11 September 2014
EMA/PRAC/501208/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 7-10 July 2014

Chair: June Raine – Vice-Chair: Almath Spooner

Disclaimers

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

Note on access to documents

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

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Explanatory notes

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1. Introduction

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

The Chairperson opened the 7-10 July 2014 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Jan Neuhauser as the new alternate for Austria.

1.2. Adoption of agenda of the meeting of 7-10 July 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 10-13 June 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 10-13 June 2014 were published on the EMA website on 21 July 2014 (EMA/PRAC/438418/2014).

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

2.1. Newly triggered procedures

None

2.2. Ongoing Procedures

None

2.3. Procedures for finalisation

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

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)
PRAC Co-Rapporteur: Karen Pernille Harg (NO)

Administrative details:

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

Background

A referral procedure under Article 107i of Directive 2001/83/EC for methadone medicinal products for oral use containing povidone (see 10-13 June 2014 PRAC minutes for background) was to be concluded. An ad-hoc expert group meeting was held in the framework of the review on 16 June 2014 and a final assessment of the data submitted was produced by the Rapporteurs.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs as well as the outcome of the ad-hoc expert group meeting. An oral explanation took place at the meeting.

The PRAC discussed all available data on the safety of oral methadone products containing povidone in particular with regards to the risks associated with the misuse of the products by injection, which is a well-known risk in the target population, and the potential harm caused by the accumulation of povidone in organs and tissues when injected repeatedly.

The PRAC considered that a potential for harm was likely to be associated with the misuse by injection of methadone oral solutions containing high molecular weight povidone K90 and that the proposed risk minimisation measures could not mitigate the risk. Therefore the benefit-risk balance for products containing high molecular weight povidone was no longer considered favourable.

The PRAC considered that the injection of low molecular weight povidone contained in the methadone tablets (K25 or K30) was not associated with the same risk as it was expected to be readily excreted by the kidneys and will therefore not accumulate in tissues. The PRAC concluded that the benefit-risk balance of methadone tablets containing low molecular weight povidone (K25, K30), provided that amendments were introduced in the product information to reinforce the message that tablets are for oral administration only and must not be injected, was still favourable.

Summary of recommendation(s)/conclusions

The PRAC adopted by consensus a recommendation, to be considered by CMDh, to suspend the marketing authorisations for methadone oral solutions containing high molecular weight povidone (K90) and to vary the marketing authorisation for methadone tablets that contain low molecular weight (K25 or K30) povidone - see 'PRAC recommends suspension and reformulation of oral methadone solutions containing high molecular weight povidone (EMA/415507/2014).
In order for suspension of the marketing authorisations for methadone oral solutions containing high molecular weight povidone (K90) to be lifted, the PRAC recommended that the MAHs should appropriately reformulate the product taking into account its misuse potential.

Post-meeting note: the press release 'CMDh endorses suspension of methadone oral solutions containing high molecular weight povidone' representing the position/opinion provided by the CMDh was published on the EMA website on 24 July 2014 (EMA/444346/2014).

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

3.1. Newly triggered Procedures

None

3.2. Ongoing Procedures

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

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000598/A20/0031, EMEA/H/C/000597/A20/0032
MAH(s): Les Laboratoires Servier

Background

A referral procedure under Article 20(8) of Regulation (EC) No 726/2004 is ongoing for ivabradine-containing medicines (see PRAC minutes of the PRAC 11-13 June 2014 meeting). Following receipt of further information from the MAH, the Rapporteurs prepared an assessment report for discussion at the meeting.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusion reached by the Rapporteurs on the new findings of the SIGNIFY study in the context of other results from clinical trials performed with ivabradine and agreed that further data were needed before a recommendation was issued. Furthermore the PRAC agreed that experts should be consulted on the matter and that a meeting of the cardiovascular Scientific Advisory Group (SAG) should be convened.

Therefore the PRAC agreed on a list of outstanding issues for the MAH, a list of questions for the SAG and a revised timetable (EMA/PRAC/281251/2014 Rev.1) for the review to take into account these steps.

3.2.2. **Testosterone** (NAP)

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

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for testosterone-containing medicines (see PRAC minutes 5-8 May 2014).

The PRAC Rapporteur prepared an assessment report based on the available evidence. The EMA secretariat facilitated exchange of information with other regulatory authorities outside the EU who are performing a parallel review on testosterone and reported on the information obtained.

Summary of recommendation(s)/conclusions

The PRAC discussed some outstanding aspects to be clarified and noted that ongoing research including clinical trials is likely to yield substantial new evidence that will need to be taken into account in the review. The PRAC also recommended making contact with the investigators of two ongoing (soon to be finalised) randomized clinical trials to gather further information.

The PRAC adopted a list of outstanding issues to be addressed by the MAHs and a revised timetable (EMA/PRAC/178709/2014 Rev.1) for the procedure.

3.2.3. **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(s): EMEA/H/C/002695/A-20/0003
MAH(s): Ariad Pharma Ltd

Background

A referral procedure under Article 20(8) of Regulation (EC) No 726/2004 for Iclusig (ponatinib, see minutes of the PRAC 11-13 June 2014 meeting for background) was discussed. An assessment of the data submitted by the MAH was produced by the Rapporteurs according to the agreed timetable.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and agreed that further information was needed before a recommendation is issued. Therefore the PRAC agreed a number of points to be clarified and supported the need for expert advice in the review. The Committee agreed to convene a meeting of the oncology SAG, with membership boosted with additional experts to address the questions raised by the PRAC.

The PRAC adopted a list of questions for the SAG and a list of outstanding issues for the MAH as well as an updated timetable (EMA/PRAC/746118/2013 Rev.2) for the procedure.

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

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

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for valproate and related substances and their use in pregnant women and in women of childbearing potential (see PRAC minutes 5-8 May 2014).

The PRAC Rapporteurs prepared an assessment report based on the information received following a previously agreed list of outstanding issues and a meeting with valproate patient families and carers had been held at the EMA.

Summary of recommendation(s)/conclusions

The PRAC noted the conclusions of the meeting with valproate patient families and carers, discussed outstanding points to be addressed in the review and agreed on the need for additional input from experts in the review. Therefore the PRAC decided to convene a neurology SAG and agreed a list of questions for the SAG experts. The PRAC also agreed some questions to be addressed by healthcare professional organisations and a list of outstanding issues to be addressed by the MAHs. A revised timetable for the review to take into account these steps was adopted (EMA/PRAC/606970/2013 Rev.2).

3.3. Procedures for finalisation

3.3.1. **Bromocriptine** (NAP)

- Review of the benefit-risk balance following the notification by France 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: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/A-31/1379
MAH(s): Meda Pharma, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC for bromocriptine-containing medicines (see PRAC minutes 10-13 June 2014 for background) was to be concluded. A final assessment of the data submitted was produced by the Rapporteurs.

Discussion

The PRAC discussed the relationship between the use of oral bromocriptine-containing medicinal products for post-partum inhibition of lactation and the occurrence of serious cardiovascular, neurological and psychiatric adverse events. The PRAC recommended limiting the use of oral bromocriptine-containing medicinal products (1 mg and 2.5 mg strengths) in the post-partum inhibition of lactation to cases where they are medically indicated.

The use of these products is not recommended for routine suppression of lactation or for relief of symptoms of post-partum pain and engorgement which can be adequately treated with non-

pharmacological intervention or with analgesics. Furthermore the blood pressure of patients should be carefully monitored.

In addition, the PRAC recommended all strengths of these products to be contraindicated in patients with uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension post-partum and in the puerperium and in patients with a history of coronary artery disease or other severe cardiovascular conditions, or symptoms or a history of severe psychiatric disorder.

Summary of recommendation(s)/conclusions

The PRAC adopted, by majority, a recommendation to be considered by CMDh, to vary the marketing authorisations for the use of oral bromocriptine-containing medicinal products for post-partum inhibition of lactation (see communication PRAC recommends restricted use of bromocriptine for stopping breast milk production EMA/409529/2014).

Twenty-eight members voted in favour of the recommendation together with Iceland and Norway whilst two members had a divergent view[1].

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

None

3.5. Others

3.5.1. **Diacerein** (NAP)

- Review of recommendations of a referral procedure under Article 31 of Directive 2001/83/EC adopted in March 2014, at the request of the European Commission

Regulatory details:
PRAC Rapporteur (re-examination): Margarida Guimarães (PT)
PRAC Co-Rapporteur (re-examination): Harald Herkner (AT)

Administrative details:
Procedure number(s): EMEA/H/A-31/1349
MAH(s): Negma-Wockhardt, TRB Chemedica, various

Background

In June 2014, the PRAC received a letter from the EC asking the PRAC to review the recommendation on diacerein (see PRAC minutes 10-13 June 2014 for background). The Rapporteurs prepared a reply to the letter for discussion.

Summary of recommendation(s)/conclusions

The PRAC discussed the proposed letter of clarification and adopted - revised PRAC recommendations reflecting the necessary clarifications with a majority vote consistent with the latest position reached in March 2014 (see PRAC minutes 3-6 March 2014).

[1] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded.

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Buprenorphine**, transdermal patches (NAP)

- Signal of skin depigmentation

Regulatory details:
PRAC Rapporteur: *Not applicable*

Administrative details:
EPITT 18040 – New signal
MAH(s): various
Lead MS: FR

Background

Buprenorphine is an opioid analgesic. Buprenorphine transdermal patches are indicated for the treatment of non-malignant, moderate pain, for which an opioid is needed in order to achieve sufficient reduction in pain.

During routine signal detection activities, a signal of skin depigmentation was identified by NL, based on 2 cases retrieved from Netherlands Pharmacovigilance Centre Lareb. FR, lead Member State for signal management activities for buprenorphine confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted that beyond the two cases that triggered the signal a limited number of cases was retrieved from EudraVigilance and from the WHO database. A few cases of skin depigmentation were reported with suggestive temporal association. The PRAC concluded that the number of reports was low considering the high population exposure to the medicine. Furthermore a causality link could not be established and therefore no changes to the product information for buprenorphine patches were currently warranted.

Summary of recommendation(s)

- No change to product information is warranted at this stage. The signal should remain under close monitoring and be reviewed in the next PSURs.

4.1.2. **Sildenafil – VIAGRA** (CAP)

- Signal of increased risk of incident melanoma

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

Administrative details:
EPITT 17997 – New signal
MAH(s): Pfizer Limited

Background

Sildenafil is a phosphodiesterase type 5 (PDE5) used in the treatment of erectile dysfunction. The worldwide exposure to medicines containing sildenafil in the period from first authorisation in 1998 to 2013 is estimated to be more than 68 million patients.

A signal of increased risk of incident melanoma was identified by the EMA following a communication provided by an MAH concerning a recently published scientific study[2] reporting an association with an increased risk, which in turn triggered a further search in EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the main findings of the study and commented on its limitations, including limitations with regard to exposure to treatment, incomplete adjustment for confounders related to health status and lifestyle, and possibly compromised by misclassification of disease.

The PRAC noted that *in vitro* research suggested a plausible biological rationale for the reaction. Nevertheless the clinical relevance of the *in vitro* data was considered to be doubtful, taking into account the short half-life of sildenafil. Results of a search performed in EudraVigilance were also discussed but the Committee noted the limits of spontaneous reporting in detecting such suspected reactions.

Overall, despite the methodological limitations of the study that triggered the signal, in view of the high population exposure to sildenafil and the possible impact of this potential risk, the PRAC considered it appropriate to request additional data to further investigate the signal.

