10 July 2014
EMA/PRAC/438418/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 10-13 June 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 and start of referrals will also be made available. For orphan medicinal products, the applicant name is published as this information is already publicly available.

Note on access to documents

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

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Explanatory notes

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1. Introduction

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

The Chairperson opened the meeting, welcoming all participants to the 10-13 June 2014 meeting of the PRAC.

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

All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC noted that Alexandra Martinovic had stepped down as alternate for Austria and thanked her for her contribution to the work of the PRAC.

1.2. Adoption of agenda of the meeting on 10-13 June 2014

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

1.3. Minutes of the previous PRAC meeting on 5-8 May 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 5-8 May 2014 EMA/PRAC/324055/2014 were published on the EMA website on 1 July 2014.

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

2.1. Newly triggered procedures

None

2.2. Ongoing Procedures

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

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

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

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

Background

A referral procedure under Article 107i of Directive 2001/83/EC is ongoing for methadone medicinal products for oral use containing povidone (see PRAC minutes 5-8 May 2014). The (Co)-Rapporteurs prepared an assessment of the responses to the list of questions provided by the marketing authorisation holders involved in the referral procedure and by the stakeholders who submitted replies. An ad-hoc expert meeting is planned on 16 June 2014 and the PRAC heard a presentation from an independent researcher[1] who submitted data considered in the review.

Summary of recommendation(s)/conclusions

The PRAC noted the final agenda for the ad-hoc expert meeting, and adopted the list of experts and a revised list of questions to be answered by the experts. The PRAC also adopted a list of outstanding issues to be addressed by the marketing authorisation holders (MAHs).

2.3. Procedures for finalisation

None

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

3.1. Newly triggered Procedures

3.1.1. **Ibuprofen** (NAP)

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

Regulatory details:
PRAC Rapporteur: Dolores Montero Corominas (ES)
PRAC Co-Rapporteur: Julie Williams (UK)

Administrative details:
MAH(s): various

Background

Following the conclusion of the review of available data on cardiovascular risk relating to diclofenac under Article 31 which recommended the same cardiovascular precautions for diclofenac as for selective COX-2 inhibitors (see EMA/353084/2013), it was identified the need to further consider the available data relating to high-dose (2400 mg daily) ibuprofen and consequently the UK Medicines Agency (MHRA) sent a letter of notification dated 09 June 2014 of a referral under Article 31 of Directive 2001/83/EC for the review of systemic high-dose (2400 mg daily) ibuprofen containing medicines.

[1] Dr Leh, University hospital of Haukeland, Norway

Discussion

The PRAC noted the notification letter from the UK Medicines Agency highlighting the more recent scientific data that had become available on cardiovascular safety of the NSAIDs - including published results from a large meta-analysis of more than 600 randomised clinical trials from the Coxib and traditional NSAID Trialists' (CNT) collaborative group [2] - indicating that the cardiovascular risk associated with high-dose ibuprofen (2400 mg) may also be similar to that of COX-2 inhibitors.

The PRAC noted that, in addition, there was accumulating evidence that ibuprofen may also inhibit the antiplatelet action of low-dose aspirin for cardiovascular prophylaxis and agreed that related data should be further examined.

The PRAC considered that in the majority of individuals ibuprofen is usually taken at lower doses and for short periods of time and there is no suggestion that such use is associated with an increase in cardiovascular risk with ibuprofen. However, it was agreed that a review of available clinical trial and epidemiological data relating to high dose ibuprofen (2400 mg) including published and unpublished data on the risk of thrombotic events in adults along with new evidence on interaction with low-dose aspirin should be performed.

The PRAC appointed Dolores Montero Corominas (ES) as Rapporteur and Julie Williams (UK) as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/332909/2014) and a timetable for the procedure (EMA/PRAC/332908/2014) both published on the EMA website.

3.2. Ongoing Procedures

3.2.1. **Bromocriptine** (NAP)

- Review of the benefit-risk balance following 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: EMEA/H/A-31/1379
MAH(s): Sanofi-aventis, Meda Pharma, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for bromocriptine-containing medicines (see PRAC minutes 3-6 March 2014). The PRAC (Co)-Rapporteurs prepared an assessment report on the responses received to the list of questions from the MAHs.

Summary of recommendation(s)/conclusions

[2] Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Coxib and traditional NSAID Trialists' (CNT) Collaboration. The Lancet - 30 May 2013

The PRAC discussed the conclusion reached by the Rapporteurs and agreed on a list of outstanding issues, to complete the review and to address a few remaining aspects, to be addressed in an expedited way in accordance with a revised timetable (EMA/PRAC/493206/2013 rev.2).

