07/2014). This review should include all cases of spontaneous origin, clinical trials and the literature, the outcomes of the cases and their CIOMS forms.

4.2. New signals detected from other sources

4.2.1. Bisphosphonates (CAP, NAP): **alendronate** (NAP), **risedronate** (NAP); **alendronate, colcalciferol – ADROVANCE** (CAP), **FOSAVANCE** (CAP)**, VANTAVO** (CAP); **strontium ranelate – OSSEOR** (CAP), **PROTELOS** (CAP)

- Signal of heart valves disorders

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 13832 – New signal
Leading MS: SE, UK
MAH(s): Merck Sharp & Dohme Limited (Adrovance, Fosavance, Vantavo), Les Laboratoires Servier (Osseor, Protelos), various

[3] Faje AT, Nachtigall L, Wexler D, Miller KK, Klibanski A, Makimura H. Central diabetes insipidus: a previously unreported side effect of temozolomide. J Clin Endocrinol Metab. 2013;98(10):3926-31.

Background

Bisphosphonates and other substances like strontium ranelate are used to prevent the loss of bone mass and decrease the risk of fracture due to various conditions including osteoporosis.

In 2010 a cohort study was published which reported that nitrogen-containing bisphosphonate therapy was associated with an increased prevalence of cardiovascular calcification in women less than 65 years of age and decreased prevalence of cardiovascular calcification in women aged 65 years of age or above[4] .

A signal of disproportionate reporting of heart valve disorders/calcification associated with the use of bisphosphonates (zoledronate, alendronate, ibandronate and pamidronate) was also observed in EudraVigilance and this signal led to review of the available data and previous discussions by the Pharmacovigilance Working Party (PhVWP).

Given the number of both active substances and MAHs involved, the EMA commissioned a signal strengthening study on the risk of cardiac valve disorders associated with the use of bisphosphonates. A further observational study with a nested case-control design was performed, the results of which are now available. UK confirmed this as a signal for prioritisation by the PRAC[5].

Discussion

The PRAC discussed the results of this large study including data from 6 databases (approximately 30 million patients) over 3 countries which applied a common data extraction protocol and study design. Potential confounders, including a range of co-morbidities, were adjusted for. Within the sub-population of new users of bisphosphonates an increased risk of cardiac valve disorders was found in current users of bisphosphonates compared to distant past users (OR=1.18, 95% CI: 1.12-1.23). Similar increased risks were found specifically for alendronate and risedronate. Within the extended sub-population of users of all anti-osteoporosis drugs an increased risk of cardiac valve disorders was found for current users of alendronate, risedronate, and strontium ranelate. The study found no increased risk of cardiac valve disorders with increased duration of treatment. The PRAC discussed some limitations of the study but agreed that it needed to be further reviewed.

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

Summary of recommendation(s)

- A review of the study results and the relevant literature published since the last review by PhVWP should be conducted by the PRAC Rapporteur.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation on the need to seek further information and/or clarification from the study investigators and also on whether, in light of these data and the published literature, there were questions that should be taken forward with the relevant MAHs.

4.2.2. Ivabradine – **CORLENTOR** (CAP), **PROCORALAN** (CAP)

- Signal of cardiovascular risk

[4] Elmariah S et al. Bisphosphonate Use and Prevalence of Valvular and Vascular Calcification in Women MESA (The Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2010 Nov 16;56(21): 1752-9
[5] Preciosa M. Coloma, Maria de Ridder, Gianluca Trifirò, Miriam Sturkenboom. 2014. Risk of cardiac valve disorders associated with the use of bisphosphonates. (Results not yet published). Tender ID: EMA/2011/39/CN BISPHOSPHONATES (ENCePP/SDPP/2616).

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

Administrative details:
EPITT 17961 – New signal
Leading MS: NL
MAH(s): Les Laboratoires Servier

Background

Ivabradine is a heart rate lowering agent, used in the treatment of coronary-artery disease and of chronic heart failure in selected patients.

The exposure for Procoralan and Corlentor, centrally authorised medicine containing ivabradine, is estimated to have been more than 1.5 million patient-years worldwide, in the period from first authorisation in 2005 to October 2013.

A signal of cardiovascular risk was identified by the NL, following notification by the MAH of preliminary results in a subpopulation of angina patients in the treatment groups of the SIGNIFY study. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the preliminary results of the study and an oral explanation of the MAH took place at the meeting.

The SIGNIFY trial is an international, multicentre, randomised, double-blind, parallel-group, placebo-controlled, event-driven study in patients with stable CAD (coronary artery disease), LVEF (left ventricular ejection fraction) above 40% and HR (heart rate) >70bpm. The therapeutic scheme used is different than recommended in the SmPC, with higher doses of ivabradine (starting dose 7.5 mg b.i.d. or 5 mg b.i.d if age > 75 year and maintenance dose up to 10 mg b.i.d).

In a pre-specified subgroup of symptomatic angina patients (CCS Class II or more) (n=12049), a statistically significant increase in the primary composite endpoint (PCE) of cardiovascular deaths and non-fatal MI was observed: hazard ratio (HR) 1.18, 95% CI [1.03–1.35], p=0.018. Similar trends were observed in the components of the PCE, with a non-statistically significant difference between treatment groups in cardiovascular deaths and non-fatal MI.

The PRAC agreed that the SIGNIFY study showed a modest but consistent increase of cardiovascular risk in a pre-specified subgroup of patients with symptomatic angina using ivabradine with a different therapeutic scheme and agreed that in depth prompt review was warranted (see above 2.1.1.)

Summary of recommendation(s)

- A full benefit-risk review should be undertaken for ivabradine-containing medicines in their authorised indications.

See above 2.1.1.

4.2.3. **Valproic acid** (NAP)

- Signal of mitochondrial toxicity

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
EPITT 17956 – New signal
Leading MS: DE
MAH(s): Sanofi- Aventis, Neuraxpharm Arzneimittel GmbH, various

Background

Valproate is a well-known anti-epileptic substance. In most EU Member States nationally authorised medicines containing valproate (as valproic acid, sodium valproate and, valproate semisodium) are also authorised for the treatment of patients with bipolar disorder. In some Member States valproate-containing medicines are also approved for the prophylactic treatment of migraine.

A signal of mitochondrial toxicity in association with valproate had been received by the German Agency from a MAH of generic valproate-containing products. The signal included 10 case reports identified in the literature describing a temporal association between the administration of valproate and the unmasking of mitochondrial disorders (MID) or aggravation of symptoms in patients suffering from MIDs. DE confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

MIDs are predominantly but not exclusively due to dysfunction of the respiratory chain, which is more frequently inherited than acquired. Epilepsy is a frequent central nervous system (CNS) manifestation of MIDs.

Comparative studies of the safety of antiepileptic drugs revealed that adverse effects on the respiratory chain and other mitochondrial functions or structures differ between the most commonly used drugs. In these studies, valproate was the compound with the greatest potential to interfere with mitochondrial pathways. This suggested that valproic acid should only be the last option to treat epilepsy in patients with MID. The PRAC acknowledged that the current product information did not include warnings/contraindications for use of valproic acid in patients with MIDs and concluded that further investigation was warranted.

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

Summary of recommendation(s)

- The MAH for the innovator valproate medicines (Depakine, Epilim) should submit within 90 days to the PRAC Rapporteur a review of mitochondrial toxicity following the administration of valproate and the MAH should propose wording to be included in the product information as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. **Azithromycin** (NAP)

- Signal of potentially fatal heart events

Regulatory details:
PRAC Rapporteur: Terhi Lehtinen (FI)

Administrative details:
EPITT 16156 – Follow up October 2013

MAH(s): Pfizer, various

Background

For background information, see PRAC minutes of 7-10 October 2013.

The MAH submitted as requested the expert review of the data in the randomised, controlled clinical trials to address the issue of the long-term safety of azithromycin and ischemic cardiovascular events and these data were assessed by the Rapporteur.

Discussion

The PRAC acknowledged the conclusion of the assessment that the collated data from randomised clinical trials neither confirmed nor refuted the association between azithromycin and harmful cardiac affects and further information may be available upon completion of an ongoing observational study.

The MAH emphasised a new publication by Rao et al, 2014 on the use of azithromycin and levofloxacin and increased risk of cardiac arrhythmia and death. The PRAC agreed that although the study suggested a possible association between azithromycin and increased cardiac mortality it did not provide robust evidence to confirm a causal association. However, the PRAC will evaluate the MAH's review of the mentioned literature article once this is submitted by the MAH in May 2014.

Overall the PRAC agreed that there were outstanding uncertainties arising from the analysed evidence but noted that further information will be sought through observational research.

As highlighted in previous PRAC recommendations, the observational study should include an analysis of other non-cardiac causes of death. Relevant updates of the product information should be considered upon completion of the observational study or if new data becomes available.

Summary of recommendation(s)

- The MAHs for the originator azithromycin containing products Zithromax and Zithromax IV, should submit to the PRAC Rapporteur by 31 May 2014 a review of the new publication by Rao et al (2014).
- The PRAC should be kept informed if the plan for the development of the observational study needs to be modified in the future.

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

- Signal of accidental exposure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
EPITT 17778 – Follow up April 2014
MAH(s): Janssen-Cilag, various

Background

For background information, see PRAC minutes of 7-10 April 2014.

In line with the PRAC recommendations the MAH proposed an improved wording for the product information and a proposal for a DHPC that were assessed by the Rapporteur.

Discussion

The PRAC supported the core messages of the DHPC informing healthcare professionals that cases of accidental exposure to transdermal fentanyl in non-patch wearers, especially children, continued to be reported.