Summary of recommendation(s)

- The MAH for Viagra (sildenafil) should submit to the EMA, within 60 days, a cumulative review of the signal including the publication by Wen-Qing Li et al. and other published literature, mechanistic studies, epidemiological studies, and clinical trials, as well as any relevant preclinical studies or long term clinical trials.
- A 60-day timetable was recommended for this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. **Rivaroxaban – XARELTO** (CAP)

- Signal of spontaneous splenic rupture/haemorrhage

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

Administrative details:
EPITT 18020 – New signal
MAH(s): Bayer Pharma AG

[2] JAMA Intern Med. 2014 Jun;174(6):964-70. doi: 10.1001/jamainternmed.2014.594.
Sildenafil use and increased risk of incident melanoma in US men: a prospective cohort study.
Li WQ1, Qureshi AA2, Robinson KC3, Han J4.

Background

Rivaroxaban is an antithrombotic agent used in the prevention of venous thromboembolism (VTE) in various conditions including: adult patients undergoing elective hip or knee replacement surgery; in the prevention of stroke and systemic embolism in selected adult patients with non valvular atrial fibrillation with one or more risk factors; in the treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults; and, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

The exposure for Xarelto, a centrally authorised medicine containing rivaroxaban, is estimated to have been more than 2.4 million patient-years worldwide from the time of its authorisation in 2008 to 2014.

During routine signal detection activities, a signal of spontaneous splenic rupture was identified by the UK, based on 23 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of suspected splenic rupture or splenic haemorrhage reported in association with rivaroxaban. Given the mechanism of action of rivaroxaban, members commented that haemorrhage at any site may be considered an expected adverse reaction and bleeding is known to be associated with rivaroxaban use.

However, it was suggested that splenic rupture could be missed early on during patient assessment in the absence of known trauma and it was emphasised that spontaneous splenic haemorrhage/rupture is a life-threatening event which can be difficult to identify. Therefore the PRAC agreed that it would be useful to clarify certain aspects on this signal and that consideration should be given to informing prescribers of the risks of spontaneous splenic rupture secondary to splenic haemorrhage.

Summary of recommendation(s)

- The MAH for Xarelto (rivaroxaban) should submit to the EMA a cumulative review of the signal, including an analysis of all case reports of splenic haemorrhage and related terms in the next PSUR (DLP 15/09/2014). Special consideration should be given to non-traumatic cases and cases with minor trauma, as they represent the most difficult cases to identify.

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 May 2014
MAH(s): Pfizer, various

Background

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

The MAH provided a review of the recently published study Rao et al. 2014[3] and a feasibility analysis to measure the statistical power of the Kaiser Permanente Northern California (KPNC) and Kaiser Permanente Southern California (KPSC) databases, which are to be used in a planned observational study to examine the acute effects of azithromycin use on cardiovascular deaths.

Data from the study by Rao et al and another study by Khosropour et al [4] were also assessed by the Rapporteur.

Discussion

The PRAC discussed the analysis submitted and, based on the feasibility study results, agreed that the planned observational study using data from the Kaiser Permanente Northern California and Kaiser Permanente of Southern California databases should be carried out. A feasibility analysis within the Veterans Affairs database should be conducted once the data are available.

The PRAC noted that a draft study protocol was expected in August 2014 and highlighted some aspects that will need careful consideration, including the analysis of the other non-cardiac causes of death (besides cardiovascular and all-cause mortality) to provide reassurance that any increased cardiovascular mortality is not due to confounding by the indication.

The PRAC concluded that the data described in the publication by Rao et al. 2014 did not provide strong evidence of a causal association and, based on the published data, there were no changes in the benefit-risk balance of azithromycin.

The PRAC acknowledged the limitations of the study published by Khosropour et al. 2014 and noted that the outcome of the study did not directly suggest an increase in the risk of cardiac mortality with short-term azithromycin use in the relatively young and healthy population studied.

Summary of recommendation(s)

- Pfizer, the MAH for the innovator product, should inform the PRAC if the plan for the development of above mentioned planned observational study needs to be modified in the future. The MAH is recommended to consider measures to avoid confounding by the indication. Relevant updates of the product information should be considered upon completion of the observational study or if new data become available.

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

- Signal of heart valve disorders

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 13832 – Follow-up May 2014
MAH(s): Merck Sharp & Dohme Limited (Adrovance, Fosavance, Vantavo), Les Laboratoires Servier (Osseor, Protelos), various

[3] Rao et al. 2014, Azithromycin and Levofloxacin Use and Increased Risk of Cardiac Arrhythmia and Death, Ann Fam Med 2014;12:121-127
[4] Khosropour et al., Lack of association between Azithromycin and Death from Cardiovascular Causes, N Engl J Med 2014;370:1961-2

Background

For background information, see PRAC minutes of 5-8 May 2014.
As agreed in May 2014, a further review of the study results of a commissioned EMA[5] study on the risk of cardiac valve disorders associated with the use of bisphosphonates was performed by the Rapporteur for discussion at PRAC.

Discussion

The PRAC discussed the assessment of the study results in the context of already known evidence on the signal[6][7] and concluded that several small observational studies had either suggested that osteoporosis treatment and bisphosphonate therapy may reduce the progression of aortic stenosis - which is commonly associated with valve calcification - or had found no effect of bisphosphonates. Overall the currently available evidence did not appear to support a causal relationship between bisphosphonates and strontium ranelate with an increased risk of cardiac valve disorders.
However, given the earlier concerns and in light of other evidence suggesting a possible beneficial effect of bisphosphonate use on aortic stenosis, clarifications of the study results were needed. Therefore the PRAC agreed on a list questions for the authors.

Summary of recommendation(s)

- Further clarification should be sought on the results of the EMA commissioned study on the risk of cardiac valve disorders associated with the use of bisphosphonates by means of a list of questions to be sent to the study authors for a reply expected by September 2014.
- Follow-up discussion should be planned after responses to the questions have been received and assessed.

4.3.3. **Bupropion** (NAP)

- Signal of pancytopenia

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
EPITT 17727 - Follow-up March 2014
MAH(s): GlaxoSmithKline, various

Background

For background information, see PRAC minutes of 3-6 March 2014. The MAH provided further information on the signal of pancytopenia and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the additional information received on cases of blood dyscrasia, with particular focus on the cases describing de-challenge and re-challenge information, and noted that in several

[5] Tender ID: EMA/2011/39/CN BISPHOSPHONATES (ENCePP/SDPP/2616)
[6] Preciosa M. Coloma, Gianluca Trifirò, Miriam Sturkenboom (EMC). 2012. Risk of cardiac valve disorders associated with the use of bisphosphonates (Signal strengthening study). Tender ID: EMA/2011/39/CN BIPHOSPHONATES (ENCePP/SDPP/2616).
[7] 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.

cases there were no alternative explanations for the suspected reported adverse events; furthermore de-challenge and sometimes re-challenge with bupropion (while treatment with other drugs was continued) was described.
Therefore the PRAC, notwithstanding the inherent limitations of spontaneous reporting and low absolute number of cases considered, agreed that a possible causal association cannot be excluded and that the product information for bupropion containing medicines should be updated.

Summary of recommendation(s)

- The MAHs for the nationally authorised bupropion-containing medicines[8] should submit to the NCAs within 60 days a variation to update the product information to include "blood and lymphatic system disorders: anaemia, leukopenia and thrombocytopenia"[9] as undesirable effects[10] .

4.3.4. Calcium channel blockers (CAP, NAP):
Aliskiren, amlodipine - RASILAMLO (CAP)
Amlodipine, telmisartan - ONDUARP (CAP), **TWYNSTA** (CAP)
Amlodipine, valsartan – **COPALIA** (CAP), **DAFIRO** (CAP), **EXFORGE** (CAP), **IMPRIDA** (CAP)
Amlodipine, valsartan, hydrochlorothiazide - **COPALIA HCT** (CAP), **DAFIRO HCT** (CAP), **EXFORGE HCT** (CAP)

- Signal of increased breast cancer risk

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

Administrative details:
EPITT 17750 – Follow-up November 2013
MAH(s): Novartis Europharm Ltd (Copalia, Copalia HCT, Dafiro, Dafiro HCT, Exforge, Exforge HCT, Imprida, Rasilamlo), Boehringer Ingelheim (Onduarp, Twynsta), various

Background

For background information, see PRAC minutes of 4-7 November 2013. Following discussion at the November 2013 meeting, results from an observational study conducted within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Work Package 2 and Working Group 1 on CPRD became available and were assessed by the Rapporteur.

Discussion

The PRAC could not exclude the possibility that study results reported in the JAMA article[11] by Li et al may not have taken into account relevant confounding factors. The PROTECT study – which included a larger data set using the CPRD - for 5-10 years' use or more than 10 years' use, did not observe any

[8] 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
[9] Section 4.8 of the Summary of Product Characteristics
[10] Section 4.8 of the Summary of Product Characteristics, frequency not known. The patient leaflet should be updated accordingly
[11] Li CI, Daling JR, Tang MT, Haugen KL, Porter PL, Malone KE. Use of Antihypertensive Medications and Breast Cancer Risk Among Women Aged 55 to 74 Years. JAMA Intern Med. 2013 Sep 23;173(17):1629-37. doi: 10.1001/jamainternmed.2013

increased risk for breast cancer or all cancers and was considered to have better control on possible sources of biases and confounding.

In addition the PRAC noted that results obtained from the case-control study on calcium channel blockers (CCB) and breast cancer commissioned by the Swedish National Board for Health and Welfare, covering use for up to five years' duration, did not raise concerns of an increased risk of breast cancer.

Summary of recommendation(s)

- No association between use of CCBs for up to 5 years - which was the longest observation time available in both studies - and increased risk of breast cancer was confirmed. Furthermore, since the CPRD study did not observe any increased risk for breast cancer or all cancers observed for 5-10 years' use or more than 10 years' use, no further regulatory action is necessary at this point in the time and the signal can be considered addressed.

4.3.5. **Tacrolimus** for systemic use **- ADVAGRAF** (CAP), **MODIGRAF** (CAP), NAP **Febuxostat** – **ADENURIC** (CAP)

- Signal of potential drug-drug interaction between systemic tacrolimus and febuxostat

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
EPITT 17809 – Follow-up March 2014
MAH(s): Astellas Pharma Europe B.V. (Advagraf, Modigraf), Menarini International Operations Luxembourg S.A. (Adenuric), various

Background

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

Discussion

The PRAC discussed the evidence on potential interaction between systemic tacrolimus and febuxostat, including data from spontaneous reports, literature cases and relevant studies concerning a potential mechanism for interaction, in particular the potential for a transporter-based interaction.

The PRAC noted that the post-marketing experience in organ transplant patients receiving febuxostat had been regularly reviewed in the PSURs. The current review of febuxostat post-marketing cases provided little evidence of a potential interaction between tacrolimus and febuxostat. Similarly, a review of tacrolimus post-marketing cases with febuxostat reported as co-suspect or concomitant drug did not provide additional evidence to support the existence of an interaction between the two drugs.

Since no plausible mechanism for this interaction could be identified, the PRAC concluded that overall the available evidence on the risk of drug-drug interaction between systemic tacrolimus and febuxostat did not support an update of the product information.

This safety issue should, however, remain under close monitoring including experience with reports outside the transplant populations.

Summary of recommendation(s)

- The available evidence is not sufficient to confirm a signal of drug-drug interaction between medicines containing tacrolimus or febuxostat. The relevant MAHs for the centrally and nationally authorised[12] tacrolimus- and febuxostat-containing medicines should continue to monitor this signal and in particular any experience with reports outside the transplant populations.