3.2.2. **Hydroxyzine** (NAP)

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

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

Administrative details:
Procedure number: EMEA/H/A-31/1400
MAH(s): UCB, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for hydroxyzine-containing medicines (see, PRAC Minutes 8-11 May 2014). The PRAC previously agreed that input from the Paediatric Committee (PDCO) was needed on the procedure and a draft list of questions was prepared by the Rapporteur.

Summary of recommendation(s)/conclusions

The PRAC discussed and agreed a list of questions to be transmitted to the PDCO in order to obtain additional information on the clinical use of these products in paediatric patients.

3.3. Procedures for finalisation

None

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

None

3.5. Others

3.5.1. **Diacerein** (NAP)

- Review of recommendations of the 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: EMEA/H/A-31/1349
MAH(s): Negma-Wockhardt, TRB Chemedica, various

Background

The CMDh position on diacerein (see EMA/162540/2014), which followed the related PRAC recommendations, was adopted in March 2014 by majority vote and sent to the European Commission for a final legally binding decision valid throughout the European Union (EU).

Summary of recommendation(s)/conclusions

The PRAC noted a letter from the EC addressed to the PRAC and CMDh asking for review of the CMDh position and PRAC recommendations in light of some scientific points raised by the Standing Committee on Medicinal Products for Human Use. It was agreed that the Rapporteurs would prepare a reply to the letter to be discussed at the July 2014 PRAC.

4. Signals assessment and prioritisation[3]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Vildagliptin – GALVUS (CAP), JALRA (CAP), XILIARX (CAP)
Vildagliptin, metformin - EUCREAS (CAP), ICANDRA (CAP), ZOMARIST (CAP)

- Signal of rhabdomyolysis

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

Administrative details:
EPITT 17959 – New signal
Leading MS: SE
MAH(s): Novartis Europharm Ltd

Background

Vildagliptin is a dipeptidyl peptidase 4 (DPP-4) -inhibitor indicated in the treatment of type 2 diabetes mellitus in adults.

The exposure for centrally authorised medicine containing vildagliptin (alone or in combination with metformin) is estimated to have been more than 7.8 million patient-years worldwide, in the period from first authorisation in 2007 to 2014.

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

Discussion

The PRAC noted that the suspected cases of rhabdomyolysis described were generally well documented, all providing information on positive de-challenge and, in one case, on re-challenge. Although there could have been confounding by the medication reported in a number of cases, the temporal relationship with vildagliptin treatment as well as the reports of positive dechallenge and rechallenge indicated a plausible link between vildagliptin and rhabdomyolysis/myalgia. A possible biological explanation can be suggested by findings from a phase I dose-ranging study and non-clinical

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

findings in the toxicology studies. Furthermore, "muscle events/myopathy with and without concurrent statin use" were currently included as an important potential risk in the RMP due to previous observation of myalgia in studies in healthy volunteers.
Given this information the PRAC agreed that there was sufficient evidence to suggest a causal association between the event reported and vildagliptin and that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAH for Marketing Authorisation Holder (MAH) for Galvus (vildagliptin) and Eucreas (vildagliptin/metformin) should submit to the EMA, within 60 days, a variation to include 'rhabdomyolysis' in the product information[4] and include further information as requested by the PRAC.

For the full PRAC recommendations, see EMA/PRAC/337405/2014 published on the EMA website.

4.2. New signals detected from other sources

4.2.1. **Chlorhexidine** (NAP)

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

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 18000 – New signal
Leading MS: UK
MAH(s): various

Background

Chlorhexidine is an antiseptic and products containing various compositions of chlorhexidine (various strengths, aqueous and alcohol based) are widely used for skin disinfection prior to invasive procedures in the paediatric population including for central vascular catheter insertion, in order to avoid neonatal sepsis in neonatal intensive care units (NICUs).

A signal of chemical injury including burns when used in skin disinfection in premature infants was identified by the UK, based on 13 serious cases reported in the United Kingdom some with fatal outcome. UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases reported and noted the severity of the reactions, which ranged from severe erythema without skin breakdown to severe chemical burns with or without skin loss. Severe comorbidities associated with prematurity might have contributed to the outcome in the fatal cases reported. Both aqueous and alcohol based solutions were involved and the most severe cases occurred when solutions were allowed to pool around the umbilicus or under the infant during umbilical catheterisation.
The PRAC also discussed an analysis of cases reported in the literature and information collected from the Member States by means of an NUI and noted that there was no consensus on which solution

[4] SmPC Section 4.8

provides the best antimicrobial activity and lowest risk of ADRs for skin antisepsis during invasive procedures in neonates.