To prevent potential life-threatening harm from accidental exposure to fentanyl, healthcare professionals are reminded of the importance to provide clear information to patients and caregivers regarding the risk of accidental patch transfer, accidental ingestion of patches and the need for appropriate disposal of patches.

Summary of recommendation(s)

- The PRAC agreed the core information to be included in a direct healthcare professional communication, which should be implemented according to the agreed communication plan with the MAH for Durogesic (fentanyl patch).
- Regarding the best distribution options the PRAC suggested that all concerned MAHs will be encouraged to collaborate so that a single DHPC is prepared and circulated in each Member State. The originator company (where available) in each Member State is encouraged to act as the contact person with the national competent authority, on behalf of the other concerned MAHs in the same Member State.

4.3.3. **Fluticasone furoate - AVAMYS** (CAP)

- Signal of oral and upper respiratory fungal infection

Regulatory details:
PRAC Rapporteur: Adam Przybylkowski (PL)

Administrative details:
EPITT 17769 – Follow up January 2014
MAH(s): Glaxo Group Ltd

Background

For background information, see PRAC minutes 6-9 January 2014.

The MAH replied to the request for information on the signal of oral and upper respiratory fungal infections and the responses were assessed by the Rapporteur.

Discussion

The PRAC noted that literature review did not provide strong evidence for an association between fluticasone furoate and oral or upper respiratory fungal infections given that there were only a few published case reports concerning a possible association between nasal corticosteroids and oral and upper respiratory fungal infections and no report published in the literature that referred to fluticasone furoate. There were published data for inhaled corticosteroids and fungal infections and the mechanism of action of corticosteroids seemed plausible; however this was not clearly reported in the literature reviewed.

An observational analysis in commercial claims Medicare Database suggested that the use of concomitant corticosteroids appears to influence the risk of developing oral or oesophageal candidiasis and other fungal infections. The majority of the suspected reported cases were poorly documented.

Therefore the PRAC agreed that the data reviewed did not provide particularly strong evidence for a specific association between intranasal fluticasone furoate and oral and upper respiratory fungal infections. However, the issue of oral and upper respiratory fungal infections as well as oesophageal fungal infections associated with the use of intranasal fluticasone furoate should be kept under monitoring with particular attention to the body of evidence concerning the pharmacological class.

Summary of recommendation(s)

- Current product information for Avamys (fluticasone furoate) was considered to be still appropriate.
- However, the MAHs for Avamys (fluticasone furoate) should keep the signal of upper respiratory fungal infections as well as oesophageal fungal infections under close monitoring and this should be reviewed in the coming periodic safety update reports.

4.3.4. Leuprorelin, suspension for injection (NAP)

- Signal of medication error - wrong technique in drug usage process

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
EPITT 17753 – Follow up January 2014
MAH(s): Astellas, various

Background

For background information, see PRAC minutes of 6-9 January 2014.

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

Discussion

The PRAC noted that all safety information received relating to the signal of medication error described with Eligard had been reviewed. The cumulative review of cases reporting a medication error event revealed a variety of errors during the prescription, preparation, mixing and the administration of the product.

The additional information received from the MAH included proposed risk minimisation measures to correct the risk of erroneous administration, which as demonstrated by some case reports was suspected to have led to some under dosage. The PRAC discussed the potentially serious clinical consequences of inadvertent underdosing considering the population and therapeutic context for the use of the product. The MAH proposed to undertake additional actions to mitigate the risk of medication errors specifically in France, due to the high reporting level of errors compared with the rest of the world. These risk minimisation measures include education and information tools.

The PRAC agreed that, in the interim, communication to healthcare professionals should be progressed promptly. A new presentation for Eligard with fewer and easier handling steps would be desirable. Furthermore more information on the modalities of administration of Eligard (HCP or the patient) in the different MSs of the EU for the various strengths available would be needed to conclude on appropriate risk minimisation to address the signal.

Summary of recommendation(s)

- The MAH for the nationally authorised leuprorelin containing product[6] Eligard should submit a proposal of risk minimisation measures with a Direct Healthcare Professional Communication and a communication plan to inform healthcare professionals (HCPs) about the correct product reconstitution and administration and about the importance of the different steps. These measures should be accompanied by a draft study protocol to assess their effectiveness. In parallel the MAH is asked to consider the development of an improved presentation which would facilitate fewer and easier handling steps. Further information on population exposure and usage should be provided.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.5. **Paracetamol** (NAP)

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

Regulatory details:
PRAC Rapporteur: Veerle Verlinden (BE)

Administrative details:
EPITT 17796 – Follow up February 2014
MAH(s): Bayer Pharma AG, various

Background

For background information, see PRAC minutes 3-6 of February 2014.

The Rapporteur performed a review of the study recently published, and of relevant preclinical data, on the effect of paracetamol on neurodevelopment. The authors of the study that triggered this signal had also provided further clarification to the Rapporteur.

Discussion

The PRAC discussed the findings of the review of observational data including recently available studies[7] as well as preclinical data and discussed their strengths and limitations. The PRAC concluded that a causal relationship between paracetamol exposure during pregnancy and neurodevelopmental disorders cannot be established. The current guidance that paracetamol can be used during pregnancy if clinically needed remains valid, however, as with any medicine, it should be used at the lowest effective dose for the shortest possible time.

Summary of recommendation(s)

- Current evidence is insufficient to support the conclusion of an association between paracetamol exposure in pregnancy and neurodevelopmental effects.

[6] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to
[7] Brandlistuen et al. Int J Epidemiol. 2013;42(6):1702-13, Liew et al. JAMA Pediatr. 2014;168(4):313-20

4.3.6. Sitagliptin – **JANUVIA** (CAP), **RISTABEN** (CAP), **TESAVEL** (CAP), **XELEVIA** (CAP); **Sitagliptin**, **metformin – EFFICIB** (CAP), **JANUMET** (CAP), **RISTFOR** (CAP), **VELMETIA** (CAP); **Angiotensin-converting enzyme (ACE) inhibitors** (NAP)

- Signal of angioedema due to interaction between sitagliptin and ACE inhibitors

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

Administrative details:
EPITT 17608 – Follow up December 2013
MAH(s): Merck Sharp & Dohme Ltd, various

Background

For background information, see PRAC minutes of 2-5 December 2013. The MAH replied to the request for information on the signal of angioedema due to an interaction between sitagliptin and ACE inhibitors and the responses were assessed by the Rapporteur.

Discussion

Regarding the methodology of the meta-analysis of clinical trials previously discussed by the PRAC, information was provided regarding the exclusion criteria and sensitivity analyses performed. Angioedema is a known adverse drug reaction of both sitagliptin and ACE-inhibitors. The incidence rates observed following sensitivity analyses were comparable with those reported in the initial analysis and did not show any increased risk of angioedema during concomitant administration of sitagliptin and ACE inhibitors.
The analysis of these data showed similar incidence rates of angioedema in patients treated with sitagliptin with or without concomitant treatment with an ACE inhibitor.
Regarding a further review of the post-marketing spontaneous case reports, a diagnosis of angioedema cannot be inferred from the limited information available in the cases. Regarding the pharmacokinetic mechanism of interaction it was explained that there is no relevant potential for sitagliptin to increase ACE inhibitors levels through an interaction via human Organic Anion Transporter 3 (OAT3), as previously hypothesised. Furthermore, a PK interaction through OAT3 is unlikely to be causally linked to an increased risk of angioedema.

Summary of recommendation(s)

- Current evidence does not indicate an increased risk of angioedema for patients due to concomitant use of sitagliptin and ACE inhibitors. No other regulatory action except routine pharmacovigilance is necessary at the moment.

4.3.7. **Tiotropium bromide** (NAP)

- Signal of increased mortality from cardiovascular disease and all-cause mortality – results of TIOSPIR[8] trial

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
EPITT 17406 – Follow up December 2013
MAH(s): Boehringer Ingelheim Limited, various

[8] Tiotropium Safety and Performance in Respimat

Background

For background information, see PRAC minutes of 13-16 May 2014.

The MAH for Spiriva Respimat (tiotropium bromide solution for inhalation) submitted the results of further analysis of the Tiotropium Safety and Performance in Respimat (TIOSPIR) study to the Rapporteur as previously requested by the PRAC.

Discussion

The PRAC noted that based on the further analysis received it became apparent that in the TIOSPIR study similar proportions of patients within each treatment group had cardiac disorders at baseline. No increased risk of all-cause mortality was observed with any treatment in the subgroup of patients with cardiac disorders at baseline and, similarly, no increased risk of fatal cardiac events. Based on the analysis received, a history of cardiac disorder would not seem to be a predictive factor for future MI in patients treated with 'Respimat' compared with 'Handihaler' and the overall risk of MI would not be affected by the history of cardiac disorder, although the number of MI cases was low.
Given the evidence reviewed so far it was possible to conclude that the higher risk of fatal MI observed in TIOSPIR trial for Respimat most likely reflected variability of rare events.

The PRAC noted that the evaluation of a variation to update the product information of Spiriva (tiotropium) Respimat with the results of the TIOSPIR trial is ongoing and will include the most recent findings.

Summary of recommendation(s)/conclusion

- The available evidence from the TIOSPIR trial showed no difference in the overall or cardiovascular mortality between tiotropium Respimat and Handihaler in patients with and without baseline cardiac disorders or cardiac arrhythmia. Given that a variation is ongoing to fully reflect the study results in the product information no other additional regulatory action is considered necessary at this time.

For the full PRAC recommendations, see EMA/PRAC/272621/2014 published on the EMA website.