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. Eliglustat

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

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

5.1.2. Naltrexone, bupropion

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

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

5.1.3. Nintedanib

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

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

[12] 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

5.2. Medicines already authorised

RMP in the context of a variation[13] – PRAC-led procedure

See Annex 14.1

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

5.2.1. Denosumab – PROLIA (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/001120/II/0036
Procedure scope: Update of SmPC section 4.4 upon request by PRAC following the assessment of PSU/027, to revise the warnings on osteonecrosis of the jaw (ONJ)
MAH(s): Amgen Europe B.V.

Procedure number(s): EMEA/H/C/001120/II/0037
Procedure scope: Update of the SmPC, upon request by PRAC following the assessment of PSU 027, to refine the warnings on hypocalcaemia including a description of the clinical manifestations of severe symptomatic hypocalcaemia and increases in parathyroid hormone in sections 4.4 and 4.8, and to add musculoskeletal pain as an identified risk in section 4.8 further to post-marketing experience
MAH(s): Amgen Europe B.V.

Background

For background, see PRAC minutes 7-10 April 2014. The Rapporteur assessed a revised RMP submitted by the MAH in accordance with the previous advice of the PRAC.

Summary of advice

- The RMP version 0.1 for Prolia (denosumab) in the context of the variations under evaluation by the CHMP was now considered acceptable.
- Some comments were provided on a DHPC to be disseminated following these variations. The content of the DHPC was agreed together with a communication plan.

5.2.2. Denosumab – XGEVA (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/002173/II/0027
Procedure scope: Update of the SmPC, upon request by PRAC following the assessment of PSU/014, to revise the warnings in section 4.4 on osteonecrosis of the jaw (ONJ), and to add information in sections 4.4 and 4.8 on the incidence of ONJ based on duration of exposure
MAH(s): Amgen Europe B.V.

Procedure number(s): EMEA/H/C/002173/II/0028

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

Procedure scope: Update of the SmPC, upon request by PRAC following the assessment of PSU 014, to refine the warnings on hypocalcaemia including a description of the clinical manifestations of severe symptomatic hypocalcaemia and increases in parathyroid hormone in sections 4.4 and 4.8, and to add musculoskeletal pain as an identified risk in section 4.8 further to post-marketing experience. Further, sections 4.2 and 5.2 of the SmPC have been updated with respect to recommendations for monitoring of calcium levels, and information regarding patients with renal impairment
MAH(s): Amgen Europe B.V.

Background

For background, see PRAC minutes 7-10 April 2014. The Rapporteur assessed a revised RMP submitted by the MAH in accordance with the previously request of the PRAC.

Summary of advice

- The updated RMP for Xgeva (denosumab) in the context of the variations under evaluation by the CHMP was considered acceptable.
- Some comments were provided on a DHPC to be disseminated following these variations. The DHPC was agreed together with a communication plan.

5.2.3. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (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/002617/II/0020
Procedure scope: Seasonal update of the composition of the strains to those officially recommended by WHO and CHMP for the season 2014/2015
MAH(s): MedImmune LLC

Background

Fluenz Tetra is a centrally authorised attenuated influenza vaccine for nasal administration, indicated for the prophylaxis of influenza in children and adolescents 24 months to less than 18 years of age. The use of Fluenz Tetra should be based on official recommendations.

The CHMP is evaluating a type II variation procedure for Fluenz Tetra to update the RMP with a proposal for enhanced surveillance based on the guidance issued by the EMA regarding enhanced safety surveillance for seasonal influenza vaccines in the European Union (EU; EMA/PRAC/222346/2014) consisting of a study evaluating potential new safety concerns that might be associated with the annual release of live attenuated influenza vaccine (LAIV).

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 updated RMP for Fluenz Tetra in the context of the variation under evaluation by the CHMP was considered acceptable pending some final minor modifications to be introduced before the procedure is concluded.

5.2.4. Influenza vaccine (split virion, inactivated) – IDFLU (CAP), INTANZA (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000966/II/0026, EMEA/H/C/000957/II/0029
Procedure scope: Update of the product information to reflect that the strains are in accordance with the WHO recommendation and the EU decision for the 2014/2015 season. There is no change in the strains selected for the composition of the influenza vaccines compared to the previous season and the variation is therefore limited to an administrative update of the product information and a stability data update. In addition an update of the RMP to include an enhanced safety surveillance plan is provided
MAH(s): Sanofi Pasteur, Sanofi Pasteur MSD SNC

Background

IDflu and Intanza are centrally authorised inactivated influenza vaccines indicated for prophylaxis of influenza in adults up to 59 years(9 micrograms/strain) and 60 years of age and over (15 micrograms/strain), especially in those who run an increased risk of associated complications. Their use should be based on official recommendations.

The CHMP is evaluating a type II variation procedure for IDflu and Intanza, to include an update of the product information to reflect that the strains are in accordance with the WHO recommendation and the EU decision for the 2014/2015 season. A new version of the RMP is submitted in the context of this variation to include the MAH commitment to develop enhanced safety surveillance for the 2014/2015 influenza season in the EU. 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 7.0 for IDflu and Intanza in the context of the variation under evaluation by the CHMP was considered acceptable pending some modifications to be introduced before the procedure is concluded.

5.2.5. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (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/000758/II/0069
Procedure scope: Update of the product information to reflect that the strains are in accordance with the WHO recommendation and the EU decision for the 2014/2015 season. There is no change in the strains selected for the composition of the influenza vaccines compared to the previous season and the variation is therefore limited to an administrative update of the product information and a stability data update. In line with the adopted interim guidance on safety surveillance for seasonal influenza vaccines in the EU, an updated RMP including an enhanced safety surveillance plan is submitted
MAH(s): Novartis Vaccines and Diagnostics GmbH

Background

Optaflu is an inactivated influenza vaccine used in prophylaxis of influenza for adults, especially in those who run an increased risk of associated complications. Optaflu should be used in accordance to official guidance.

The CHMP is evaluating a type II variation procedure for Optaflu, to include an update of the product information to reflect that the strains are in accordance with the WHO recommendation and the EU decision for the 2014/2015 season. A new version of the RMP has been submitted in the context of this variation to include the MAH commitment to develop and enhanced safety surveillance for the 2014/2015 influenza season in the EU. 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 3.2 for Optaflu in the context of the variation under evaluation by the CHMP was considered acceptable provided some points raised by the PRAC regarding modalities of the conduct of the enhanced safety surveillance are adequately addressed by the MAH before conclusion of the procedure.

5.2.6. Insulin lispro – **HUMALOG** (CAP), **LIPROLOG** (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000088/X/0125, EMEA/H/C/000393/X/092
Procedure scope: Addition of a new strength (200 U/ml KwikPen presentation)
MAH(s): Eli Lilly Nederland B.V.

Background

For background, see PRAC minutes 7-10 April 2014. The PRAC had suggested some modification to the RMP and requested further information. The revised RMP was assessed by the Rapporteur.

Summary of advice

- The updated RMP version 5 for Humalog / Liprolog Kwikpen (insulin lispro) in the context of variation for a line extension under evaluation by the CHMP was considered acceptable. Targeted communication to patients and healthcare professionals (DHPC and patient communication materials) on appropriate measures to minimise any risk of medication errors potentially arising due to confusion with different presentations with different strengths of Humalog was agreed.
- During the discussion the PRAC highlighted the need for an overall strategy to appropriately address the potential risk of medication errors with new presentation of insulins containing higher strength.

The PRAC advice was finalised via written procedure on 22 July 2014.

5.2.7. Interferon beta-1a – **REBIF** (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/000136/II/0106
Procedure scope: Update of the SmPC sections 4.4 and 4.8 to include class labelling information on thrombotic microangiopathy (TMA), thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS). In addition the RMP is being updated to version 7.0
MAH(s): Merck Serono Europe Limited

Background

For background see PRAC minutes 2-6 February 2014. An updated RMP submitted by the MAH as requested by the PRAC was assessed by the Rapporteur.

The RMP is in support of a type II variation to include therapeutic class labelling information on thrombotic microangiopathy (TMA), thrombotic thrombocytopenic purpura (TTP) and haemolytic uremic syndrome (HUS) in the product information.

Summary of advice

- The RMP version 2 for Rebif (interferon beta-1a) in the context of the variation under evaluation by the CHMP was considered acceptable; however, some points raised by the PRAC and in particular the feasibility of a case control study to further investigate TMA should be further explored before finalisation of the procedure.

See also 10.1.2.

RMP evaluated in the context of a PSUR procedure

See also Besilesomab – SCINTIMUN 15.1.5. , C1 inhibitor, human – CINRYZE 6.1.2. , Canakinumab – ILARIS 6.1.4. , Eptacog alfa (activated) – NOVOSEVEN 15.1.10. , Roflumilast – DALIRESP, DAXAS, LIBERTEK 15.1.21.

RMP evaluated in the context of PASS results

See also Dabigatran – PRADAXA 16.4.1. , Dolutegravir – TIVICAY 16.4.3. , Human rotavirus, live attenuated – ROTARIX 16.4.4.

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

See Annex 14.1

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

5.2.8. Sulfur hexafluoride – SONOVUE (CAP)

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

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000303/LEG

Procedure scope: Subsequently to the CHMP positive adoption of variation II-25, review of a DHPC to inform of the deletion of a contraindication for use of SonoVue in patients with acute coronary syndrome or clinically unstable ischaemic cardiac disease and the new contraindication in combination with dobutamine in patients with conditions suggesting cardiovascular instability due to the risk of severe cardiac arrhythmia (5 cases reports) and the need to update the educational material to reflect these changes
MAH(s): Bracco International B.V.

Background

SonoVue, containing sulphur hexafluoride, is a centrally authorised medicine for use in ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal-to-noise ratio.

PRAC was to consider any necessary changes to the RMP based on a recently concluded variation to revise contraindications and warnings and precautions based on recent new evidence.

Summary of advice

- The Committee provided comments on the core messages of a proposed DHPC to inform on the new contraindication for SonoVue concerning combination with dobutamine in patients with conditions suggestive of cardiovascular instability which has been added due to the risk of severe cardiac arrhythmia. The DHPC informed also of the removal of an existing contraindication in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease which was replaced by a warning.
- The PRAC discussed the need to update the educational materials to reflect these changes and agreed that this should be done at the next update of the RMP.

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[14]

6.1.1. **Abatacept – ORENCIA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000701/PSUV/0079
MAH(s): Bristol-Myers Squibb Pharma EEIG

Background

Abatacept is a selective immunosuppressant indicated in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis and for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) under certain conditions.

[14] 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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Orencia, a centrally authorised medicine containing abatacept, 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 Orencia (abatacept) 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 closely monitor cases of angioedema (see PRAC Minutes January 2014), cardiovascular events, autoimmune disorders, interstitial lung disorders, neurological events, drug related hepatic disorders as well as any fatal cases.

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

6.1.2. C1 inhibitor, human – CINRYZE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001207/PSUV/0023 (with RMP version 9.0)
MAH(s): ViroPharma SPRL

Background

C1 inhibitor (human) is a serine protease inhibitor indicated for the treatment and pre-procedure prevention of angioedema attacks in patients with hereditary angioedema (HAE) and for the routine prevention of angioedema attacks in patients with severe and recurrent attacks of hereditary angioedema (HAE) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cinryze, a centrally authorised medicine containing C1 inhibitor (human), 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 Cinryze (C1 inhibitor (human)) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add hypersensitivity as an undesirable effect 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 serious adverse events (SAEs) of HAE in clinical trials a well as spontaneous reports of lack of efficacy. The MAH should use data on lack of efficacy from the European post authorisation patient registry (protocol 0624-

[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

401) and from spontaneous reports to estimate frequency and should provide a detailed analysis of these cases.