The PRAC agreed that it was important to further review the data on the use of chlorhexidine cutaneous solutions - in preterm and term newborn infants - for disinfection of the skin prior to invasive medical procedures, including whether the data highlighted particular at risk populations.

Additionally the PRAC agreed that the advice of the Paediatric Committee (PDCO) should be sought on the matter and a list of questions was adopted to explore with the PDCO the availability of European guidelines and recommendations regarding skin antisepsis prior to invasive procedure (i.e. central venous catheterisations) in term and preterm newborn infants.

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

Summary of recommendation(s)

- The MAHs for chlorhexidine containing products[5] should provide further information on the signal, within 60 days.
- The PDCO should be consulted on the matter by means of the agreed list of questions.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. **Ipilimumab – YERVOY** (CAP)

- Signal of posterior reversible encephalopathy syndrome (PRES)

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
EPITT 17955 – New signal
Leading MS: NL
MAH(s): Bristol-Myers Squibb Pharma EEIG

Background

Ipilimumab is a monoclonal antibody used in the treatment advanced (unresectable or metastatic) melanoma in adults.

The exposure to Yervoy, a centrally authorised medicine containing ipilimumab, is estimated to have been more than 14 000 patients worldwide, in the period from first authorisation in 2011 to 2014.

A signal of posterior reversible encephalopathy syndrome (PRES) was identified by the UK, following a review of case reports in the Medicines and Healthcare products Regulatory Agency (MHRA) database performed as part of routine signal detection activities. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Posterior Reversible Encephalopathy Syndrome (PRES) is a sub-acute neurological syndrome, which can be life-threatening and typically manifests with headache, cortical blindness, and seizures.
The PRAC discussed the information on the four reported cases of suspected PRES, as well as cases of

[5] Medlock, Ecolab Ltd, CareFusion UK, Regent Medical Overseas Limited and Engelhard Arzneimittel GmbH

leukoencephalopathy and non-specific encephalopathy reported, and agreed that although other factors or concomitant conditions could have explained the development of the reaction in some cases, in others it was not possible to exclude a causal association.
Therefore the signal should be further investigated.

Summary of recommendation(s)

- The MAH for Yervoy (ipilimumab) should submit to the EMA a cumulative review of the signal of PRES/leukoencephalopathy, including related MedDRA terms or relevant SMQ within the next PSUR (DLP 24/9/2014).

4.3. Signals follow-up and prioritisation

4.3.1. **Dexmedetomidine – DEXDOR** (CAP)

- Signal of infantile apnoeic attack

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 17657 – Follow-up January 2014
MAH(s): Orion Corporation

Background

For background information, see PRAC minutes of 6-9 January 2014.
The MAH replied to the request for further information on the signal infantile apnoeic attack and the responses were assessed by the Rapporteur.

Discussion

The PRAC noted that the number of suspected cases was small against the population exposure and concluded that the available data submitted by the MAH of respiratory related events in the paediatric population did not provide strong evidence of a causal association.
However, due to the fact that dexmedetomidine is used off-label in neonates, adverse reaction reporting in this population was considered less likely and this may have led to the small number of cases reported. Furthermore, the cases reported in adults did provide some evidence to support a causal association particularly the cases with no obvious alternative explanation for the respiratory-related events.

The PRAC acknowledged that the mechanism of action of respiratory-related effects remains unclear and therefore it was possible that any risk that occurs in adult patients would also apply to paediatric patients. Overall the PRAC considered that in the context of additional data, a causal association between respiratory depression/apnoea and dexmedetomidine cannot be ruled out and it was considered possible that dexmedetomidine, in combination with other factors, may have contributed to the development of apnoea. Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to enhancement of its effects.
Based on these conclusions the PRAC agreed that it would be important to update the product information for dexmedetomidine containing products to reflect these findings.

Summary of recommendation(s)

- The MAHs for the reference, centrally authorised[6] dexmedetomidine containing product should be requested to submit to the EMA within 60 days a variation to update the product information[7] to include the risk of respiratory depression and apnoea as well as enhancement of effects.

For the full PRAC recommendations, see EMA/PRAC/337405/2014 published on the EMA website.

4.3.2. Enzalutamide - XTANDI (CAP)

- Signal of myalgia

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

Administrative details:
EPITT 17792 – Follow-up February 2014
MAH(s): Astellas Pharma Europe B.V.