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

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

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

5.1.1. 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: Treatment of obesity

5.2. Medicines already authorised

RMP in the context of a variation[9] – PRAC-led procedure

See Annex 14.2

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

5.2.1. Alogliptin – VIPIDIA (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/002182/II/0001
Procedure scope: Update of SmPC sections 4.2, 4.4, 4.8, and 5.1 to reflect results of study 402, a phase 3b, randomized, double-blind, placebo-controlled, event-driven study, designed to demonstrate that no excess risk of a major adverse cardiovascular event (MACE) exists following treatment with alogliptin compared with placebo when added to standard of care in adults with T2DM and acute coronary syndrome (ACS)
MAH(s): Takeda Pharma A/S

Background

Vipidia is a centrally authorised medicine containing alogliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, indicated in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

The CHMP is evaluating a type II variation procedure for Vipidia, to include information from the results of study 402 (phase 3b, randomized, double-blind, placebo-controlled, event-driven study, designed to demonstrate that no excess risk of a major adverse cardiovascular event (MACE) exists following treatment with alogliptin compared with placebo when added to standard of care in adults with T2DM and acute coronary syndrome (ACS)). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 6 for Vipidia (alogliptin) in the context of the variation under evaluation by the CHMP was considered acceptable pending finalisation of the variation procedure by the CHMP.

5.2.2. Alogliptin, pioglitazone – INCRESYNC (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/002178/II/0002

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

Procedure scope: Update of SmPC sections 4.4 and 4.8 to reflect results of study 305, a phase 3, randomized, double-blind, active-controlled, 2-year study, designed to assess the efficacy and safety of alogliptin in combination with metformin compared with glipizide in combination with metformin in adults with type 2 diabetes mellitus
MAH(s): Takeda Pharma A/S

Background

Incresync is a centrally authorised medicine containing the combination of alogliptin and pioglitazone used as a second- or third-line treatment in adult patients aged 18 years and older with type-2 diabetes mellitus in selected patients.

The CHMP is evaluating a type II variation procedure for Incresync, to reflect results of study 305, a phase 3, randomized, double-blind, active-controlled, 2-year study, designed to assess the efficacy and safety of alogliptin in combination with metformin compared with glipizide in combination with metformin in adults with type 2 diabetes mellitus. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 6 for Incresync (alogliptin, pioglitazone) in the context of the variation under evaluation by the CHMP was considered acceptable provided some sections are amended before finalisation of the variation procedure by the CHMP.
- No new safety concerns were identified with the studies. Therefore areas of missing information should then be updated and the studies should be removed from the RMP.
- The safety concerns in the RMP for alogliptin-containing products should be reflected consistently. The MAH should include "Patients requiring renal or peritoneal dialysis", should re-include "Patients with severe hepatic impairment", and add "Patients with severe heart failure (NYHA class IV)" among the safety concerns.

5.2.3. Alogliptin – VIPIDIA (CAP)
alogliptin, metformin - VIPDOMET (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/002182/WS0520/0002, EMEA/H/C/002654/WS0520/0001
Procedure scope: Update of SmPC sections 4.4, 4.8, and 5.1 to reflect results of study 305, a phase 3, randomized, double-blind, active-controlled, 2-year study, designed to assess the efficacy and safety of alogliptin in combination with metformin compared with glipizide in combination with metformin in adults with type 2 diabetes mellitus
MAH(s): Takeda Pharma A/S

Background

Vipidia is a centrally authorised medicine containing alogliptin, a dipeptidyl peptidase 4 (DPP-4)inhibitor, indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Vipidomet is a combination product containing alogliptin and metformin indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients, inadequately controlled on their maximal

tolerated dose of metformin alone, or those already being treated with the combination of alogliptin and metformin as well as in other Type II diabetes mellitus therapeutic regimens.

The CHMP is evaluating a type II variation procedure for Vipidia and Vipidomet, to reflect results of study 305, a phase 3, randomized, double-blind, active-controlled, 2-year study, designed to assess the efficacy and safety of alogliptin in combination with metformin compared with glipizide in combination with metformin in adults with type 2 diabetes mellitus. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 6 for Vipidia (alogliptin) and Vipdomet (alogliptin, metformin) in the context of the variation under evaluation by the CHMP was considered acceptable pending finalisation of the variation procedure by the CHMP.

5.2.4. Alogliptin, pioglitazone – INCRESYNC (CAP)
alogliptin, metformin - VIPDOMET (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/002178/WS0519/0003, EMEA/H/C/002654/WS0519/0003
Procedure scope: Update of SmPC sections 4.4, 4.8, and 5.1 to reflect the results of study 402, a phase 3b, randomized, double-blind, placebo-controlled, event-driven study, designed to demonstrate that no excess risk of a major adverse cardiovascular event (MACE) exists following treatment with alogliptin compared with placebo when added to standard of care in adults with type 2 diabetes mellitus and acute coronary syndrome (ACS)
MAH(s): Takeda Pharma A/S

Background

Incresync is a centrally authorised medicine containing the combination of alogliptin and pioglitazone used as second- or third-line treatment in adult patients aged 18 years and older with type-2 diabetes mellitus in selected patients.

Vipdomet is a combination product containing alogliptin and metformin indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients, inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of alogliptin and metformin as well as in other Type II diabetes mellitus therapeutic regimens.

The CHMP is evaluating a type II variation procedure for both products, to include information from the results of study 402 (a phase 3b, randomized, double-blind, placebo-controlled, event-driven study, designed to demonstrate that no excess risk of a major adverse cardiovascular event (MACE) exists following treatment with alogliptin compared with placebo when added to standard of care in adults with T2DM and acute coronary syndrome (ACS)). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 6 for Vipdomet (alogliptin, metformin) and for Incresync (alogliptin, pioglitazone) in the context of the variation under evaluation by the CHMP was considered

acceptable provided some requests for amendments agreed by the PRAC are addressed before finalisation of the procedure at CHMP level.

5.2.5. Saxagliptin – ONGLYZA (CAP)
saxagliptin, metformin - KOMBOGLYZE (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/002059/WS0529/0014/G, EMEA/H/C/001039/WS0529/0024/G
Procedure scope: Update of SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1 of Onglyza and Komboglyze, respectively, with regard to information from the results from study D1680C00003 (SAVOR), a cardiovascular outcome study, and study D1680L00002 (GENERATION), a study comparing saxagliptin with glimepiride in elderly patients
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

Background

Komboglyze and Onglyza are two centrally authorised antidiabetic medicines containing saxagliptin dipeptidyl peptidase-4 (DPP-4) inhibitor and saxagliptin in combination with metformin used in the treatment of Type II diabetes mellitus as monotherapy and as dual or triple oral therapy in selected patients.

The CHMP is evaluating a type II variation procedure for Komboglyze and Onglyza, to include updates to the product information and to the RMP necessary following completion of the SAVOR[10] and GENERATION[11] studies. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the respective RMPs to support this variation.

Summary of advice

- The RMP version 5 for Onglyza (saxagliptin) Komboglyze (saxagliptin, metformin) in the context of the variation under evaluation by the CHMP was considered acceptable provided that some modifications are implemented before finalisation of the variation procedure by the CHMP. The protocol for the planned pharmacoepidemiology study should be provided and the important potential risks 'skin lesions' and 'opportunistic infections' should remain included in the RMP. The PRAC agreed that cardiac failure' should also be included as an important potential risk.

RMP evaluated in the context of a PSUR procedure

See also Alglucosidase alfa (MYOZYME) under 2.1.1. ; Dapagliflozin (FORXIGA) under 2.1.7. ; Decitabine (DACOGEN) under 6.1.3. ; Doripenem (DORIBAX) under 2.1.8. ; Micafungin (MYCAMINE) under 2.1.18. ; Pyronaridine, artesunate (PYRAMAX) under 2.1.25. ; Regadenoson (RAPISCAN) under 6.1.12. ; Sodium oxybate (XYREM) under 2.1.27. ; Thalidomide (THALIDOMIDE CELGENE) under 2.1.29.

[10] Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus
[11] Saxagliptin Compared to Glimepiride in Elderly Type 2 Diabetes Patients, With Inadequate Glycemic Control on Metformin

RMP evaluated in the context of PASS results

See also Pioglitazone (ACTOS, GLUSTIN), pioglitazone combinations (COMPETACT, GLUBRAVA, TANDEMACT) under 3.4.2.

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

5.2.6. Dronedarone – MULTAQ (CAP)

- Evaluation of an RMP in the context of a 5-renewal of the marketing authorisation

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

Administrative details:
Procedure number(s): EMEA/H/C/001043/R/0030 (with RMP version 9.0)
MAH(s): Sanofi-aventis groupe

Background

Dronedarone is an antiarrhythmic indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF).

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP in the context of the 5 year-renewal of the marketing authorisation(s) for Multaq, a centrally authorised product containing dronedarone.

Summary of advice

- The updated RMP version 9.0 for Multaq (dronedarone) was considered acceptable.
- Based on the review of the available pharmacovigilance data for Multaq and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation was warranted based on the prior Article 20 referral that restricted the indication and the implementation of additional risk minimisation measures. This advice is supported by the need to assess the effectiveness of the risk minimisation measures implemented.

RMP in the context of a stand-alone RMP procedure

See Annex 14.2

Others

Bisphosphonates, denosumab and risk of osteonecrosis of the jaw (ONJ): consultation with Healthcare Healthcare Professionals Working Group (HPWG) and Patients and Consumers Working Party (PCWP), see under 12.12.1.1.