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. Cabazitaxel – JEVTANA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002018/PSUV/0023
MAH(s): Sanofi-Aventis Groupe

Background

Cabazitaxel is an antineoplastic agent indicated in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jevtana, a centrally authorised medicine containing cabazitaxel, 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 Jevtana (cabazitaxel) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to amend the current warning on the risk of anaemia in patients treated with cabazitaxel in order to advise that blood haemoglobin and haematocrit should be checked before treatment and in the event of anaemia symptoms or blood loss during treatment. Therefore the current terms of the marketing authorisation should be varied[16].
- In the next PSUR, the MAH should provide a detailed review of cases of multi-organ failure and information on a probable cumulative dose-dependent effect, as well as reviews of cases of: respiratory disorders; osteonecrosis of the jaw and abscess of the jaw; and, cases of bleeding. Finally, the MAH should add central nervous system haemorrhages as an important potential risk in the RMP.

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

6.1.4. Canakinumab – ILARIS (CAP)

- Evaluation of a PSUR procedure

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

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

Administrative details:
Procedure number(s): EMEA/H/C/001109/PSUV/0032 (with RMP version 8.0)
MAH(s): Novartis Europharm Ltd

Background

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS), for the treatment of systemic juvenile idiopathic arthritis (SJIA) and for the symptomatic treatment of frequent gouty arthritis attacks under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ilaris, a centrally authorised medicine containing canakinumab, 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 Ilaris (canakinumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the existing warning on opportunistic infections to specify that a causal relationship between the occurrence of cases of unusual or opportunistic infections and treatment with canakinumab cannot be excluded. The undesirable effects section should also be updated accordingly. In addition, the product information should be updated to reflect that reported experience with overdose is limited. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- The MAH should update the RMP in the course of the next regulatory procedure to postpone study CACZ885H2401[18] (the gouty arthritis registry) following difficulties in patients' recruitment due to the limited use of canakinumab in this indication and should consider starting it when there is a change in the marketing conditions or if there is an increase in the number of patients receiving canakinumab for the treatment of gouty arthritis attacks.

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. Clopidogrel – PLAVIX (CAP), CAP, NAP
clopidogrel, acetylsalicylic acid – DUOCOVER (CAP), **DUOPLAVIN** (CAP)

- Evaluation of a PSUSA[19] procedure

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00000820/201311
MAH(s): Sanofi Clir SNC (Plavix), Sanofi-aventis groupe (DuoCover), Sanofi Pharma Bristol-Myers Squibb SNC (DuoPlavin), various

[17] Update of SmPC sections 4.4, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[18] Category 3 study in the RMP
[19] PSUR single assessment, referring to CAP, NAP

Background

Clopidogrel and clopidogrel/acetylsalicylic acid is indicated for the prevention of atherothrombotic and ischaemic complications in a broad spectrum of patients with cardiovascular disease.

Based on the assessment of the individual PSURs, part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of clopidogrel- and clopidogrel/acetylsalicylic acid-containing products[20] 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 clopidogrel- and clopidogrel/acetylsalicylic acid-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- In the next PSURs, MAHs should provide a review of cases of off-label use in the primary prevention of cardiovascular events. MAHs should also provide details on optimal loading and maintenance dosages and treatment duration and on inter-individual variability in responsiveness to clopidogrel/proton pump inhibitors and dual antiplatelet therapy in acute coronary syndrome. In addition, MAHs should provide a detailed review of paraoxonase-1 polymorphism with clopidogrel. Finally, MAHs for clopidogrel/acetylsalicylic acid-containing products should continue investigating the risk of exacerbation of small bowel injury.

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.

Considering that data from PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended did not raise any safety concerns, the PRAC agreed that no further PSURs are required for those products. This will be reflected in the EURD list.

6.1.6. **Ferumoxytol – RIENSO** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002215/PSUV/0014
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).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rienso, a centrally authorised medicine containing ferumoxytol, and issued a recommendation on its marketing authorisation(s) (see also PRAC Minutes June 2014).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy the PRAC agreed, by majority vote, that the risk-benefit balance of Rienso (ferumoxytol) remains favourable provided the terms of the marketing authorisation(s) are varied and that additional risk minimisation measures and conditions are imposed. The Committee adopted a recommendation for consideration by the CHMP. Twenty members/alternates out of 36 eligible to vote, together with Iceland and Norway, voted in favour of the recommendation, while eleven[21] members/alternates had divergent views. (see EMA website Home>Find medicine>Human Medicines - PRAC PSUR assessment report to be published following EC decision).
- The product information should be updated to state that the medicinal product should only be administered as a 15 minute infusion, to include a recommendation to carefully monitor patients for signs and symptoms of hypersensitivity (monitoring of blood pressure and pulse during, and 30 minutes after, administration) and to advise that patients should be in a reclining/semi-reclining position during and after administration. The product information should also include a new contraindication in patients with any known drug allergy and a warning that fatal and life-threatening hypersensitivity reactions have been observed in the post-marketing setting with hypersensitivity reactions listed as an undesirable effect. Moreover, the conditions of the marketing authorisation should be changed to require the MAH to conduct a post-authorisation safety study (PASS) to further characterise the safety concerns with hypersensitivity reactions, and this needs to be reflected in an updated RMP.
- Therefore the current terms of the marketing authorisation(s) should be varied[22].
- The MAH should inform healthcare professionals of these changes via a Direct Healthcare Professional Communication (DHPC).
- In the next PSUR, the MAH should update the company core safety information (CCSI) in accordance with the SmPC and in line with the outcome of the Article 31 referral procedure on intravenous iron-containing medicinal products (EMEA/H/A-31/1322) and provide a draft protocol for a study to investigate the mechanism of hypersensitivity associated with ferumoxytol. The MAH should also provide a synopsis for an adequately powered study to further investigate the risk of hypersensitivity in EU CKD patients comparing ferumoxytol with iron sucrose and a draft protocol for a study to measure the effectiveness of the new risk minimisation measures recommended by the PRAC. In addition, the MAH should provide detailed reviews of cases of hypersensitivity. Finally, the MAH should provide an updated RMP including a proposal for key elements of educational materials for HCPs and patients, highlighting the risks and warnings with respect to hypersensitivity reactions.

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

6.1.7. Lenalidomide – REVLIMID (CAP)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Isabelle Robine (FR)

[21] Jean-Michel Dogné (BE); Eva Jirsovà (CZ); Martin Huber (DE); Carmela Macchiarulo (IT); Tatiana Magálová (SK); Dolores Montero Corominas (ES); Viola Macolić Šarinić (HR); Jan Neuhauser (AT); Milena Radoha-Bergoč (SI); Isabelle Robine (FR); Roxana Stefania Stroe (RO)

[22] Update of SmPC sections 1, 3, 4.2, 4.3, 4.4, 4.8, 6.4 and Annex II. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Administrative details:
Procedure number(s): EMEA/H/C/000717/PSUV/0074
MAH(s): Celgene Europe Limited

Background

Lenalidomide is an immunomodulating agent indicated for the treatment of multiple myeloma (MM) in combination with dexamethasone in adult patients who have received at least one prior therapy. It is also indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Revlimid, a centrally authorised medicine containing lenalidomide, 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 Revlimid (lenalidomide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add gastrointestinal perforation as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide a detailed review of cases of tumour flare reactions in MM and MDS patients and an updated review of cases of convulsions.

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

6.1.8. Plerixafor – MOZOBIL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001030/PSUV/0021
MAH(s): Genzyme Europe BV

Background

Plerixafor is a bicyclam derivative indicated in combination with granulocyte-colony stimulating factor (G-CSF) for enhancing the mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma and multiple myeloma whose cells mobilise poorly.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Mozobil (plerixafor) in the approved indication(s) remains favourable.
- The product information should be updated to add abnormal dreams and nightmares as undesirable effects with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].
- The MAH should submit to EMA within 60 days a detailed analysis on the potential risk factors reported in the cases of lack of effect and consider updating the product information accordingly as warranted.
- In the next PSUR, the MAH should provide a detailed review of cases of myelodysplastic syndrome/acute myelogenous leukaemia. In addition, the MAH should continue to closely monitor cases relating to lack of efficacy and provide a detailed analysis of these cases.

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

6.1.9. **Ponatinib – ICLUSIG** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002695/PSUV/0009
MAH(s): Ariad Pharma Ltd

Background

Ponatinib is an antineoplastic agent indicated for the treatment of chronic myeloid leukaemia (CML) and of Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Iclusig, a centrally authorised medicine containing ponatinib, 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 Iclusig (ponatinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to reflect the recalculation of the incidence of adverse reactions and a change to a higher frequency category for the following undesirable effects already labelled: upper respiratory tract infection, insomnia, dizziness, eyelid oedema, aspartate aminotransferase increased, dermatitis exfoliative, muscle spasms and pain. Therefore the current terms of the marketing authorisation should be varied[25].

[24] 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
[25] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- The PRAC recommendation following the assessment of the current PSUR is without prejudice to the outcome of the ongoing procedure under Article 20 of Regulation (EC) 726/2004 (see 3.2.3.).
- In the next PSUR, the MAH should provide an updated review of neuropathy events. The MAH should also provide a follow-up report on a case of JC[26] virus positive in a patient's spinal fluid and cases of neurological events and a follow-up report on a suspected case of progressive multifocal leukoencephalopathy (PML).

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[27]

6.2.1. **Ruxolitinib – JAKAVI** (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002464/LEG 011
Procedure scope: MAH's response to PSUV/0011 (PSUR#2) RSI as adopted in March 2014
MAH(s): Novartis Europharm Ltd

Background

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

Summary of recommendation(s)/conclusions

- The MAH should submit to EMA within 60 days a variation to update the product information to add sepsis as an undesirable effect.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[28]

7.1.1. **Ethinylestradiol, gestodene** transdermal patch (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

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

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

Background

For background see PRAC minutes 10-13 June 2014. A protocol for the study had been assessed by the Rapporteur in accordance with the agreed timetable.

Conclusion

The PRAC, having considered the draft protocol version ZEG2014-03 of 17 April 2014 in accordance with Article 107n of Directive 2001/83/EC, considered that the design of the study did not fulfil the study objectives. Therefore the MAH should submit a revised PASS protocol including questionnaires within 2 months and an assessment will follow a 30-day review procedure.

7.1.2. Hydroxyethyl starch (HES) (NAP)

- Evaluation of an imposed PASS protocol

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

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

Background

A protocol for a drug utilisation study to assess the effectiveness of the risk minimisation measures introduced following EC decision of 19 December 2013 on an Article 31 referral procedure (EMA/809470/2013) for HES was submitted to the PRAC by MAHs in accordance with conditions to the marketing authorisation included in the EC decision Annex IV.

Conclusion

The PRAC appointed Qun-Ying Yue (SE)) as Rapporteur for the assessment of the protocol and adopted a timetable for the review of the protocol in time for a PRAC decision in October 2014.

The PRAC will strengthen interaction with the Scientific Advice Working Party and the CMDh in the follow-up of conditions of the MA following the referral for HES solutions. EMA secretariat will plan follow-up discussion on this aspect at the October 2014 meeting.

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 5-8 May 2014. The protocol had been assessed by the Rapporteur in accordance with the agreed timetable.