Background

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

Discussion

The PRAC discussed the new information received, including data from clinical trials, spontaneous reports and published literature. Some of the cases of myalgia, muscle spasm, muscular weakness, and back pain that were identified, reported a plausible temporal association as well as information on positive dechallenge. Therefore the PRAC agreed that the product information for enzalutamide containing products should be updated as regards to myalgia and related reactions.

Summary of recommendation(s)

- The MAHs for the reference, centrally authorised enzalutamide containing products [8] should be requested to submit to the EMA within 60 days a variation to update the product information to include "myalgia, muscle spasms, muscular weakness, back pain"[9] as undesirable effects.
- The MAH should also provide a cumulative review of rhabdomyolysis in the next periodic safety update report (DLP 28/2/2015), using the broad SMQ rhabdomyolysis/myopathy.

For the full PRAC recommendations, see EMA/PRAC/337405/2014 published on the EMA website.

[6] In line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, the marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 (EMA website). For nationally authorised medicines, it is the responsibility of the National Competent Authorities of the Member States to oversee that these recommendations are adhered to
[7] Section 4.4, 4.5 and 48 of the SmPC and PL.
[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

4.3.3. Fluoroquinolones:
ciprofloxacin (NAP), **enoxacin** (NAP), **flumequine** (NAP), **lomefloxacin** (NAP), **levofloxacin** (NAP), **moxifloxacin** (NAP), **norfloxacin** (NAP), **ofloxacin** (NAP), **pefloxacin** (NAP), **prulifloxacin** (NAP), **rufloxacin** (NAP)

- Signal of retinal detachment

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
EPITT 15914 – Follow-up April 2013
MAH(s): Bayer, Sanofi, various

Background

For background information, see PRAC minutes of 8-11 April 2013.
Following the last discussion at PRAC further epidemiological studies on the association between fluoroquinolones and retinal detachment had been published[10] and the EMA secretariat had conducted an analysis in The Health Improvement Network (THIN) database as previously recommended by the PRAC. The newly published literature and the outcome of the THIN analysis were critically reviewed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the newly available studies and agreed that they had limitations with regard to their ability to address the complex situation of ophthalmologic confounding factors and concurrent risk factors for retinal detachment.
Furthermore, most studies were based on secondary analyses of health care data with limited information on confounders. However, two studies[11] had found a statistically significant increased risk of retinal detachment in association with fluoroquinolone treatment.

Since October 2012, new cases of retinal detachment with fluoroquinolones were reported, some of them assessed as at least 'possibly related' to fluoroquinolone use.

The PRAC concluded that a causal relationship between fluoroquinolone intake and retinal detachment could neither be established nor firmly excluded based on the available data. Therefore, as a precautionary measure, a warning on visual disorders should be included in the product information of systemic fluoroquinolones, when no such warning exists.

[10] Kuo SC, Chen YT, Lee YT, Fan NW, Chen SJ, Li SY, Liu CJ, Chen TL, Chen TJ, Fung CP. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. Clin Infect Dis. 2014 Jan;58(2):197-203.
Fife D, Zhu V, Voss E, Levy-Clarke G, Ryan P. Exposure to oral fluoroquinolones and the risk of retinal detachment: retrospective analyses of two large healthcare databases. Drug Saf. 2014 Mar;37(3):171-82.
Chui CS, Man KK, Cheng CL, Chan EW, Lau WC, Cheng VC, Wong DS, Yang Kao YH, Wong IC. An investigation of the potential association between retinal detachment and oral fluoroquinolones: a self-controlled case series study. J Antimicrob Chemother. 2014 May 15. pii: dku145.
Kapoor KG, Hodge DO, St Sauver JL, Barkmeier AJ. Oral Fluoroquinolones and the Incidence of Rhegmatogenous Retinal Detachment and Symptomatic Retinal Breaks: A Population-Based Study. Ophthalmology. 2014 Jan 28. pii: S0161-6420(13)01181-0. doi: 10.1016/j.ophtha.2013.12.006.
[11] Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. JAMA. 2012 Apr 4;307(13):1414-9.
Kuo SC, Chen YT, Lee YT, Fan NW, Chen SJ, Li SY, Liu CJ, Chen TL, Chen TJ, Fung CP. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. Clin Infect Dis. 2014 Jan;58(2):197-203

Summary of recommendation(s)

- The MAHs for the nationally authorised[12] fluoroquinolone-containing medicines should be requested to submit to the NCAs of the MSs, within 3 months, a variation to update the product information to include a warning on vision disorders[13].

For the full PRAC recommendations, see EMA/PRAC/337405/2014 published on the EMA website.