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[12]

6.1.1. **Abiraterone – ZYTIGA** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002321/PSUV/0019 (without RMP)
MAH(s): Janssen-Cilag International N.V.

Background

Abiraterone is an androgen biosynthesis inhibitor indicated in combination for the treatment of metastatic castration resistant prostate cancer in adult men under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zytiga, a centrally authorised medicine containing abiraterone, 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 Zytiga (abiraterone) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add myocardial infarction as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[13].

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

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000697/PSUV/0023 (without RMP)
MAH(s): RB Pharmaceuticals Ltd.

[12] 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
[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.

Background

Buprenorphine/naloxone used in combination is indicated for the substitution treatment for opioid drug dependence under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Suboxone, a centrally authorised medicine containing buprenorphine/naloxone, 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 Suboxone (buprenorphine/naloxone) 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 on the need to upgrade the current warning on drug-drug interaction with naloxone to a contraindication, taking into account that the product information already recommends against this concomitant use, to avoid severe withdrawal syndromes associated with buprenorphine. The MAH should also include a proposal for an update of the product information, taking into consideration the existing labelling in the product information for naltrexone- and nalmefene-containing products as well as the ongoing variation procedure for buprenorphine (Subutex (FR/H/1047/1-3/II/038)). In addition, the MAH should provide a detailed analysis of cases of misuse and abuse associated with buprenorphine/naloxone, including information on the used route of administration. Finally, the MAH should provide a detailed analysis of EU cases of medication errors and propose risk minimisation measures as warranted.

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

6.1.3. Decitabine – DACOGEN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002221/PSUV/0011 (with RMP version 3.0)
MAH(s): Janssen-Cilag International N.V.

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dacogen, a centrally authorised medicine containing decitabine, 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 Dacogen (decitabine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add enterocolitis including neutropaenic colitis and caecitis with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should provide a detailed review of cases of fatigue, peripheral oedema and cardiomyopathy and propose to update the product information as warranted.

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

6.1.4. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type b conjugate vaccine (adsorbed) – **HEXACIMA** (CAP), **HEXAXIM** (Art 58), **HEXYON** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002702/PSUV/0006, EMEA/H/W/002495/PSUV/0015, EMEA/H/C/002796/PSUV/0006 (without RMP)
MAH(s)/Scientific Opinion Holder(s): Sanofi Pasteur

Background

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type b conjugate vaccine (adsorbed) (DTaP-IPV-HB-Hib) is indicated for primary and booster vaccination of infants and toddlers from six weeks to 24 months of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae type b* (Hib).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Hexacima, Hexaxim and Hexyon, DTaP-IPV-HB-Hib vaccines, and issued a recommendation on their marketing authorisation(s)/scientific opinion.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Hexacima, Hexaxim and Hexyon (DTaP-IPV-HB-Hib vaccines) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s)/scientific opinion(s) should be maintained.

The PRAC discussed an increased rate of complaints related to a sluggish plunger or increased pressure needed while using the vaccine pre-filled syringes. The MAH clarified that some modification of the syringe design is ongoing and the first batches implementing this change are expected in early 2015. Since the vaccine is marketed so far in three Member States only and all cases were reported in

[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.

Germany, the PRAC considered that at present, there was no need to distribute an EU-wide DHPC to provide recommendations on how to use the syringe to avoid potential cases of under-dosing. Instead, communication will be agreed at national level.

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. Exenatide – **BYDUREON** (CAP), **BYETTA** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002020/PSUV/0018, EMEA/H/C/000698/PSUV/0042 (without RMP)
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bydureon and Byetta, centrally authorised medicines containing exenatide, and issued a recommendation on their 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 Bydureon and Byetta (exenatide) in the approved indication(s) remains favourable.
- With regard to exenatide twice daily (Byetta), the current terms of the marketing authorisation(s) should be maintained.
- With regard to exenatide once weekly (Bydureon), the product information should be updated to add injection site abscess and cellulitis as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should provide a detailed review of cases of increased liver enzymes and of cases of cholecystitis/cholelithiasis and propose an update of the product information as warranted. The MAH should continue to closely monitor cases of pancreatitis, pancreatic cancer and thyroid cancer.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.6. Ferumoxytol – **RIENSO** (CAP)

- Evaluation of a PSUR procedure

[15] 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.

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002215/PSUV/0014 (without RMP)
MAH(s): Takeda Pharma A/S

Background

Ferumoxytol is a colloidal iron-carbohydrate complex indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD).

The PRAC is currently reviewing the benefit-risk balance of Rienso (ferumoxytol), a centrally authorised medicine, in the framework of a single assessment PSUR procedure due for PRAC recommendation in July 2014.

Summary of recommendation(s) and conclusions

The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUR procedure identifying some risks that potentially impact on the overall benefit-risk balance of the products. The PRAC was concerned by the higher rates for hypersensitivity reactions compared to other intravenous iron containing products and the absolute number of serious and fatal cases for Rienso. The PRAC noted that these reporting rates were based on spontaneous reports; the majority of the case reports came from the US, where patient exposure is much higher than in Europe.

Considering the known limitations of comparing reporting rates from spontaneous reports, that additional data will be available and given that the product information already includes warnings and precautions on hypersensitivity reactions, the PRAC recommended as a first step a targeted communication with emphasis on the existing risk minimisation measures and warnings on hypersensitivity reactions included in the product information. The PRAC agreed a DHPC for distribution to HCPs promptly. The PRAC recommendation is expected for July 2014.

Post-meeting note: On 19 May 2014, the PRAC adopted by written procedure a final DHPC and communication plan.

6.1.7. Granisetron – SANCUSO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Jolanta Gulbinovic (LT)

Administrative details:
Procedure number(s): EMEA/H/C/002296/PSUV/0030 (without RMP)
MAH(s): ProStrakan Limited

Background

Granisetron is a serotonin 5-HT_3 receptor antagonist indicated in adults for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Sancuso (granisetron transdermal patch) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on the risk of serotonin syndrome associated with the use of the 5-HT_3 antagonist drug-class when used alone or concomitantly administered with other serotonergic drugs. Therefore the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should provide a detailed analysis of cases of medication error and provide clarification on cases reported as drug ineffective. In addition, the MAH should closely monitor cases of serotonin syndrome, hypersensitivity reactions and product adhesion-related issues.
- The MAH should submit to EMA an updated RMP to add serotonin syndrome as an important potential risk at the next procedure opportunity.

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.

To the extent that other medicinal products containing granisetron not listed above nor in the PRAC assessment report are currently authorised in the EU, or are subject to future authorisation procedures by the Member States, the PRAC recommends that the concerned Member States and MAHs take due consideration of this PRAC recommendation. The PRAC also concluded that this warning on serotonin syndrome should be added to the product information of all HT_3 antagonists due to the mechanistic plausibility for the occurrence of such adverse events.

6.1.8. Melatonin – CIRCADIN (CAP), NAP

- Evaluation of a PSUSA[17] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00000283/201309
MAH(s): RAD Neurim Pharmaceuticals EEC Ltd., various

Background

Melatonin acts on the MT1, MT2 and MT3 receptors and is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Circadin (melatonin) in the approved indication(s) remains favourable.

[16] The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.
[17] PSUR single assessment, referring to CAP, NAP

- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide additional information, in particular, a detailed review of the published scientific literature and a detailed analysis of cases of enuresis, hypothermia, decreased appetite and dyspnoea including a discussion on the possible causal relationship with melatonin.
- The MAH should submit to EMA an updated RMP to reflect dyspnoea and an effect on bone repair time as important potential risks at the next procedure opportunity.

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002226/PSUV/0020 (without RMP)
MAH(s): GlaxoSmithKline Biologicals S.A.

Background

Meningococcal group a, c, w135 and y conjugate vaccine is indicated for active immunisation of individuals from the age of 12 months and above against invasive meningococcal diseases caused by *Neisseria meningitidis* group A, C, W-135 and Y.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nimenrix, a centrally authorised meningococcal 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 Nimenrix (meningococcal group a, c, w135 and y conjugate vaccine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add extensive limb swelling (ELS) as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation should be varied[18].
- The MAH should submit an updated RMP to upgrade extensive limb swelling (ELS)/severe injection site reactions to an identified risk at the next procedure opportunity.

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

6.1.10. Panitumumab – VECTIBIX (CAP)

- Evaluation of a PSUR procedure

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000741/PSUV/0057 (without RMP)
MAH(s): Amgen Europe B.V.

Background

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds to the epidermal growth factor receptor (EGFR) and is indicated for the treatment of adult patients with wild-type rat sarcoma (RAS) metastatic colorectal cancer (mCRC) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vectibix, a centrally authorised medicine containing panitumumab, 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 Vectibix (panitumumab) 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 cardiac toxicity, including arrhythmias and ischaemic heart disease, with particular emphasis on any additional toxicity in combination with fluoropyrimidines. In addition, the MAH should provide a detailed analysis of panitumumab off-label use and of cases of pneumonia and respiratory failure and propose an update of the product information as warranted.

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

6.1.11. **Pazopanib – VOTRIENT** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001141/PSUV/0024 (without RMP)
MAH(s): Glaxo Group Ltd

Background

Pazopanib is a potent and selective multi-targeted receptor tyrosine kinase inhibitor indicated in adults for the treatment of advanced Renal Cell Carcinoma (RCC) and indicated for the treatment of adult patients with selective subtypes of advanced Soft Tissue Sarcoma (STS) under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Votrient (pazopanib) in the approved indication(s) remains favourable.
- 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 retinal tear and retinal detachment as well as of cases of pericardial effusion. The MAH should also further evaluate the reported fatal hepatic serious events and the potential relatedness of combining pazopanib with gemcitabine. In addition, based on data from clinical trials, the MAH should discuss if vinorelbine and temsirolimus should also be included in the warning section of the product information regarding combination with other systemic anti-cancer therapies. The MAH should also closely monitor any racial differences in the efficacy and risks with regard to pazopanib treatment. The MAH should propose to update the product information as warranted.
- The MAH should submit to EMA an updated RMP as described in the assessment report to add serotonin syndrome as an important potential risk at the next procedure opportunity.