Conclusion

The PRAC, having considered the draft protocol for study 7032-001 dated 3rd of July 2014 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol of the study.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[29]

See Annex 16.2

7.3. Results of PASS imposed in the marketing authorisation(s)[30]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[31]

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[32]

See Annex 16.5

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

See under 5.2

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. On-going or concluded pharmacovigilance inspection

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

[29] 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
[30] In accordance with Article 107p-q of Directive 2001/83/EC
[31] 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
[32] In line with the revised variations regulation for any submission before 4 August 2013

9.3. Others

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

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

10.1.1. **Basiliximab – SIMULECT** (CAP)

- PRAC consultation on a safety-related variation, upon CHMP request

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

Administrative details:
Procedure number(s): EMEA/H/C/000207/II/0078
Procedure scope: Update of SmPC sections 4.1 and 4.4 with information on the lack of efficacy of Simulect for the prophylaxis of acute rejection in recipients of other solid organ allografts following a recommendation by the PRAC
MAH(s): Novartis Europharm Ltd

Background

For background, see PRAC minutes 3-6 February 2014. Following a PRAC request in respect of an evaluation of a signal of fatal cardiovascular instability following off-label use in heart transplantation, a variation was submitted by the MAH, which included a proposal for a DHPC and relevant updates to the product information.

Summary of advice

- The PRAC recommended some changes to the key messages proposed and recommended that further background information be included in the DHPC, stating that the efficacy and safety of Simulect (basiliximab) for the prophylaxis of acute rejection in recipients of solid organ allografts other than renal, have not been demonstrated and that in several small clinical trials in heart transplant recipients, serious cardiac adverse events have been reported more frequently with Simulect than with other induction agents. Details of the dissemination of the DHPC are to be agreed at Member State level in accordance with local prescribing practice and the clinicians involved.

10.1.2. **Interferon beta-1a – AVONEX** (CAP), **Interferon beta-1a – REBIF** (CAP), **Interferon beta-1b – BETAFERON** (CAP), **EXTAVIA** (CAP)

- PRAC consultation on a safety-related variation, upon CHMP request

Regulatory details:
PRAC Rapporteurs: Dolores Montero Corominas (ES), Julie Williams (UK), Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000102/II/0143, EMEA/H/C/000081/II/0095, EMEA/H/C/000933/II/0064
Procedure scope: Update of the SmPC Sections 4.4 and 4.8 to include class labelling wording on thrombotic microangiopathy (TMA), thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS). The Package leaflet has been updated accordingly
MAH(s): Biogen Idec (Avonex), Bayer Pharma AG (Betaferon), Novartis Europharm Ltd (Extavia), Merck Serono Europe Limited (Rebif)

Background

For background see PRAC minutes 2-6 February 2014. MAHs were requested to submit variations to update the product information to include thrombotic microangiopathy as an undesirable effect and to introduce an appropriate warning together with a proposal for a Direct Healthcare Professional Communication (DHPC). Information on nephrotic syndrome and collapsing focal segmental glomerulosclerosis (FSGS) should also have been included.

Summary of advice

The PRAC suggested improvements to the product information, commented on the proposed DHPC prepared jointly by the MAHs, and agreed a communication plan. The PRAC was of the view that there should be a single DHPC written by or on behalf of all the MAHs concerned in order to facilitate clear and effective communication of the new information.

The PRAC emphasised that the dissemination of this DHPC was also a good an opportunity to communicate on the risk of nephrotic syndrome, previously discussed at the PRAC.

See also 5.2.7.

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

None

10.3. Other requests

10.3.1. Antiretroviral medicinal products:
Abacavir – ZIAGEN (CAP); **abacavir, lamivudine – KIVEXA** (CAP); **abacavir, lamivudine, zidovudine – TRIZIVIR** (CAP); **atazanavir– REYATAZ** (CAP); **darunavir – PREZISTA** (CAP); **efavirenz – STOCRIN** (CAP), **SUSTIVA** (CAP); **efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA** (CAP); **elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD** (CAP); **emtricitabine – EMTRIVA** (CAP); **emtricitabine, tenofovir disoproxil – TRUVADA** (CAP); **emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA** (CAP); **etravirine – INTELENCE** (CAP); **fosamprenavir – TELZIR** (CAP); **indinavir – CRIXIVAN** (CAP); **lamivudine – EPIVIR** (CAP); **lamivudine, zidovudine – COMBIVIR** (CAP); **lopinavir, ritonavir – KALETRA** (CAP); **nevirapine – VIRAMUNE** (CAP); **rilpivirine – EDURANT** (CAP); **ritonavir – NORVIR** (CAP); **saquinavir – INVIRASE** (CAP); **stavudine – ZERIT** (CAP); **tenofovir disoproxil – VIREAD** (CAP); **tipranavir - APTIVUS** (CAP)

- PRAC consultation on post-authorisation measures, upon CHMP request

Regulatory details:
PRAC Rapporteur (lead): Qun-Ying Yue (SE)
PRAC Co-Rapporteur: Isabelle Robine (FR), Julie Williams (UK)

Administrative details:
Procedure number(s): N/A
Procedure scope: Review of class labelling on mitochondrial dysfunction, lactic acidosis and lipodystrophy
MAH(s): AbbVie Ltd (Kaletra, Norvir), Boehringer Ingelheim International GmbH (Aptivus, Viramune), Bristol-Myers Squibb Pharma EEIG (Reyataz, Sustiva, Zerit), Bristol-Myers Squibb and Gilead Sciences Ltd.(Atripla), Gilead Sciences International Ltd.(Emtriva, Eviplera, Stribild, Truvada, Viread), Janssen-Cilag International N.V.(Edurant, Intelence, Prezista), Merck Sharp & Dohme Ltd (Crixivan, Stocrin), Roche Registration Ltd. (Invirase), ViiV Healthcare UK Limited (Combivir, Epivir, Kivexa, Telzir, Trizivir, Ziagen)

Background

For background, see PRAC minutes 10-14 June 2014. As discussed previously a list of questions for the MAHs was prepared by the Rapporteur for agreement.

Summary of advice

PRAC agreed that currently the product information for the above mentioned antiviral medicines, including their patient leaflets, did not reflect the most up-to-date evidence with regard to lactic acidosis, mitochondrial dysfunction and lipodystrophy.

Therefore, MAHs should propose amendments of the existing warning as necessary and should provide evidence on whether monitoring for blood lipids/glucose is to be recommended for the various products, based on what was reported on metabolic profiles in clinical trials.

Further PRAC advice will be provided following submission of the MAHs' responses and their assessment.

10.3.2. Epoetins:
Darbepoetin alfa – ARANESP (CAP);
Epoetin alfa – ABSEAMED (CAP), **BINOCRIT** (CAP), **EPOETIN ALFA HEXAL** (CAP);
Epoetin beta – MIRCERA (CAP), **NEORECORMON** (CAP);
Epoetin theta – BIOPOIN (CAP), **EPORATIO** (CAP);
Epoetin zeta – RETACRIT (CAP), **SILAPO** (CAP)

- PRAC consultation on post-authorisation measures, upon CHMP request

Regulatory details:
PRAC Rapporteur (overall): Valerie Strassmann (DE)
PRAC Co-Rapporteurs: Isabelle Robine (FR), Dolores Montero Corominas (ES)

Administrative details:
Procedure scope: Erythropoiesis-stimulating agents: outcome of statistical analysis of clinical trial data in chronic kidney disease (CKD) patients on dialysis/not on dialysis (treatment of anaemia)
Procedure number(s): EMEA/H/C/000332/LEG 083.3 (Aranesp), EMEA/H/C/000727/LEG 023.3 (Abseamed), EMEA/H/C/000725/LEG 022.3 (Binocrit), EMEA/H/C/000726/LEG 023.3 (epoetin Alfa Hexal), EMEA/H/C/000739 LEG 032.3 (Mircera), EMEA/H/C/000116/LEG 049.3 (NeoRecormon), EMEA/H/C/001036/LEG 019.3 (Biopoin), EMEA/H/C/001033/LEG 019.3 (Eporatio), EMEA/H/C/000872/LEG 036.3 (Retacrit), EMEA/H/C/000760/LEG 035.3 (Silapo)
Scope: Erythropoiesis-Stimulating Agents (ESA): Outcome of Statistical analysis of clinical trial data in chronic kidney disease (CKD) patients on dialysis/not on dialysis (treatment of anaemia).
MAH(s): Amgen Europe B.V. (Aranesp), Medice Arzneimittel Pütter GmbH & Co. KG (Abseamed), Sandoz GmbH (Binocrit), Hexal AG (Epoetin Alfa Hexal), Roche Registration Ltd (Mircera, NeoRecormon), CT Arzneimittel GmbH (Biopoin), Ratiopharm GmbH (Eporatio)

Background

For background, see PRAC minutes 13-16 May 2013. In May 2013 specific statistical analysis plans (SAP) and common core elements of an analysis plan (CCE) for the MAHs to re-analyse their clinical trial data - to evaluate the risk of cardiovascular events associated with epoetins used to obtain haemoglobin levels of 11g/dL or higher in chronic kidney disease (CKD) patients (on dialysis or not on dialysis) for the treatment of anaemia - were agreed by PRAC/CHMP and transmitted to the MAHs.

Since then clinical data have been reviewed and submitted by the MAHs and assessed by the Rapporteurs for discussion at PRAC.

Summary of advice

The PRAC discussed the results provided jointly by all MAHs. The studies in these pooled analyses have different trial designs, target haemoglobin concentrations, and dose regimen, as well as varied collection of historic and on-study variables. On study variables and the outcomes of interest were influenced by subject baseline characteristics.

Pooled data were analysed to explore the relationship between achieved haemoglobin concentrations and administered erythropoiesis-stimulating agents (ESA) doses and response to therapy (initial response, haemoglobin rate of change, haemoglobin variability) and adverse outcomes of interest (all-cause mortality, cardiac events, cerebrovascular events) in diabetic versus non-diabetic and dialysis versus non-dialysis patients.

Based on the results of the analysis, the PRAC agreed that an update to reflect the outcome in the product information and to provide details of the results of the analyses should be considered. The PRAC agreed on proposals and questions to be sent to the MAHs for their feedback.

It was further considered that it might be helpful to obtain additional information on study results concerning increased risks observed in poor responders, e.g. information on comorbidities and concomitant parenteral iron therapy as well as information on causes of mortality in poor responders.

The MAHs should provide responses on the above points to be addressed by 60 days. Further PRAC advice will be provided once responses are fully assessed.

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Influenza vaccine (inactivated, split-virion trivalent) (NAP)

- PRAC consultation on a safety-related variations upon CHMP request, upon Member State's request

Regulatory details:
Lead member: Isabelle Robine (FR)

Administrative details:
Procedure number: FR/H/0122/001/II/68, FR/H/0121/001/II/72, FR/H/0139/001/II/46
Procedure scope: Consultation on safety variations on annual enhanced active safety surveillance for the 2014-2015 influenza vaccination campaign
MAH(s): Sanofi Pasteur, Sanofi Pasteur MSD (Mutagrip, Vaxigrip, Vaxigrip Enfants)

Background

Vaxigrip and Mutagrip are inactivated split-virion trivalent influenza vaccines (TIV) which contain the NH 2014-2015 influenza strains. These vaccines are indicated for active immunization against flu disease caused by the strains of influenza virus types A and B contained in the vaccine in subjects from 6 months of age and older.

The MAH plans to conduct an annual active safety surveillance through an open-label multicentre uncontrolled Phase IV clinical trial able to rapidly detect a significant increase in the frequency and/or severity of expected reactogenicity (local, systemic or allergic reactions) of its newly released TIV used for the 2014-2015 influenza vaccination campaign (compared to what was known or expected of the previous year's TIV), in accordance with the interim guidance on enhanced safety surveillance for

seasonal influenza vaccines in the EU (EMA/PRAC/222346/2014). A PRAC advice was requested by the RMS (FR) on this plan.