4.3.4. **Lansoprazole** (NAP)

- Signal of haemolytic anaemia

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
EPITT 17805 – Follow-up February 2014
MAH(s): various

Background

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

Discussion

The PRAC discussed the new information assessed on the suspected cases of haemolytic anaemia reported in association with the use of lansoprazole. Considering the large population exposure to lansoprazole, the number of reported adverse haemolytic anaemia was overall considered very small and precluded drawing any conclusion on the signal. Some of the cases were confounded by concomitant medications or concurrent diseases and cumulatively, the post-marketing cases did not provide sufficient evidence to confirm that lansoprazole is associated with haemolytic anaemia.

Summary of recommendation(s)

- There is currently insufficient evidence to support any change to the product information of lansoprazole containing medicines in regard to haemolytic anaemia and no further regulatory action is required at this point in time.

4.3.5. **Mycophenolate mofetil - CELLCEPT** (CAP)

- Signal of bronchiectasis and hypogammaglobulinaemia - publication from *Boddana et al*.; Clinical Transplantation 2011

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

[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
[13] Section 4.4 of the Summary of Product Characteristics and package leaflet.

Administrative details:
EPITT 17760 – Follow-up February 2014
MAH(s): Roche Registration Ltd

Background

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

Discussion

The PRAC discussed the assessment of the review of the suspected cases of both bronchiectasis and hypogammaglobulinaemia (occurring both individually and concurrently) reported in association with mycophenolate mofetil (MMF). There were several cases of bronchiectasis in patients receiving an MMF-containing immunosuppressive regimen for which a causal relationship was likely. The majority of these were published cases (Boddana et al, Pijnenburg et al, Rook et al), which provide particularly strong evidence of a causal association. Three retrospective studies of renal transplant patients who received an MMF-containing regimen (n= 93, 96 and 289) found that an unusually high percentage (2–5%) of them subsequently developed bronchiectasis. There were no cases of bronchiectasis in patients who had not received MMF; although it was recognised that the retrospective nature of these three studies may have under-estimated the true incidence in these patients.

The review identified several cases where hypogammaglobulinaemia was likely to be causally related to MMF given in combination with other immunosuppressants (including MMF combined with ciclosporin and corticosteroids). The direct effect of MMF on B lymphocytes (as well T cells) seemed to provide a plausible biological mechanism to explain the reaction. Also, studies showed that the addition of MMF to prednisolone and ciclosporin profoundly decreased humoral (IgG) responsiveness in renal transplant recipients (Rentenaar et al 2002; Smith et al 1998).

Based on the evidence presented, the PRAC agreed that there was a reasonable possibility that MMF, as part of an immunosuppression regimen, was causally related to bronchiectasis. This should be reflected in the product information so that clinicians and patients are aware of this risk and, more importantly, can detect it at an early stage. Similarly, PRAC concluded that use of MMF, in combination with other immunosuppressants, was causally related to hypogammaglobulinaemia. As with bronchiectasis, the product information should be updated so that clinicians are aware of this risk and advised to test for it in patients with recurrent infections. Appropriate communications should be issued to inform prescribers of these changes.

Summary of recommendation(s)

- The MAH for the centrally authorised [14] mycophenolate mofetil containing medicines should be requested to submit to the EMA within 60 days a variation to include information on bronchiectasis and hypogammaglobulinaemia in the product information[15] and include a Direct Healthcare Professional Communication (DHPC) as an additional risk minimisation measure.

[14] 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
[15] Section 4.4 and 4.8 of the Summary of Product Characteristics and package leaflet.

- The MAHs of nationally authorised medicines containing mycophenolic acid and their salts including generic products should also submit within 60 days a variation to amend the product information (in line with that of the reference product) to the national competent authorities of the Member States.

For the full PRAC recommendations, see EMA/PRAC/337405/2014 published on the EMA website.

4.3.6. Vildagliptin – **GALVUS** (CAP), **JALRA** (CAP), **XILIARX** (CAP)
Vildagliptin, metformin – EUCREAS (CAP), **ICANDRA** (CAP), **ZOMARIST** (CAP)

- Signal of interstitial lung disease

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

Administrative details:
EPITT 17793 – Follow-up February 2014
MAH(s): Novartis Europharm Ltd

Background

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

Discussion

The PRAC discussed the assessment of the review of the signal including published literature, post-marketing and clinical trial data. Several of the clinical trial cases had confounding factors, and therefore it was difficult to draw any firm conclusions from the clinical trial data.