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. **Regadenoson – RAPISCAN** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001176/PSU 012 (with RMP version 5.0)
MAH(s): Rapidscan Pharma Solutions EU Ltd.

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Rapiscan (regadenoson) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to reflect that aminophylline, used to attenuate severe and/or persistent adverse reactions to regadenoson, should not be administered solely for the purpose of terminating a seizure induced by regadenoson. The product information should be also amended to reflect that consideration should be given to delaying regadenoson administration in patients with elevated blood pressure until the latter is well controlled. Finally, the risk of transient ischaemic attack (TIA) and cerebrovascular accident (CVA) associated with regadenoson administration should be added as a warning and

undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[19].

- In the next PSUR, the MAH should provide a discussion on the evidence to support the use of aminophylline for the treatment of specific adverse reactions, in particular, those potentially life-threatening or resulting in hospitalisation. In addition, the MAH should provide the outcome of the follow-up questionnaire exploring information collection for cases suggestive of TIA or CVA.
- The MAH should submit to EMA an updated RMP to reclassify CVA as an important identified risk, add prolongation of regadenoson-induced seizures following administration of aminophylline as an important identified risk at the next procedure opportunity. In addition, elevation of blood pressure should be re-classified as elevation of blood pressure and hypertensive crisis. Finally, the MAH should update the routine risk minimisation measures for seizure, CVA and elevated blood pressure in line with the product information update.

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[20]

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

- Evaluation of a follow-up to a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000703/LEG 079, EMEA/H/C/000732/LEG 074.1
Procedure scope: MAH's response to PSUR#13 as adopted in January 2014
MAH(s): Sanofi Pasteur MSD, SNC

Background

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

Summary of advice and conclusions

- Following the review of the MAHs' proposal to submit a variation application to include the adverse event (AE) from post-marketing cases of leukoencephalomyelitis/acute disseminated encephalomyelitis (ADEM), the PRAC acknowledged the difficulties of establishing a causal link and a frequency of AE due to the type of reporting and the rarity of the AE.
- Nevertheless, due to a compatible temporal relationship, the PRAC considered that a causal relationship between the vaccination and the event could not be excluded. Therefore, the MAH should submit to the EMA within 60 days a variation to include ADEM in the product

[19] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.
[20] Follow up as per the conclusions of the previous PSUR procedure, assessed outside next PSUR procedure

information, reflecting also the limited evidence in the available data and uncertainties in the causality. Further investigation and research may be considered.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[21]

7.1.1. **Ethinylestradiol, chlormadinone** (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure scope: Evaluation of a PASS protocol (following conclusion of Art.31 referral procedure for combined hormonal contraceptives with CHMP opinion adopted in November 2013) to study the risk of venous thromboembolism (VTE) associated with chlormadinone/ethinylestradiol (CMA/EE) containing products
MAH(s): joined PASS by Gedeon Richter and other companies[22]

Background

Oral contraceptives containing ethinylestradiol and chlormadinone were included in the Art.31 referral procedure for combined hormonal contraceptives concluded in November 2014. According the EC decision Annex IV conditions to the marketing authorisation, the MAHs for chlormadinone containing CHCs should carry out a post-authorisation safety study to compare the risk of VTE with chlormadinone/ethinylestradiol versus levonorgestrel/ethinylestradiol.

A protocol for such study was submitted for assessment by the PRAC by one of the MAHs.

Conclusion

The PRAC appointed Valerie Strassmann (DE) as Rapporteur for the assessment of the protocol and adopted a timetable for review of the protocol for PRAC decision in July 2014.

7.1.2. **Flupirtine** (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure scope: Protocol for a non-interventional post-authorisation safety study to evaluate the effectiveness of the risk minimisation measures for the use of flupirtine 100 mg immediate-release capsules in daily practice
MAH(s): Meda Pharma

[21] In accordance with Article 107n of Directive 2001/83/EC
[22] Aristo Pharma GmbH, Dr. Kade Pharmazeutische Fabrik GmbH, Gynial GmbH, Hexal AG, Hormosan Pharma GmbH, Jenapharm GmbH & Co. KG, Kwizda Pharma GmbH, Madaus GmbH, mibe GmbH Arzneimittel, acis GmbH Arzneimittel, Dermapharm GmbH, Sun-Farm SP.zo.o., Mithra Pharmaceuticals, Mylan, Pfizer Austria Gesellschaft m.b.h. Pfizer Pharma GmbH, Pharmacia Grupo Pfizer, Gedeon Richter P.c., Gedeon Richter Romania, STADA Arzneimittel AG, Aliud Pharma GmbH, Stadapharm GmbH, LABORATORIO STADA, S.L., SH-Pharma s.r.o, Zentiva Pharma GmbH (Sanofi)

Background

Flupirtine is an analgesic currently indicated for the treatment of acute pain (orally) and for postoperative pain (intravenously) which was subject to the Art.107i referral procedure concluded in July 2014. According to the EC decision Annex IV conditions the marketing authorisation holders for flupirtine containing medicines, MAHs should carry out a post-authorisation safety study to evaluate the effectiveness of the risk minimisation activities.

A protocol for such study was submitted for assessment by the PRAC by Meda Pharma.

Conclusion

The PRAC appointed Valerie Strassmann (DE) as Rapporteur for the assessment of the protocol and adopted a timetable for review of the protocol for PRAC decision in June 2014.

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

- Evaluation of an imposed PASS protocol

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

Administrative details:
Procedure scope: Evaluation of a PASS protocol (following conclusion of 107i Referral) on a multicentre, non-interventional, uncontrolled, open-label, observational study in children to evaluate serum mg levels associated with the intake of Numeta G 16% E
MAH(s): Baxter

Background

For background, see PRAC minutes 3-6 February 2014.

The protocol for a PASS submitted by the MAH was assessed by the Rapporteur.

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, agreed that overall the design was acceptable, although further justification is needed on the proposed small sample size. In addition, some other points also need to be addressed before the protocol can be agreed. Therefore the PRAC objected to the draft protocol and recommended that:

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[23]

See Annex 16.2

[23] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

7.3. Results of PASS imposed in the marketing authorisation(s)[24]

None

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

See Annex 16.4

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[26]l

See Annex 16.5

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

See dronedarone (MULTAQ) under 5.2.6. and also Annex 17

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

9.1.1 Risk-based programme for routine pharmacovigilance inspections of Marketing Authorisation Holders of Centrally Authorised Products for human use

The PRAC agreed the list of planned pharmacovigilance inspections 2014-1017, first revision, reviewed according to a risk based approach. This list is subsequently due for agreement at CHMP.

9.2. On-going or concluded pharmacovigilance inspection

The PRAC discussed the results of some inspections conducted in the EU. 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 published minutes.

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

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

None

10.2. Timing and message content in relation to MS safety announcements

None

[24] In accordance with Article 107p-q of Directive 2001/83/EC
[25] 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
[26] In line with the revised variations regulation for any submission before 4 August 2013

10.3. Other requests

10.3.1. Fluticasone furorate, vilanterol – RELVAR ELLIPTA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002673/ANX 002.1
Procedure scope: CHMP request for PRAC advice on clinical trial protocol for study HZC115151: interventional post-authorisation safety study to further investigate the risk of pneumonia with Relvar Ellipta compared with other inhaled corticosteroid (ICS)/ long-acting beta2 agonists (LABA) FDC in the treatment of chronic obstructive pulmonary disease (COPD)
MAH(s): Glaxo Group Ltd

Background

For background, see PRAC minutes February 2014.

The PRAC had discussed the revised PASS protocols for studies HZA115150 and HZC115151 and concurred that the study design was not yet be considered acceptable. Revised protocols were submitted by the MAH.

Summary of advice

The PRAC agreed that the MAH has responded satisfactorily to the questions posed by the PRAC and updated the protocols accordingly. Overall, the protocols are acceptable. However, some outstanding points need further refinement for both studies regarding the analysis plan (it is important that the analysis of the study ensures that any possible differential misclassification in the diagnosis of serious pneumonia is appropriately recognized and managed); protocol HZA115150 version 2 and protocol HZC115151 version 5 can otherwise be endorsed by the CHMP.

10.3.2. Fluticasone furorate, vilanterol – RELVAR ELLIPTA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002673/ANX 004.1
Procedure scope: CHMP request for PRAC advice on clinical trial protocol for study HZA115150: interventional post-authorisation safety study to further investigate the risk of pneumonia with Relvar Ellipta compared with other inhaled corticosteroid (ICS)/ long-acting beta2 agonists (LABA) FDC in the treatment of asthma
MAH(s): Glaxo Group Ltd

See above 10.3.1.

10.3.3. Laquinimod

- PRAC consultation on a re-examination procedure of an initial marketing authorisation

Administrative details:
Procedure number(s): EMEA/H/C/002546
Intended indication: Treatment of multiple sclerosis

Background

The CHMP) adopted a negative opinion in January 2014 recommending the refusal of the marketing authorisation for the medicinal product Nerventra, intended for the treatment of multiple sclerosis.

The MAH requested a re-examination of the CHMP opinion and CHMP asked PRAC advice concerning aspects relating to the proposed risk management plan.