Summary of advice

The previously raised PRAC questions on the risk management plan, had been addressed the MAH by means of an updated RMP. However the PRAC stressed that there were some additional points to be addressed in the final study protocol, recommending the recruitment of supplementary investigators in the event that there is a low recruitment rate or a prolonged enrolment period.

11.2. Renewals of the Marketing Authorisation

None

11.3. Other requests

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

- PRAC consultation on risk of accidental exposure, upon Member State's request

Regulatory details:
Lead member: Sabine Straus (NL)

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

Background

For background, see PRAC Minutes May 2014. Following the recommendations of the PRAC to improve the visibility for fentanyl patches, the brand leader MAH submitted a proposal to change the patches but suggested to await study results before any improvement of the visibility of the patches could be introduced in the EU. The advice of the PRAC was requested on the lead Member State assessment of this proposal.

Summary of advice

The PRAC agreed that the timeframe for implementing improvements in the visibility of the patches in the EU, as proposed by the MAH, especially in consideration of feasible interim measures adopted in other regions, was not satisfactory. There was a consensus on the need to discuss further at EU level, taking into account existing guidance and expertise on best strategies for risk minimisation in the field of medication errors. The brand leader should be requested for revised proposals.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Pharmacovigilance audits and inspections

12.2.1. Pharmacovigilance Systems and their Quality Systems

- Update on the Pharmacovigilance Programme

At the organisational matters teleconference on 24 July 2014, the EMA secretariat gave an overview of the current implementation programme on shared IT tools to support pharmacovigilance systems, including EudraVigilance, the database implemented under Article 57(2) of Regulation (EC) No 726/2004 and the platform for literature monitoring as well as the PSUR repository. The PRAC stressed the importance of on-going dialogue with the Committee, Member States, EudraVigilance Working Group, and the project team leading the implementation of the pharmacovigilance legislation and underlined the importance of training as new IT tools emerge.

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

12.3.1. Periodic Safety Update Reports

None

12.3.2. PSURs Repository

- Update on the PSUR repository Project

The EMA secretariat gave feedback from the PSUR Repository Project Advisory Group to the PRAC on the outcome of discussions on a revised timetable for delivery of the functionality to support the submission of non-Single Assessment PSURs and Assessment Reports (PSURs for substances that are authorised in just one Member State and are not included in the EURD list) which is an auditable requirement.

At the organisational matters teleconference on 24 July 2014, the PRAC was also given feedback on the outcome of initial discussions on the same proposal with the CMDh. The PRAC agreed on the proposal pending agreement from CMDh.

12.3.3. Union Reference Date List

- Consultation on the draft List, version July 2014

At the organisational matters teleconference on 24 July 2014, the PRAC endorsed the draft revised EURD list version July 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 July 2014, the updated EURD list was adopted by the CHMP at its July 2014 meeting and published on the EMA website on 08/08/2014 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.4. Signal Management

12.4.1. Signal Management

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

At the organisational matters teleconference on 24 July 2014, the PRAC was informed that the SMART group discussed progress on ongoing developments in the process for the provision of assessment reports of signals to MAHs. It was highlighted that, so far, advance notification of new signals to Industry had been well received. Regarding current business processes under revision, it was announced that the PRAC will shortly be consulted on the 'eRMR' (electronic reaction monitoring reports) and EudraVigilance access policy interface.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

- Guideline on good pharmacovigilance practices (GVP) Module VI on management and reporting of adverse reactions to medicinal products: revision of the post-authorisation studies reporting requirements

At the organisational matters teleconference on 24 July 2014, the PRAC noted the revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.

This revision mainly provides new simplified requirements on the management of adverse events occurring in non-interventional post-authorisation studies. The draft revised document was published for public consultation in June 2013. The PRAC noted the latest version of the revision taking into consideration comments received from stakeholders which, once adopted by EMA Executive Director, will be published on the EMA website.

12.5.2. List of Product under Additional Monitoring

- Consultation on the draft List, version July 2014

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

Post-meeting note: The updated additional monitoring list was published on 30/07/2014 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.6. EudraVigilance Database

12.6.1. Activities related to the confirmation of full functionality

None

12.6.2. Changes to EudraVigilance Database and functional specifications

- Project plan on EudraVigilance auditable requirements

At the organisational matters teleconference on 24 July 2014, the PRAC heard a presentation on the Project plan on EudraVigilance auditable requirements and activities to be carried out, which as of September 2014 include user acceptance testing, training on website review and user documentation publication. An audit strategy document is also to be prepared and the GVP module VI is to be updated. The PRAC will be kept informed periodically of progress made.

12.6.3. Others

- Revision of the EudraVigilance Access Policy in accordance with Regulation 726/2004

At the organisational matters teleconference on 24 July 2014, feedback was requested from the PRAC on aspects of the draft Revision of EudraVigilance Access Policy for Medicines for Human Use in advance of publication for public consultation. Since 2007 the Agency has been granting Medicines Regulatory Authorities in the EEA unrestricted access to all ICSRs held in EudraVigilance. Since May 2012, healthcare professionals, consumers and patients, MAHs and research organisations have been given some access to spontaneous reports held in the European pharmacovigilance database concerning centrally authorised medicinal products. As of September 2014, this access will be gradually extended to active substances contained in all other medicinal products authorised in the EEA starting with substances included in the work sharing for signal management.

Taking into account the important developments in transparency, the EudraVigilance Access Policy has been updated with due consideration given to personal data protection requirements pursuant to the provisions of Regulation (EC) No 45/2001. The PRAC provided the requested feed-back and supported the update.

12.7. Risk Management Plans and Effectiveness of risk Minimisations

None

12.8. Post-authorisation Safety Studies

None

12.9. Community Procedures

None

12.10. Risk communication and Transparency

12.10.1. Public Participation in Pharmacovigilance

- Draft rules of procedure on the organisation and conduct of public hearings

The EMA Secretariat presented to PRAC a revised Rules of Procedures for public hearings to be published on the EMA website for public consultation. The PRAC endorsed this revised version to launch the public consultation (open until 15 October 2014).

Post-meeting note: the Draft rules of procedures on the organisation and conduct of public hearings at the Pharmacovigilance Risk Assessment Committee (PRAC) (EMA/624809/2013) were published on the EMA website on 24/7/2014.

12.11. Continuous pharmacovigilance

12.11.1. Marketing cessation, marketing suspension and withdrawals of medicinal products from the market

- Update on the list of withdrawn products

In June 2014, the EMA Secretariat presented the list of "withdrawn products" provided in Article 123(4) of Directive 2001/83/EC to the CMDh and the PRAC. As an outcome, the EMA was asked to set up a process to optimise the sharing of information between Competent Authorities that is relevant to the list of "withdrawn products" taking into account the requirements laid down in Article 123(1) of Directive 2001/83/EC.

At the organisational matters teleconference on 24 July 2014, the EMA Secretariat provided PRAC with some feedback. While MA revocations, supply prohibitions, or withdrawals of products from the market should be communicated within the EU regulatory network via the established Pharmacovigilance Rapid Alert channel as applicable (since these actions constitute grounds for triggering a referral procedure under Article 107i), refused national MA applications should be notified by NCAs to the EMA using a dedicated template (made available via the Eudraportal) to the dedicated EMA inbox (withdrawnproducts@ema.europa.eu). Refused MRP/DCP applications can be retrieved by EMA from Communication and Tracking System and do not need to be notified. This process was agreed with the CMDh in July 2014. The PRAC was invited to provide further comments until 5 September 2014, after which the process and related template will be considered adopted by the PRAC.

Post-meeting note: On 13 August 2014, the PRAC was informed about the publication of the first version of the list of withdrawn products.

12.12. Interaction with EMA Committees and Working Parties

None

12.13. Interaction within the EU regulatory network

12.13.1. European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

- EU Post-Authorisation Studies (PAS) Register

At the organisational matters teleconference on 24 July 2014, the PRAC was informed that in the context of a recent survey of ENCePP Centres' experience with the EU PAS Register (ENCePP E-Register of Studies), the publicly available register referred to in GVP VIII, a technical upgrade including additional functionalities had been proposed. The EMA is therefore inviting feedback from Member States on their experience with the EU PAS Register to inform the proposed upgrade. A follow-up discussion based on feedback received is planned for the October 2014 meeting.

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

None

12.15. Others

None

13. Any other business

13.1. Regulation on Pharmacovigilance Fees

The PRAC was presented a summary of the content of the recently published Regulation (EU) No 658/2014 of the European Parliament and of the Council of 15 May 2014 on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use. The EMA informed the Committee that rules for appointment of Rapporteurs currently under revision will take into account the principles included in the new Regulation.

14. ANNEX I Risk Management Plans

Medicines in the pre-authorisation phase

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

14.1.1. Aclidinium, formoterol

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

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

14.1.2. Allogeneic t cells genetically modified to express suicide gene

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

Administrative details:
Product number(s): EMEA/H/C/002801, *ATMP, Orphan*
Intended indication: Treatment in haploidentical haematopoietic stem cell transplantation

14.1.3. Budesonide, formoterol

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

Administrative details:
Product number(s): EMEA/H/C/003951, EMEA/H/C/003952
Intended indication: Treatment of asthma and treatment of patients with severe COPD
Procedure number EMEA/H/C/003953
Intended indication: Treatment of asthma

14.1.4. 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)

14.1.5. Ceritinib

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

Administrative details:
Product number(s): EMEA/H/C/003819
Intended indication: Treatment of adult patients with previously treated anaplastic lymphoma; treatment of anaplastic lymphomakinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC)

14.1.6. Duloxetine

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

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

14.1.7. Ferric citrate coordination complex

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

Administrative details:
Product number(s): EMEA/H/C/003776
Intended indication: Treatment of hyperphosphataemia

14.1.8. Filgrastim

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

Administrative details:
Product number(s): EMEA/H/C/003956, *Duplicate*
Intended indication: Reduction in the duration of neutropenia and the incidence of febrile

14.1.9. Guanfacine

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

Administrative details:
Product number(s): EMEA/H/C/003759
Intended indication: Treatment of attention deficit hyperactivity disorder (ADHD)

14.1.10. Human papillomavirus (rDNA)

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

Administrative details:
Product number(s): EMEA/H/C/003852
Intended indication: Treatment of human papillomavirus (HPV) diseases

14.1.11. Ibrutinib

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

Administrative details:
Product number(s): EMEA/H/C/003791, *Orphan*
Intended indication: Treatment of mantle cell lymphoma, chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma

14.1.12. Idelalisib

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

Administrative details:
Product number(s): EMEA/H/C/003843
Intended indication: Treatment of patients with relapsed chronic lymphocytic leukaemia (CLL) and for the treatment of patients with refractory indolent non-Hodgkin lymphoma (iNHL)

14.1.13. Lamivudine, raltegravir

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

Administrative details:
Product number(s): EMEA/H/C/003823
Intended indication: Treatment of human immunodeficiency virus (HIV-1)

14.1.14. Nonacog gamma

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

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

14.1.15. Ospemifene

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

Administrative details:
Product number(s): EMEA/H/C/002780
Intended indication: Treatment of vulvar and vaginal atrophy (VVA)

14.1.16. Sofosbuvir, ledipasvir

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

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

14.1.17. Voriconazole

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

Administrative details:
Product number(s): EMEA/H/C/003737, *Generic*
Intended indication: Treatment of fungal infections