Many of the cases reported were confounded by the patient's medical history and/or concomitant medication (e.g. statins) that could provide an alternative explanation for the development of the reaction; or an infectious aetiology was suspected. However a causal role of vildagliptin could not be excluded in a number of cases, due to a plausible temporal relationship the fact that there was no effect of antibiotic treatment, and recovery upon discontinuation of vildagliptin and steroid treatment. Therefore the PRAC agreed that it was appropriate to include interstitial lung disease in the product information.

Summary of recommendation(s)

- The MAHs for the reference, centrally authorised [16] vildagliptin containing medicines should be requested to submit to the EMA within 60 days a variation to update the product information to include "interstitial lung disease"[17] as an undesirable effect.

For the full PRAC recommendations, see EMA/PRAC/337405/2014 published on the EMA website.

[16] 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
[17] Section 4.8 of the Summary of Product Characteristics and package leaflet

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. Bazedoxifene, estrogens conjugated

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

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

5.1.2. Dolutegravir, abacavir, lamivudine

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

Administrative details:
Product number(s): EMEA/H/C/002754
Intended indication: Treatment of human immunodeficiency virus (HIV) infection in adults and adolescents from 12 years of age who are antiretroviral treatment-naïve or are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral agents in Triumeq

5.1.3. Dulaglutide

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

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

5.1.4. 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, small lymphocytic lymphoma

5.1.5. 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 refractory indolent non-Hodgkin lymphoma (iNHL)

5.1.6. Insulin degludec, liraglutide

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

Administrative details:
Product number(s): EMEA/H/C/002647
Intended indication: Treatment of type 2 diabetes mellitus

5.1.7. Insulin glargine

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

Administrative details:
Product number(s): EMEA/H/C/002835*, Biosimilar*
Intended indication: Treatment of diabetes mellitus

5.1.8. Ketoconazole

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

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

5.1.9. Olaparib

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

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

5.1.10. Oritavancin

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

Administrative details:
Product number(s): EMEA/H/C/003785
Intended indication: Treatment of complicated skin and soft tissue infections (cSSTI)

5.2. Medicines already authorised

RMP in the context of a variation[18] – PRAC-led procedure

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

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

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

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

Background

Bretaris Genuair and Eklira Genuair contain aclidinium bromide, a muscarinic receptor antagonist used as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
A type II variation procedure for Bretaris Genuair and Eklira Genuair, to introduce some revisions to the RMP is under evaluation. Previously the PRAC had made some recommendations for improving the RMP and asked for some amendments (see, PRAC minutes February 2014) before finalisation of the procedure at CHMP. A revised version was presented by the MAH which was assessed by the Rapporteur.

Summary of advice

- The RMP version 4.1 for Bretaris Genuair and Eklira Genuair (aclidinium bromide) was considered acceptable.
  The PRAC added that routine risk minimisation measures were sufficient to minimise the risk of medication errors and device usage error and that the distribution of the demo kits should not be considered as an additional risk minimisation activity. However, some amendments were requested for the follow-up questionnaire for reports of medication/use of device errors

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

5.2.2. Ferumoxytol – RIENSO (CAP)

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

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002215/II/0008
Procedure scope: Extension of indication to include all cause iron deficiency anaemia when oral therapy is ineffective or inappropriate or where there is a need for rapid iron repletion. As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 were proposed to be updated
MAH(s): Takeda Pharma A/S

Background

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

The CHMP is evaluating a type II variation procedure for Rienso, a centrally authorised product containing ferumoxytol, to extend its indication to include all cause iron deficiency anaemia when oral therapy is ineffective or inappropriate or where there is a need for rapid iron repletion. 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 PRAC agreed that the RMP in the context of the variation under evaluation by the CHMP could be only fully assessed following conclusion of the ongoing PSUR assessment. However, some questions, that needed to be addressed before the RMP version 3.2 for Rienso (ferumoxytol) is considered approvable, were agreed.

5.2.3. 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 influenza 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 influenza vaccines (split virion, inactivated). The CHMP is evaluating a type II variation procedure for these vaccines to update the product information to reflect that the strains are in accordance with the WHO recommendation and the EU decision for the 2014/2015 season. 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 for Idflu and Intanza (influenza vaccines: split virion, inactivated) in the context of the variation under evaluation by the CHMP was considered acceptable. However, in the next update to the RMP the protocol for the open-label multicentre uncontrolled clinical trial to support active safety surveillance should be included as a category 3 measure in the Pharmacovigilance Plan taking into account some modifications as requested by the PRAC. If the implementation of a clinical trial is also envisaged for the next seasons, details should also be included.