Summary of advice

The PRAC agreed on the main elements of the risk minimisation programme expected to be put in place should the CHMP reach a positive opinion on its marketing authorisation. However the PRAC was not convinced about the effectiveness of the company's proposed pregnancy prevention measures.

Post-meeting note: after considering the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 22 May 2014. See EMA/311892/2014.

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

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Work Programme

- Draft PRAC Work Programme 2014-2015

PRAC discussed a consolidated list of key contributors for some areas of the work programme who will be working in defining the deliverables for each item, to be completed by the end of 2014/15. Further discussion will also take place at the informal meeting of the PRACmeeting under the Greek presidency of the EU. Feedback is planned for the June 2014 meeting of the PRAC.

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 May 2014

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

Post-meeting note: following the PRAC meeting in May 2014, the updated EURD list was adopted by the CHMP at its May 2014 meeting and published on the EMA website on 28/05/2014 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.4. Signal Management

12.4.1. Signal Management

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

The topic was deferred to the June 2014 meeting.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

12.5.2. Monitoring of Medical Literature

- Detailed guide for the monitoring of medical literature and the entry of relevant information into EudraVigilance database

The EMA Secretariat presented to the PRAC a draft detailed guide dedicated to the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by EMA. The PRAC agreed with the content of the detailed guide, which will be released for public consultation for a 2 month-period in June 2014.

Post-meeting note: On 5 June 2014, the EMA published the draft detailed guide (EMA/161530/2014) for public consultation until 27 July 2014

12.5.3. List of Product under Additional Monitoring

- Consultation on the draft List, version May 2014

The PRAC was informed of the products newly added to the additional monitoring list and the updated list.

Post-meeting note: The updated additional monitoring list was published on 28/05/2014 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of Risk Minimisations

12.7.1. Risk Management Systems

12.7.1.1. Principles for RMP assessment revised process in the pre-authorisation phase

Following previous discussions the EMA secretariat prepared some principles for a revised process for assessment of RMPs as part of new MAAs that were agreed by the PRAC with some refinements. The principles will be presented also to CHMP and then to the EMA MB for agreement and to the HMA before becoming effective. EMA secretariat anticipated that further details of the process will be delivered in the framework of the 'Review and Reconnect' exercise and presented at PRAC in the coming months.

12.7.1.2. Progressive multifocal leukoencephalopathy (PML): possibilities for monitoring and labelling

- Possibilities for monitoring and labelling: Development of an evidence-based strategy

The PRAC reviewed a proposal for a systematic approach to address product labelling in relation to spontaneously reported PML cases. Over the past year, a subgroup of PRAC members and EMA secretariat had reviewed evidence from EudraVigilance on PML cases and the labelling status of CAPs (SPC and RMP). Based on that data, the subgroup made a proposal for a harmonized approach to review evidence and apply harmonized labelling practices. Following discussion, the PRAC members were invited to provide comments on the draft strategy.

12.8. Post-authorisation Safety Studies

None

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. Working Parties

12.12.1.1. Healthcare Professionals Working Group (HPWG) and Patients and Consumers Working Party (PCWP)

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

Following discussion at the April 2014 meeting the relevant PRAC Rapporteurs and EMA secretariat elaborated on a proposal to collect further information on cases of ONJ associated with bisphosphonates and denosumab, and potential to strengthen risk minimisation in the terms of awareness for patients and prescribing physicians. The previously presented EudraVigilance data on reporting rates of ONJ for bisphosphonates was also clarified.

A proposal for consultation of patient organisations was discussed by the PRAC and a list of questions to be addressed was agreed. Patients and consumers eligible to participate in EMA activities will be involved in a structured information gathering exercise on the effectiveness of the current ONJ risk minimisation measures.

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

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

12.14.1.1. ICH E2C(R2) Guideline on Periodic Benefit-Risk Evaluation Report

- Publication of ICH Q&A document

The PRAC was informed that the ICH E2C(R2) implementation working group had recently finalised under Step 4 of the ICH process a Questions and Answers document addressing new concepts and principles linked to the evolution of the traditional PSUR from an interval safety report to a cumulative benefit-risk report, with a change in focus from individual case reports to more aggregate data evaluation. This supplementary Questions and Answers document intends to clarify key issues which were identified since the ICH E2C(R2) Guideline was published in the three ICH regions.

Post-meeting note: the Q&A March 2014 on ICH E2C(R2) Guideline was published on the ICH website.

12.14.2. Others

None

13. Any other business

13.1. EMA move in 2014 to new building

The monthly status update from the EMA secretariat on the preparation of the EMA's move to a new building in July 2014 was postponed to the June 2014 PRAC meeting.

1. ANNEX I Risk Management Plans

1.1. Medicines in the pre-authorisation phase

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

1.1.1. Balugrastim

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

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

1.1.2. Busulfan

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

Administrative details:
Product number(s): EMEA/H/C/002806, *Generic*
Intended indication: Conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT)

1.1.3. Mixture of polynuclear iron(iii)-oxyhydroxide, sucrose and starches

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

Administrative details:
Product number(s): EMEA/H/C/002705
Intended indication: Control of serum phosphorus levels in patients with end-stage renal disease (ESRD)

1.1.4. Netupitant, palonosetron

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

Administrative details:
Product number(s): EMEA/H/C/003728
Intended indication: Prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) induced by highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC)

1.1.5. Obinutuzumab

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

Administrative details:
Product number(s): EMEA/H/C/002799, *Orphan*
Intended indication: Treatment of chronic lymphocytic leukaemia
Applicant: Roche Registration Ltd

1.1.6. Peginterferon beta-1a

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

Administrative details:
Product number(s): EMEA/H/C/002827
Intended indication: Treatment of relapsing multiple sclerosis

1.1.7. Perflubutane

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

Administrative details:
Product number(s): EMEA/H/C/002347
Intended indication: Detection of coronary artery disease (CAD)

1.1.8. Phenylephrine, ketorolac trometamol

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

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

1.1.9. Simoctocog alfa

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

Administrative details:
Product number(s): EMEA/H/C/002813
Intended indication: Treatment and prophylaxis of bleeding (congenital factor VIII deficiency)

1.1.10. Tacrolimus

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

Administrative details:
Product number(s): EMEA/H/C/002655*, Hybrid*
Intended indication: Prophylaxis of transplant rejection in adult kidney allograft recipients

1.2. Medicines already authorised

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

RMP in the context of a variation – PRAC led procedure

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

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000916/II/0018, EMEA/H/C/000915/II/0020

Procedure scope: Update of RMP (version 17.0)
MAH(s): Servier (Ireland) Industries Ltd, Les Laboratoires Servier

1.2.2. **Dabigatran – PRADAXA** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/II/0064
Procedure scope: Submission of an updated protocol of the agreed study category 3: 1160.84 (observational cohort study to evaluate safety and efficacy of Pradaxa in patients with moderate renal impairment undergoing elective total hip replacement surgery or total knee replacement surgery)
MAH(s): Amgen Europe B.V.

1.2.3. **Pegaptanib – MACUGEN** (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/000620/II/0058
Procedure scope: Submission of a revised risk management plan (RMP version 8.2) to update information on the risk minimisation measures and their effectiveness
MAH(s): Pfizer Limited

1.2.4. **Tegafur, gimeracil, oteracil – TEYSUNO** (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/001242/II/0016
Procedure scope: Update of the RMP to modify the post-authorisation phase III clinical study to assess efficacy and safety of Teysuno versus an appropriate triplet comparator in the RMP (MEA 001). In addition the MAH took the opportunity to update the RMP with a new amendment for phase I study TPU-S1119 (MEA 002)
MAH(s): Nordic Group B.V.

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

1.2.5. **Aflibercept – EYLEA** (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002392/II/0009
Procedure scope: Extension of indication to include the treatment of adult patients with diabetic macular oedema. Consequential updates for SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2. SmPC section 4.8 was further updated to introduce a single table of adverse drug reactions

MAH(s): Bayer Pharma AG

1.2.6. Atazanavir – REYATAZ (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000494/II/0090
Procedure scope: Update of SmPC sections 4.4 and 4.8 to be in line with the latest CCDS update
MAH(s): Bristol-Myers Squibb Pharma EEIG

1.2.7. Bevacizumab – AVASTIN (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000582/II/0059
Procedure scope: Update of SmPC section 4.1 in order to extend the indication of Avastin in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma. Related changes were proposed to SmPC sections 4.2, 4.5, 4.8 and 5.1
MAH(s): Roche Registration Ltd

1.2.8. Bevacizumab – AVASTIN (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000582/II/0063
Procedure scope: Extension of indication to include the use of Avastin in combination with chemotherapy (paclitaxel, topotecan or pegylated liposomal doxorubicin) in patients with recurrent, platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube carcinoma
MAH(s): Roche Registration Ltd

1.2.9. Bosutinib – BOSULIF (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002373/II/0001, *Orphan*
Procedure scope: Update of SmPC sections 4.2, 4.4 and 5.2 further to the results of a study in patients with renal impairment conducted as a post-authorisation measure
MAH(s): Pfizer Limited

1.2.10. Cetuximab – ERBITUX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/000558/II/0066
Procedure scope: Update of SmPC section 5.1 with efficacy data by RAS (KRAS and NRAS) tumour status from the CRYSTAL (EMR 62 202-013) and FIRE3 studies
MAH(s): Merck KGaA

1.2.11. Dabrafenib – TAFINLAR (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/002604/II/0001/G
Procedure scope: Update of SmPC sections 4.4 and 4.5 with final data from a drug-drug interaction study (BRF113771) and remove a statement in section 4.5 concerning the risk of liver injury following co-administration with paracetamol
MAH(s): GlaxoSmithKline Trading Services

1.2.12. Darunavir – PREZISTA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Administrative details:

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

1.2.13. Darunavir – PREZISTA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Administrative details:

Procedure number(s): EMEA/H/C/000707/II/0067/G
Procedure scope: Grouping of two type II variations:1) Update of SmPC sections 4.3 and 4.5 with information of CYP3A mechanism based interactions; 2) Update of SmPC sections 4.3 and 4.5 with information of CYP2D6 mechanism based interactions
MAH(s): Janssen-Cilag International N.V.