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[33] – PRAC-led procedure

14.1.18. Boceprevir – VICTRELIS (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002332/II/0029
Procedure scope: Submission of an updated RMP (version 8.0) to address the CHMP requests following the evaluation of the RMP version 7 (EMEA/H/C/2332/RMP/029, dated 19 December 2013). This update includes addition of the new important identified risk of pancytopenia, modifications of the

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

timelines for P05063 and P07755 and inclusion of the completed study report for the mechanistic study of anaemia and proposes the update of the educational material. Furthermore, the MAH proposes the early termination of study P05063
MAH(s): Merck Sharp & Dohme Limited

14.1.19. 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/0062
Procedure scope: Update of the RMP (version 28.4) following the modification to the study 1160 - 144 (post-authorisation non-interventional study aiming to evaluate the potential off-label use of dabigatran in Europe)
MAH(s): Boehringer Ingelheim International GmbH

14.1.20. Octocog alfa – HELIXATE NEXGEN (CAP), KOGENATE BAYER (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000276/WS0557/0160, EMEA/H/C/000275/WS0557/0165
Procedure scope: Submission of an update to the RMP (version 6.0)
MAH(s): Bayer Pharma AG

14.1.21. Pertuzumab – PERJETA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002547/II/0009
Procedure scope: Update of the RMP to amend the protocol of the Annex II obligation PERUSE study and its due date. Annex II is updated accordingly. In addition, the MAH proposed a change to the Annex of the EU RMP description of the global enhanced pharmacovigilance pregnancy programme regarding the duration of contraception in relation to concomitant treatment
MAH(s): Roche Registration Ltd

14.1.22. Vemurafenib – ZELBORAF (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/002409/II/0017
Procedure scope: Submission of an update to the RMP (version 8.0)
MAH(s): Roche Registration Ltd

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

14.1.23. Adalimumab – HUMIRA (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000481/II/0127
Procedure scope Extension of indication in Enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet was proposed to be updated in accordance.
MAH(s): AbbVie Ltd.

PRAC Rapporteur assessment report was adopted via written procedure on 17 July 2014.

14.1.24. Alogliptin – VIPIDIA (CAP)
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 in order to reflect the results of study 402 (phase IIIb, randomised, 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

14.1.25. Alogliptin – VIPIDIA (CAP)
alogliptin, metformin – VIPDOMET (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002182/WS0520/0002, EMEA/H/C/002654/WS0520/0001
Procedure scope: Update of SmPC sections 4.4, 4.8, and 5.1 in order to reflect the results of study 305 (phase III, randomised, 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 (T2DM). The MAH took this opportunity to propose amendments to the RMP in order to reflect study 305 results. The requested worksharing procedure proposed amendments to the SmPC and RMP
MAH(s): Takeda Pharma A/S

14.1.26. 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
Procedure scope: Update of SmPC sections 4.4 and 4.8 in order to reflect the results of study 305 (phase III, randomised, 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 (T2DM). The package leaflet was proposed to be updated accordingly. The MAH took this opportunity to propose amendments to the RMP in order to reflect study 305 results. The requested variation procedure proposed amendments to the SmPC, PIL and RMP
MAH(s): Takeda Pharma A/S

14.1.27. Alogliptin, pioglitazone – INCRESYNC (CAP)
alogliptin, metformin – VIPDOMET (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002178/WS0519/0003, EMEA/H/C/002654/WS0519/0003
Procedure scope: Update of SmPC sections 4.4, 4.8, and 5.1 in order to reflect the results of study 402 (phase IIIb, randomised, 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 MAH took this opportunity to propose amendments to the RMP in order to reflect study 402 results as well updating its structure according to the new European Union (EU) template for RMPs. The requested worksharing procedure proposed amendments to the SmPC and RMP
MAH(s): Takeda Pharma A/S

14.1.28. Ambrisentan – VOLIBRIS (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000839/II/0039, *Orphan*
Procedure scope: Update of SmPC section 4.4 in relation to the current recommendations for liver function and SmPC section 5.1 with data on aminotransferase abnormalities from an analysis of the clinical study reports (CSR) for PASS 'AMB110094 (VOLT)'. The current 'Health care Professional information' in Annex II will be updated accordingly as well as the package leaflet and RMP
MAH(s): Glaxo Group Ltd

14.1.29. Bosentan – TRACLEER (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/000401/II/0066
Procedure scope: Extension of indication to include the treatment of symptomatic pulmonary arterial hypertension in paediatric patients aged from 3 months to 18 years. The SmPC has been updated in order to include the data from studies conducted according to the agreed paediatric investigation plan (PIP) for bosentan (EMEA-000425-PIP02-10-M04). As a consequence, SmPC sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 5.3 and 6.6 have been updated. The Package Leaflet has been updated accordingly. In

addition, taking into account the new data in the paediatric population, an updated version of the RMP (version 5) has been provided
MAH(s): Actelion Registration Ltd.

14.1.30. Deferiprone – FERRIPROX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000236/II/0089/G
Procedure scope: Update of SmPC section 4.5 regarding combination of deferiprone with other iron chelators further to request of the PRAC in the assessment of the PSUR (PSUV/083). Update of section 5.1 of the SmPC and the RMP with the results of Study LA37-111 conducted to evaluate the effect of deferiprone on cardiac QT and QT_C interval duration
MAH(s): Apotex Europe BV

14.1.31. 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 treatment of giant cell tumour of bone in adults or skeletally mature adolescents. As a consequence, it is proposed to update SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2
MAH(s): Amgen Europe B.V.

14.1.32. Dexamethasone – OZURDEX(CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001140/II/0015
Procedure scope: Update of SmPC section 4.1 to add a new indication for treatment of adult patients with diabetic macular oedema. Consequential updates were proposed for SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2. In addition, the MAH proposed to reduce and consolidate the current HCP leaflet, which is provided as a tear off section after the package leaflet
MAH(s): Allergan Pharmaceuticals Ireland

14.1.33. Dibotermin alfa – INDUCTOS (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000408/II/0071
Procedure scope: Extension of indication to broaden the use of Inductos in interbody lumbar spine fusion
MAH(s): Medtronic BioPharma B.V.

14.1.34. Entecavir – BARACLUDE (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000623/II/0041
Procedure scope: Extension of indication to include treatment of chronic hepatitis B virus (HBV) infection in paediatric patients from 2 to <18 years of age with compensated liver disease and evidence of active viral replication and persistently elevated serum alanine transaminase (ALT) levels
MAH(s): Bristol-Myers Squibb Pharma EEIG

14.1.35. Enzalutamide – XTANDI (CAP)

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

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

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

14.1.36. Infliximab – REMICADE (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/000240/II/0179
Procedure scope: Update of SmPC section 4.8 of to add intestinal obstruction based on the data available from clinical trials, post-marketing experience and from registries in adult Crohn's disease
MAH(s): Janssen Biologics B.V.

14.1.37. Lenalidomide – REVLIMID (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/000717/X/0073/G
Procedure scope: Grouping of type II variations to add the following indication: continuous treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant and a line extension application to add the following strength: 20 mg (21 capsules pack)
MAH(s): Celgene Europe Limited

14.1.38. Liraglutide – VICTOZA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/001026/II/0028
Procedure scope: Update of SmPC sections 4.2, 4.8 and 5.1 to reflect data from study NN2211-3916 (efficacy and safety of liraglutide as add-on to existing diabetes medications in patients with type 2 diabetes mellitus and moderate renal impairment). The Package Leaflet has been updated accordingly as well as the RMP (revised version 4 provided). In addition, the MAH takes the opportunity to update the instructions for use in the Package Leaflet to comply with EN ISO14971:2012 (application of risk management to medical devices) and to reflect residual risk mitigations
MAH(s): Novo Nordisk A/S

14.1.39. Pasireotide – SIGNIFOR (CAP)

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

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

Product number(s): EMEA/H/C/002052/X/0010
Procedure scope: Line extension application to add 20mg, 40mg and 60mg powder and solvent for suspension for injection in the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative, or who are inadequately controlled on treatment with other somatostatin analogues
MAH(s): Novartis Europharm Ltd

14.1.40. Posaconazole – NOXAFIL (CAP)

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

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000610/X/0033
Procedure scope: Line extension to add Noxafil 18mg/ml concentrate for solution for infusion
MAH(s): Merck Sharp & Dohme Limited

14.1.41. 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

14.1.42. Saxagliptin – KOMBOGLYZE (CAP)
saxagliptin, metformin – ONGLYZA (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/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

14.1.43. Telithromycin – KETEK (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/000354/II/0062
Procedure scope: Update of SmPC sections 4.4 and 4.8 with new adverse events on ventricular arrhythmias, convulsions and tremor following a request from the CHMP
MAH(s): Aventis Pharma S.A.

14.1.44. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000955/II/0032
Procedure scope: Update of SmPC sections 4.1 and 5.1 and consequential changes to section 1 of the Package Leaflet in order to extend the indication to the treatment in combination with methotrexate (MTX) of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX
MAH(s): Roche Registration Ltd

14.1.45. Trastuzumab – HERCEPTIN (CAP)

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

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000955/II/0032
Procedure scope:
-B.II.e.1.b.2- Additional presentation Herceptin 600mg solution for injection in a single-use injection device (SID). In addition, the manufacturing process requires additional manufacturing facilities and equipment. Buildings 231 and 232 at the Roche Kaiseraugst site are used for filling/pre-assembly and final assembly/secondary packaging of the new SID. The administration system is intended to enhance ease of use and increase patient convenience and compliance.

-B.II.d.1.c)- Change of the specifications of the finished product. The extractable volume specifications is changed to Dose accuracy.
-B.II.d.1.a)- Tightening of the specification of protein content from 120±12mg/mL to 120±8mg/mL to match the dose range achieved by administration of 5mL from the vial presentation.
MAH(s): Roche Registration Ltd

PRAC Rapporteur's AR adopted via written procedure on 18 July 2014.

14.1.46. Ustekinumab – STELARA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000958/II/0041
Procedure scope: Update of SmPC section 4.8 to add the adverse reactions of skin exfoliation and erythrodermic psoriasis further to the request of the CHMP to implement the outcome of a PRAC signal recommendation
MAH(s): Janssen-Cilag International N.V.

14.1.47. Zoledronic acid – ZOLEDRONIC ACID TEVA (CAP)

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

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

Administrative details:
Product number(s): EMEA/H/C/002439/X/0008
Procedure scope: Line extension to include a new pharmaceutical form, solution for infusion. The new pharmaceutical form has three new presentations
MAH(s): Teva Pharma B.V.

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

14.1.48. Alendronic acid, colecalciferol – VANTAVO (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001180/R/0019 (with RMP version 7.0)
MAH(s): Merck Sharp & Dohme Limited

14.1.49. Amifampridine – FIRDAPSE (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001032/R/0029 (with RMP version 5.0)
MAH(s): BioMarin Europe Ltd

14.1.50. Dronedarone – MULTAQ (CAP)

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

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

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

14.1.51. Sevelamer – RENAGEL (CAP)

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

Regulatory details:
PRAC Rapporteur: Terhi Lehtinen (FI)

Administrative details:
Product number(s): EMEA/H/C/000254/R/0100 (with RMP version 6.0)
Applicant: Genzyme Europe BV

14.1.52. Silodosin – SILODYX (CAP), UROREC (CAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Product number(s): EMEA/H/C/001209/R/0016 (with RMP version 11.0), EMEA/H/C/001092/R/0016 (with RMP version 11.0)
Applicant: Recordati Ireland Ltd.