5.2.4. 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 influenza 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 a centrally authorised influenza vaccine (surface antigen, inactivated, prepared in cell cultures). The CHMP is evaluating a type II variation procedure for Optaflu to reflect that the strains

are in accordance with the WHO recommendation and the EU decision for the 2014/2015 season. 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 Optaflu (surface antigen, inactivated, prepared in cell cultures) in the context of the variation under evaluation by the CHMP was not yet considered acceptable. Supplementary information relating to the proposal of enhanced surveillance activities to provide data each year, feasibility, sample size and indicators used to assess whether the proposed surveillance has achieved its objective should be submitted before finalisation of the variation procedure by the CHMP.

5.2.5. Nitric oxide – INOMAX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000337/II/0039
Procedure scope: Update of SmPC section 4.8 and Annex IID and RMP with respect to details of training and education methods to be used for INOmax and the approved nitric oxide delivery systems (NODS)
MAH(s): Linde Healthcare AB

Background

Inomax is a centrally authorised product containing nitric oxide used in conjunction with ventilatory support and other appropriate active substances, for the treatment of newborn infants ≥34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation. Inomax is also indicated as part of the treatment of peri- and post-operative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

The CHMP is evaluating a type II variation procedure for Inomax to update regarding the details of training and education methods to be used for Inomax and the approved nitric oxide delivery systems (NODS). 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 2 for Inomax (nitric oxide) in the context of the variation under evaluation by the CHMP was not yet considered acceptable and supplementary information relating to the use and effectiveness of the existing pocket guide and any proposals for alternative educational materials was required before finalisation of the variation procedure by the CHMP; moreover off- label use, device issues and accidental exposure to the product by HCPs should be added as potential risks.

5.2.6. Ofatumumab – ARZERRA (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/001131/II/0027
Procedure scope: Update of SmPC sections 4.4 and 4.8 with regard to infusion reactions
MAH(s): Glaxo Group Ltd

Background

Arzerra is a centrally authorised product containing ofatumumab, a monoclonal antibody used in the treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab. The CHMP is evaluating a type II variation procedure for Arzerra, to include information with regard to infusion reactions in the product information. 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 for Arzerra (ofatumumab) in the context of the variation under evaluation by the CHMP was considered acceptable. Minor amendments were recommended for the next update of the RMP as well as some refinements of the proposed text for the product information. The PRAC also agreed on a DHPC and communication plan.

RMP evaluated in the context of a PSUR procedure

See also Deferasirox – EXJADE under 6.1.4. , Eribulin – HALAVEN under 15.1.9. , Erlotinib – TARCEVA under 15.1.10. , Pixantrone dimaleate – PIXUVRI under 6.1.8. , Rotavirus vaccine, live, oral – ROTATEQ under 15.1.24. , Sapropterin – KUVAN under 15.1.25. , Tafamidis – VYNDAQEL under 15.1.28.

RMP evaluated in the context of PASS results

See also Ceftaroline fosamil – ZINFORO under 16.4.1. , Eltrombopag – REVOLADE under 16.4.2.

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

See Annex 14.2

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

See Annex 14.2

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[19]

6.1.1. **Aflibercept – EYLEA** (CAP)

- Evaluation of a PSUR procedure

[19] 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.

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002392/PSUV/0011
MAH(s): Bayer Pharma AG

Background

Aflibercept is a recombinant fusion protein indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD) and for visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Eylea (aflibercept) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include blindness and reduced visual acuity as undesirable effects with a frequency uncommon and very common respectively. Therefore the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should closely monitor cases of blindness and should provide further data, in particular, detailed analyses of cases of arterial thromboembolic events (ATE), cases of cataract with traumatic origin, fatal cases and cases of non-ocular haemorrhage.

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

6.1.2. Anagrelide – XAGRID (CAP), NAP

- Evaluation of a PSUSA[21] procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00000208/201309
MAH(s): Shire Pharmaceutical Contracts Ltd. (Xagrid), Orpha-Devels Handels und Vetriebs GmbH, OAP Orphan Pharmaceuticals (Thromboreductin)

Background

Anagrelide is an inhibitor of the cyclic AMP phosphodiesterase III indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients under certain conditions.