1.2.14. Denosumab – XGEVA (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/002173/II/0016
Procedure scope: Extension of indication to add the treatment of giant cell tumour of bone in adults or skeletally mature adolescents
MAH(s): Amgen Europe B.V.

1.2.15. Efavirenz – SUSTIVA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:
Procedure number(s): EMEA/H/C/000249/II/0126/G
Procedure scope: Grouped variation consisting of two consequential variations: 1) type II variation to extend the therapeutic indication to include children of 3 months of age to less than 3 year of age and weighing at least 3.5kg; 2) type IB variation to remove the oral solution pharmaceutical form for Sustiva (efavirenz) and as such upgrade the already approved "capsule sprinkle" dosing method as primary means of dosing for young patients and those that cannot swallow capsules and/or tablet
MAH(s): Bristol-Myers Squibb Pharma EEIG

1.2.16. Golimumab – SIMPONI (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000992/X/0047
Procedure scope: Line extension to include Simponi 12.5 mg/ml solution for infusion
MAH(s): Janssen Biologics B.V.

1.2.17. Iloprost – VENTAVIS (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000474/X/0043
Procedure scope: Addition of a new strength: 20 microgram/ml nebuliser solution (in 30 and 168 ampoules package sizes)
MAH(s): Bayer Pharma AG

1.2.18. Mannitol – BRONCHITOL (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/001252/II/0011
Procedure scope: Provision of further qualitative sputum microbiology data from study DPM-B-305 in relation to the safety concern of microbial infection via a contaminated inhaler device (MEA 003)
MAH(s): Pharmaxis Pharmaceuticals Limited

1.2.19. Ofatumumab – ARZERRA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001131/II/0023*, Orphan*
Procedure scope: Extension of indication to the first line treatment of chronic lymphocytic leukaemia in combination with alkylator-based regimens in patients not eligible for fludarabine-based therapy. As a result, SmPC sections 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 are updated
MAH(s): Glaxo Group Ltd

1.2.20. Ponatinib – ICLUSIG (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002695/II/0005/G
Procedure scope: Grouped variations: 1) Update of SmPC section 4.5 to reflect the results from study AP24534-12-107 (open-label, non-randomized, inpatient/outpatient clinical study to assess the effect of rifampicin on the pharmacokinetics of ponatinib, when qdministered concomitantly in healthy subjects; 2) Update of SmPC sections 4.4, 4.5, 5.2 to reflect the results from study AP24534-12-108 (clinical study to evaluate the effect of multiple doses of lansoprazole on the pharmacokinetics of ponatinib when administered concomitantly to healthy subjects; 3) Update of SmPC sections 4.2, 4.4, 4.5 and 5.2 to reflect the results from study AP24534-12- 109 (evaluation of pharmacokinetics and safety of ponatinib in patients with chronic hepatic impairment and matched healthy subjects; 4) Update of SmPC sections 4.5 to reflect the results from study ARI-001A (simcyp physiologically-based PBPK modelling to determine the impact of different ketoconazole dosing regimens (400 mg QD versus 200 mg BID; pre-dosing with ketoconazole for multiple days versus a single day prior to co-administration of ponatinib) on the pharmacokinetics of ponatinib due to CYP3A4 inhibition); 5) Update of SmPC section 5.2 to reflect the results from study ARP350 (in vitro study to determine whether co-administered drugs that are highly bound to human plasma proteins can displace ponatinib from its binding sites); Submit the results of study ARP395 - a follow up study in which plasma samples from post 24 hr collections were analyzed to determine metabolite profile; Submit the results of study XT133050 - Study on the potential for ponatinib (at concentrations up to 10 µM) to induce cytochrome P450 (CYP) enzymes in cultured human hepatocytes. In addition, the RMP is submitted to reflect the data submitted and to reflect changes requested as part of variation EMEA/H/C/002695/II/002
MAH(s): Ariad Pharma Ltd

1.2.21. Posaconazole – NOXAFIL (CAP)

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Product number(s): EMEA/H/C/000610/X/0033
Intended indication: Line extension to Noxafil 18mg/ml concentrate for solution for infusion

1.2.22. Ranibizumab – LUCENTIS (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/000715/II/0047
Procedure scope: Update of SmPC section 4.2 to harmonise the administration instructions for Lucentis across indications in line with the available clinical evidence, relevant guidelines and treatment recommendations as well as clinical practice. The proposed posology recommendations for diabetic macular oedema are further supported by the final report of the RETAIN study. In addition, SmPC sections 4.5 and 5.1 were proposed to be updated to reflect RETAIN study data including data on the concomitant treatment with thiazolidinediones. The information in SmPC section 5.1 on the RESTORE study were also proposed to be updated with data from the 2-year extension phase as previously requested by the CHMP in the context of post-authorisation procedure MEA 034
MAH(s): Novartis Europharm Ltd

1.2.23. Regorafenib – STIVARGA (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/002573/II/0001
Procedure scope: Extension of indication to include treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with 2 tyrosine kinase inhibitors. As a consequence, SmPC sections 4.1, 4.2, 4.8 and 5.1 were proposed to be updated
MAH(s): Bayer Pharma AG

RMP in the context of a PSUR procedure

Not applicable

RMP evaluated in the context of PASS results

Not applicable

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

1.2.24. Saxagliptin – ONGLYZA (CAP)

- Evaluation of an RMP in the context of a 5-renewal of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/001039/R/0023 (with RMP version 4.0)
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

RMP in the context of a stand-alone RMP procedure

1.2.25. Telbivudine – SEBIVO (CAP)

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

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000713/RMP 061.1
MAH(s): Novartis Europharm Ltd

2. 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).

2.1. Evaluation of PSUR procedures[27]

2.1.1. Alglucosidase alfa – MYOZYME (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000636/PSUV/0036 (with RMP version 7.0)
MAH(s): Genzyme Europe BV

2.1.2. Alipogene tiparvovec – GLYBERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002145/PSUV/0031 (without RMP)
MAH(s): uniQure Biopharma B.V.

2.1.3. Bazedoxifene – CONBRIZA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000913/PSUV/0034 (without RMP)

[27] 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

MAH(s): Pfizer Limited

2.1.4. **Bortezomib – VELCADE** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000539/PSUV/0070 (without RMP)
MAH(s): Janssen-Cilag International N.V.

2.1.5. **Ceftaroline fosamil – ZINFORO** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002252/PSUV/0009 (without RMP)
MAH(s): AstraZeneca AB

2.1.6. **Choriogonadotropin alfa – OVITRELLE** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000320/PSUV/0059 (without RMP)
MAH(s): Merck Serono Europe Limited

2.1.7. **Dapagliflozin – FORXIGA** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002322/PSUV/0010 (with RMP version 7.0)
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

2.1.8. **Doripenem – DORIBAX** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000891/PSUV/0025 (with RMP version 7.0)
MAH(s): Janssen-Cilag International N.V.

2.1.9. Eltrombopag – REVOLADE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001110/PSUV/0016 (without RMP)
MAH(s): GlaxoSmithKline Trading Services

2.1.10. Eslicarbazepine – ZEBINIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000988/PSUV/0043 (without RMP)
MAH(s): Bial - Portela & Cª, S.A.

2.1.11. Fenofibrate, pravastatin – PRAVAFENIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/001243/PSUV/0009 (without RMP)
MAH(s): Laboratoires SMB S.A.

2.1.12. 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/0007 (without RMP)
MAH(s): Eli Lilly Nederland B.V.

2.1.13. Human fibrinogen, human thrombin – EVICEL (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000898/PSUV/0027 (without RMP)
MAH(s): Omrix Biopharmaceuticals N. V.

2.1.14. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – FOCLIVIA (CAP)
Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) –

AFLUNOV (CAP), **PREPANDEMIC INFLUENZA VACCINE (H5N1) (SURFACE ANTIGEN, INACTIVATED, ADJUVANTED) NOVARTIS VACCINES AND DIAGNOSTIC** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:

Procedure number(s): EMEA/H/C/001208/PSUV/0013, EMEA/H/C/002094/PSUV/0014, EMEA/H/C/002269/PSUV/0009 (without RMP)
MAH(s): Novartis Vaccines and Diagnostics S.r.l.

2.1.15. 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/0007, EMEA/H/C/002499/PSUV/0007 (without RMP)
MAH(s): Novo Nordisk A/S

2.1.16. Insulin glulisine – APIDRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000557/PSUV/0055 (without RMP)
MAH(s): Sanofi-aventis Deutschland GmbH

2.1.17. Mannitol – BRONCHITOL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/001252/PSUV/0010 (without RMP)
MAH(s): Pharmaxis Pharmaceuticals Limited

2.1.18. Micafungin – MYCAMINE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000734/PSUV/0023 (with RMP version 12.0)
MAH(s): Astellas Pharma Europe B.V.

2.1.19. **Miglustat – ZAVESCA** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000435/PSUV/0044 (without RMP)
MAH(s): Actelion Registration Ltd.