15. ANNEX I Periodic Safety Update Reports (PSURs)

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

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

Evaluation of PSUR procedures

15.1.1. Ambrisentan – VOLIBRIS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000839/PSUV/0037
MAH(s): Glaxo Group Ltd

15.1.2. Amifampridine – FIRDAPSE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001032/PSUV/0028
MAH(s): BioMarin Europe Ltd

15.1.3. Avanafil – SPEDRA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002581/PSUV/0005
MAH(s): Menarini International Operations Luxembourg S.A.

15.1.4. Belatacept – NULOJIX (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002098/PSUV/0021
MAH(s): Bristol-Myers Squibb Pharma EEIG

15.1.5. Besilesomab – SCINTIMUN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001045/PSUV/0004 (with RMP version 11.0)
MAH(s): Cis Bio International

15.1.6. Bromelain enriched proteolytic enzyme preparation from ananas comosus – NEXOBRID (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002246/PSUV/0011
MAH(s): MediWound Germany GmbH

15.1.7. Darunavir – **PREZISTA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000707/PSUV/0066
MAH(s): Janssen-Cilag International N.V.

15.1.8. Dextromethorphan, quinidine – **NUEDEXTA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002560/PSUV/0003
MAH(s): Jenson Pharmaceutical Services Ltd

15.1.9. Enzalutamide – **XTANDI** (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002639/PSUV/0009
MAH(s): Astellas Pharma Europe B.V.

15.1.10. Eptacog alfa (activated) – **NOVOSEVEN** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000074/PSUV/0080 (with RMP version 1.0)
MAH(s): Novo Nordisk A/S

15.1.11. Human hepatitis B immunoglobulin – **ZUTECTRA** (CAP), NAP

- Evaluation of a PSUSA[34] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001631/201311
MAH(s): Biotest Pharma GmbH, various

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

15.1.12. Hydrocortisone – PLENADREN (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002185/PSUV/0013
MAH(s): ViroPharma SPRL

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001101/PSUV/0060, EMEA/H/C/002617/PSUV/0016
MAH(s): MedImmune LLC

15.1.14. Lutropin alfa – LUVERIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000292/PSUV/0062
MAH(s): Merck Serono Europe Limited

15.1.15. Methylthioninium – METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP), NAP

- Evaluation of a PSUSA[35] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002029/201311
MAH(s): Provepharm, various

15.1.16. Nepafenac – NEVANAC (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000818/PSUV/0024
MAH(s): Alcon Laboratories (UK) Ltd

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

15.1.17. Nitric oxide – INOMAX (CAP), NAP

- Evaluation of a PSUSA[36] procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002172/201312
MAH(s): Linde Healthcare AB, various

15.1.18. Omalizumab – XOLAIR (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000606/PSUV/0052
MAH(s): Novartis Europharm Ltd

15.1.19. Pertuzumab – PERJETA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002547/PSUV/0008
MAH(s): Roche Registration Ltd

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000973/PSUV/0077
MAH(s): GlaxoSmithKline Biologicals S.A.

15.1.21. Roflumilast – DALIRESP (CAP), DAXAS (CAP), LIBERTEK (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002398/PSUV/0016 (with RMP version 13.0), EMEA/H/C/001179/PSUV/0020 (with RMP version 13.0), EMEA/H/C/002399/PSUV/0016 (with RMP version 13.0)
MAH(s): Takeda GmbH

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

15.1.22. Saquinavir – INVIRASE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

Administrative details:
Procedure number(s): EMEA/H/C/000113/PSUV/0108
MAH(s): Roche Registration Ltd

15.1.23. Ticagrelor – BRILIQUE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001241/PSUV/0023
MAH(s): AstraZeneca AB

15.1.24. Tobramycin – TOBI PODHALER (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002155/PSUV/0021
MAH(s): Novartis Europharm Ltd

15.1.25. Ustekinumab – STELARA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000958/PSUV/0040
MAH(s): Janssen-Cilag International N.V.

15.1.26. Verteporfin – VISUDYNE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000305/PSUV/0085
MAH(s): Novartis Europharm Ltd

15.1.27. Ziconotide – PRIALT (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000551/PSUV/0044
MAH(s): Eisai Ltd

15.2. Follow-up to PSUR procedures[37]

15.2.1. Cabecitabine – XELODA (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000316/LEG 027.2
Procedure scope: MAH's response to PSU-027 (PSUR#10) as adopted in May 2013
MAH(s): Roche Registration Ltd

15.2.2. Eculizumab – SOLIRIS (CAP)

- Evaluation of a follow-up to a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000791/LEG 055
Procedure scope: MAH's response to PSUR#10 as adopted in April 2014
MAH(s): Alexion Europe SAS

16. 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.

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

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

- Evaluation of an imposed PASS protocol

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

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

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

MAH(s): Dendreon UK Ltd

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

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure scope: PASS
MAH(s): Bayer

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

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure scope: DUS
MAH(s): Bayer

16.1.4. Deferasirox - EXJADE (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number: EMEA/H/C/000670/ANX/038.4
Procedure scope: Evaluation of MAH's response to ANX 038.3 as adopted by PRAC on 10 April 2014 including a revised PASS protocol for study CICL670E2422: observational cohort study in paediatric non transfusion dependant-thalassaemia (NTDT) patients over 10 years
MAH(s): Novartis Europharm Ltd

16.1.5. Ethinylestradiol, chlormadinone (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure scope: Evaluation of a joint 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): Gideon Richter, various

16.1.6. Modified vaccinia Ankara virus - IMVANEX (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

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

16.1.7. Sodium, magnesium, potassium sulphates for bowel preparation (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure scope: Evaluation of a PASS protocol for a multi-centre European observational drug utilisation study (DUS) of post-commitment BLI800 to assess drug utilisation in the real life setting in a representative sample of the European target population
MAH(s): Ipsen Pharma (Eziclen, Izinova)

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

16.2.1. Telaprevir – INCIVO (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002313/MEA 016.1
Procedure scope: Evaluation of MAH's response to MEA 016 [study report of study VX-950-C219] as adopted at CHMP in April 2013
MAH(s): Janssen-Cilag International N.V.

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

None

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

16.4.1. Dabigatran – PRADAXA (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/II/0066 (with RMP version 28.6)
Procedure scope: Submission of the final clinical study report (CSR) for study 1160.86 (open label, non-comparative pharmacokinetic and pharmacodynamic study to evaluate the effect of Pradaxa on

[39] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004
[40] In accordance with Article 107p-q of Directive 2001/83/EC
[41] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

coagulation parameters including a calibrated thrombin time test in patients with moderate renal impairment undergoing primary unilateral elective total knee or hip replacement surgery). The RMP has been updated accordingly (version 28.6)
MAH(s): Boehringer Ingelheim International GmbH

16.4.2. Denosumab – PROLIA (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/001120/II/0040 (without RMP)
Procedure scope: Submission of the results of a category 3 PASS - study 20090695: post-marketing observational study to estimate off-label use in selected EU Member States
MAH(s): Amgen Europe B.V.

16.4.3. Dolutegravir – TIVICAY (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002753/II/0001 (with RMP version 2.0)
Procedure scope: Submission of data from a physiologically-based pharmacokinetic model in fulfilment of MEA 4 regarding the potential for a drug-drug interaction with midazolam
MAH(s): ViiV Healthcare

16.4.4. Human rotavirus, live attenuated – ROTARIX (CAP)

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000639/II/0062 (with RMP version 10.0)
Procedure scope: Submission of the final report of genetic stability study EPI-ROTA-014 VS BE – 112560 that addresses the post-approval measure ME2 005.2 in which the MAH commits to monitor the potential occurrence of genetic drifts and shifts in the vaccine strain in post-marketing settings
MAH(s): GlaxoSmithKline Biologicals S.A.

16.5. 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[42]

16.5.1. Betaine anhydrous – CYSTADANE (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

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

Administrative details:
Procedure number(s): EMEA/H/C/000678/MEA 018.3
Procedure scope: Submission of the first progress report of Cystadane surveillance PASS protocol (in collaboration with E-HOD) registry, replacing the ROCH registry. Final study report of the ROCH registry is submitted in parallel
MAH(s): Orphan Europe S.A.R.L.

16.5.2. Exenatide – BYDUREON (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002020/MEA 011.2
Procedure scope: First annual report on an epidemiologic study using one or more European databases to identify possible cases of thyroid neoplasms among type 2 diabetes mellitus patients who initiate exenatide once weekly (study B017)
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

16.5.3. Ulipristal – ESMYA (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002041/MEA 003.2
Procedure scope: Second annual progress report on a prospective multicentre non-interventional study of women treated with Esmya (ulipristal acetate) as pre-operative treatment of moderate to severe symptoms of uterine fibroids
MAH(s): Gedeon Richter Plc.

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 7 - 10 July 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***
Jan Neuhauser	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer reviewer for:	rivaroxaban, octocog alfa, ethinylestradiol, gestodene
Veerle Verlinden	Belgium	Full involvement	
Yuliyan Eftimov	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Nectaroula Cooper	Cyprus	Full involvement	
Eva Jirsová	Czech Republic	Full involvement	
Torbjörn Callréus	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Terhi Lehtinen	Finland	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
Agni Kapou	Greece	Full involvement	
Julia Pallos	Hungary	Cannot act as Rapporteur or Peer reviewer for:	bromocriptine
Hrefna Guðmundsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Ruchika Sharma	Ireland	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
Jelena Ivanovic	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	
Ingebjørg Buajordet	Norway	Full involvement	
Karen Pernille Harg	Norway	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Roxana Stroe	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Milena Radoha-Bergoč	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
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:	saxagliptin; saxagliptin, metformin; ticagrelor; exenatide
Marie Louise De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer reviewer for:	bupropion; ambrisentan; pneumococcal polysaccharide conjugate vaccine (adsorbed); human rotavirus, live attenuated
Brigitte Keller-Stanislawski		Full involvement	
Hervé Le Louet		Cannot act as Rapporteur or Peer reviewer for:	lenalidomide
Lennart Waldenlind		Full involvement	

Health care professionals and patients members	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting:**	**Topics on the current Committee Agenda for which restriction applies** **Product/substance**
Filip Babylon		Full involvement	
Kirsten Myhr		Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (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	
Michala Oron Lexner	Denmark	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Leo Niskanen	Finland	
Arnaud Batz	France	
Lotfi Boudali	France	
Carine Condy	France	
Joseph Emmerich	France	
Cyndie Picot	France	
Thomas Grüger	Germany	
Jutta Krappweis	Germany	
Vahid Taravati	Germany	
Emma Lawless	Ireland	
Ineke Crijns	Netherlands	
Andre Elferink	Netherlands	
Tamar Wohlfarth	Netherlands	
Cristel Loeb	Netherlands	
Frank Holtkamp	Netherlands	
Fakhredin Sayed Tabatabaei	Netherlands	
Diederick Slijkerman	Netherlands	
Lies Vlijmen	Netherlands	
Jozef Jodkowski	Poland	
Charlotte Backman	Sweden	
Karl-Mikael Kälkner	Sweden	
Lena Hansson	Sweden	
Anna-Lena Berg	Sweden	
Jan Sjöberg	Sweden	
Olle Karlström	Sweden	
Filip Josephson	Sweden	
Inga Bellahn	United Kingdom	
Julie Beynon	United Kingdom	
Sarah Mee	United Kingdom	
Karen Slevin	United Kingdom	
Edward Day	(independent expert)	

ANNEX III – List of abbreviations

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

www.ema.europa.eu

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