2.1.20. **Ocriplasmin – JETREA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002381/PSUV/0008 (without RMP)
MAH(s): ThromboGenics NV

2.1.21. **Ofatumumab – ARZERRA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001131/PSUV/0026 (without RMP)
MAH(s): Glaxo Group Ltd

2.1.22. **Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) – PANDEMRIX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000832/PSUV/0070 (without RMP)
MAH(s): GlaxoSmithKline Biologicals

2.1.23. **Pasireotide – SIGNIFOR** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002052/PSUV/0011 (without RMP)
MAH(s): Novartis Europharm Ltd

2.1.24. **Prucalopride succinate – RESOLOR** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001012/PSUV/0033 (without RMP)
MAH(s): Shire Pharmaceuticals Ireland Ltd.

2.1.25. Pyronaridine, artesunate – PYRAMAX (Art 58)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/W/002319/PSUV/0001 (with RMP version 7.0)
MAH(s)/Scientific Opinion Holder(s): Shin Poong Pharmaceutical Co., Ltd.

2.1.26. 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/0002 (without RMP)
MAH(s): Bayer Pharma AG

2.1.27. Sodium oxybate – XYREM (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000593/PSUV/0049 (with RMP version 6.0)
MAH(s): UCB Pharma Ltd.

2.1.28. Tadalafil – ADCIRCA (CAP), CIALIS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001021/PSUV/0017, EMEA/H/C/000436/PSUV/0074 (without RMP)
MAH(s): Eli Lilly Nederland B.V.

2.1.29. Thalidomide – THALIDOMIDE CELGENE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000823/PSUV/0039 (with RMP version 15.0)
MAH(s): Celgene Europe Limited

2.1.30. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000955/PSUV/0036 (without RMP)
MAH(s): Roche Registration Ltd

2.2. Follow-up to PSUR procedures[28]

2.2.1. Lopinavir, ritonavir – ALUVIA (Art 58), KALETRA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/W/000764/LEG 024.2, EMEA/H/C/000368/LEG 105. 2
Procedure scope: MAH's response to PSUR#5 as adopted in October 2013 (second RSI)
MAH(s): AbbVie Ltd

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

Since all comments received on the assessment of these measures were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below.

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

3.1.1. Brentuximab vedotin – ADCETRIS (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002455/SOB 008
Procedure scope: Revised protocol for an imposed PASS (study no. MA25101) to further study Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL), patient populations
MAH(s): Takeda Pharma A/S

3.1.2. Teduglutide – REVESTIVE (CAP)

- Evaluation of an imposed PASS protocol

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

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002345/ANX 003.7
Procedure scope: Revised PASS protocol for study TED R13-002 (prospective, multi-centre registry for patients with short bowel syndrome)
MAH(s): NPS Pharma Holdings Limited

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

3.2.1. Aliskiren – RASILEZ (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/MEA 036
Procedure scope: PASS protocol for a multi-database cohort study to assess the incidence rates of colorectal hyperplasia among hypertensive patients (CSPP100A2417)
MAH(s): Bristol-Myers Squibb Pharma EEIG

3.2.2. Bivalirudin – ANGIOX (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000562/MEA 022.2
Procedure scope: Updated PASS protocol for the drug utilisation study EUROVISION 2
MAH(s): The Medicines Company UK Ltd.

3.2.3. Elvitegravir – VITEKTA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002577/MEA 007
Procedure scope: PASS protocol for a drug utilisation study to determine the use of rifampicin, St. John's wort, carbamazepine, phenobarbital and phenytoin with elvitegravir (EVG) in the post-marketing setting as well as to determine the incidence/prevalence and outcome of medication errors in the post-marketing setting that may result in reduced exposure to EVG
MAH(s): Gilead Sciences International Ltd

3.2.4. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of a PASS protocol

[30] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

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

Administrative details:
Procedure number(s): EMEA/H/C/000955/MEA 041.1, EMEA/H/C/000955/MEA 045
Procedure scope: MEA 041.1: MAH's response to MEA-041 (polyarticular juvenile idiopathic arthritis (pJIA) treatment) as adopted in September 2013; MEA 045: Revised protocol for the EU BSRBR rheumatoid arthritis registry (study WA22479)
MAH(s): Roche Registration Ltd

3.3. Results of PASS imposed in the marketing authorisation(s)[31]

None

3.4. Results of PASS non-imposed in the marketing authorisation(s)[32]

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

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/002073/WS0561/0093, EMEA/H/C/000780/WS0561/0092, EMEA/H/C/000964/WS0561/0062 (without RMP)
Procedure scope: Final study report for non-interventional study CSPP100A2415 (cohort study including a nested case-control analysis using data from the United States IMS PharMetrics Plus health plan claims database – assessing the prevalence and incidence of angioedema among patients with hypertension treated with aliskiren or other antihypertensive medications in the US)
MAH(s): Novartis Europharm Ltd

3.4.2. Pioglitazone – ACTOS (CAP), **GLUSTIN** (CAP)
pioglitazone, metformin – COMPETACT (CAP), **GLUBRAVA** (CAP)
pioglitazone, glimepiride - TANDEMACT (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000285/WS0541/0061, EMEA/H/C/000286/WS0541/0059, EMEA/H/C/000655/WS0541/0046, EMEA/H/C/000893/WS0541/0032, EMEA/H/C/000680/WS0541/0036 (with RMP version 17)
Procedure scope: Final analysis report of the Kaiser Permanente Northern California (KPNC) non-bladder malignancy study extension (AD4833-403) (post approval commitment)
MAH(s): Takeda Pharma A/S

[31] In accordance with Article 107p-q of Directive 2001/83/EC
[32] 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

3.5. 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[33]

3.5.1. **Abatacept – ORENCIA** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000701/MEA 046.1, EMEA/H/C/000701/MEA 048.1
Procedure scope: MEA 046.1: Updates of the Rheumatoid Arthritis registries; MEA 048.1: Annual updates of the Juvenile idiopathic arthritis (JIA) registry
MAH(s): Bristol-Myers Squibb Pharma EEIG

3.5.2. **Infliximab – REMICADE** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000240/MEA 133.8
Procedure scope: 6th annual report of the paediatric inflammatory bowel disease (IBD) registry in the US and Europe (DEVELOP) collecting data a on long-term safety and efficacy of infliximab and other therapies, safety and efficacy of variable infliximab dosing intervals, episodic therapy, monotherapy, combined infliximab and immunomodulator therapy (AZA/6-MP or MTX)
MAH(s): Janssen Biologics B.V.

3.5.3. **Paliperidone – INVEGA** (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000746/MEA 019.1
Procedure scope: MAH's response to MEA 019 (abbreviated CSR - Studies (R076477-SCH-4015 and R076477-SCH-4016 - PILAR)) RSI adopted in September 2013
MAH(s): Janssen-Cilag International

3.5.4. **Raltegravir – TROBALT** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001245/REC 017.1
Procedure scope: Fourth quarterly update of discolouration events
MAH(s): Glaxo Group Ltd

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

3.5.5. **Tigecycline – TYGACIL** (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000644/ANX 058.4
Procedure scope: Interim results of PASS aimed to evaluate Tygacil prescription patterns and monitor superinfections and treatment outcomes
MAH(s): Pfizer Limited

4. 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 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. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

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

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

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

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 5 - 8 May 2014 meeting.

PRAC member PRAC alternate	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting***	***Topics on the current Committee Agenda for which restriction applies*** ***Product/ substance***
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer reviewer for:	paracetamol, aflibercept, iloprost, regorafenib
Veerle Verlinden	Belgium	Full involvement	
Yuliyan Eftimov	Bulgaria	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
Marin Banovac	Croatia	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Nectaroula Cooper	Cyprus	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	
Terhi Lehtinen	Finland	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer reviewer for:	azithromycin, pegaptanib, bosutinib, bazedoxifene, tigecycline
Julia Pallos	Hungary	Full involvement	
Hrefna Guðmundsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Ruchika Sharma	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Full involvement	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	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*
Ingebjørg Buajordet	Norway	Full involvement	
Karen Pernille Harg	Norway	Full involvement	
Kamila Czajkowska	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Roxana Stroe	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Gabriela Jazbec	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
June Munro Raine	Chair	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	Cannot act as Rapporteur or Peer reviewer for:	quetiapine, saxagliptin, saxagliptin metformin, ceftaroline fosamil, dapagliflozin, exenatide
Marie Louise De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer reviewer for:	fluticasone furoate, ofatumumab, pazopanib, raltegravir, vilanterol,
Brigitte Keller-Stanislawski		Full involvement	
Hervé Le Louet		Full involvement	
Lennart Waldenlind		Full involvement	

Health care professionals and patients PRAC members, PRAC alternates	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		Cannot act as Rapporteur or Peer reviewer for:	infliximab
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (2013-05-30) 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	
Laurence Defays	Belgium	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Karen De Smet	Belgium	
Javier Sawchik	Belgium	
Karen Van Malderen	Belgium	
Thomas Grüger	Germany	
Anne Kleinau	Germany	
Vahid Taravati	Germany	
Patrick Maison	France	
Frank Holtkamp	Netherlands	
Sara Khosrovani	Netherlands	
Peter Mol	Netherlands	
Charlotte Backman	Sweden	
Luisa Becedas	Sweden	
Rebecca Chandler	Sweden	
Ingela Hägglund	Sweden	
Jan Sjöberg	Sweden	
Abidali Fazal	United Kingdom	
Gary Peters	United Kingdom	
Jonathan Rowell	United Kingdom	
Karen Slevin	United Kingdom	