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of anagrelide-containing products and issued a recommendation on their marketing authorisation(s).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of anagrelide-containing products in the approved indication(s) remains favourable.
- With regard to Thromboreductin, the product information should be updated to refine the current warning on monitoring, to add the need to closely supervise the level of electrolytes (potassium, magnesium and calcium) and to add a new warning on cardiovascular risks. In addition, torsades de pointe and tubulointerstitial nephritis should be added as undesirable effects with a frequency unknown. Finally, information on effects on heart rate and QTc interval should be added to the product information under pharmacodynamic properties. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- With regard to Xagrid, the current terms of the marketing authorisation(s) should be maintained.
- With regard to Xagrid, the MAH should submit to EMA within 90 days a variation to update the product information in sections dedicated to fertility, pregnancy and lactation and preclinical safety data with newly available non-clinical data. With regard to Thromboreductin, revisions of the product information will have to be considered at the national level where the medicinal product is authorised, once the variation procedure for Xagrid is finalised.
- In the next PSURs for all anagrelide-containing products, MAHs should closely monitor cardiac events in young patients (aged 50 years and under), cardiac events related to QTc prolongation and torsade de pointes, thrombohaemorrhagic events, benign or malignant neoplasms including myelofibrosis, pulmonary adverse events from the interstitial lung disease and cases of exposure during pregnancy.

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

6.1.3. Boceprevir – VICTRELIS (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002332/PSUV/0028
MAH(s): Merck Sharp & Dohme Limited

Background

Boceprevir is an inhibitor of the hepatitis C virus (HCV) non-structural protein 3 (NS3) indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

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

[22] Update of SmPC sections 4.4, 4.8 and 5.1. 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 Victrelis (boceprevir) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add under special warnings and precautions for use a recommendation for patients with advanced liver disease and detailed advice for laboratory testing to be performed during therapy. In addition, a recommendation to avoid the co-administration of boceprevir with doxazosin or tamsulosin due to the risk of drug-drug interactions should be added to the product information. Finally, the product information should be amended to include cross-references relevant for the treatment of patients with hepatic impairment. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should include detailed analyses of cases of boceprevir-induced renal impairment and cases of reactivation of latent tuberculosis. In addition, the MAH should provide further information, in particular, the MAH should closely monitor cases of anaemia.

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

6.1.4. Deferasirox – EXJADE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000670/PSUV/0037 (with RMP version 9.0)
MAH(s): Novartis Europharm Ltd

Background

Deferasirox is an orally active chelating agent highly selective for iron (III), indicated for the treatment of chronic iron overload due to blood transfusions in patients with beta thalassaemia major under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Exjade (deferasirox) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add metabolic acidosis and gastrointestinal perforation as warnings and undesirable effects with a frequency unknown. In addition, a warning on severe skin reactions should be added. Finally, neutropenia, renal tubular necrosis and nephrolithiasis should be added to the product information as undesirable

[23] Update of SmPC sections 4.2, 4.4, 4.5 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

effects with frequencies unknown, as well as optic neuritis with a frequency rare. Therefore the current terms of the marketing authorisation(s) should be varied[24].

- The MAH should submit to EMA within 90 days detailed analyses of cases of drug interactions associated with deferasirox and cases of off-label use. In addition, the MAH should also provide clarifications on the deferasirox complex formation for Fe^{3+} and deferoxamine. The MAH should consider updating the product information accordingly as warranted.
- In the next PSUR, the MAH should provide further information, in particular detailed reviews of cases of hypocalcaemia, gastrointestinal haemorrhage and ulcers, stomatitis and mouth ulceration. The MAH should also continue to closely monitor cases of Reye's syndrome and provide a discussion on the potential link with cases of hyperammonaemia and related events. In addition, the MAH should provide detailed discussions relating to the risk of agranulocytosis and febrile neutropenia, renal disorders, posterior reversible encephalopathy syndrome (PRES) (especially in children) and necrotizing fasciitis.

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. **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).

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

Summary of conclusions

The PRAC Rapporteur provided an update to the Committee. In line with GVP module VII on PSURs, an oral explanation will be held at the July 2014 PRAC meeting.

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000598/PSUV/0030, EMEA/H/C/000597/PSUV/0031

[24] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

MAH(s): Les Laboratoires Servier

Background

Ivabradine is a heart rate lowering agent which acts purely on the sinoatrial (SA) node indicated in the treatment of coronary artery disease and of chronic heart failure in selected patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Corlentor and Procoralan, centrally authorised medicines containing ivabradine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy presented in the PSUR, the risk-benefit balance of Corlentor and Procoralan (ivabradine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add abdominal pain as an undesirable effect with a frequency uncommon. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- The PRAC recommendation following the assessment of the current PSURs is without prejudice to the outcome of the ongoing procedure under Article 20 of Regulation (EC) 726/2004 (see PRAC Minutes May 2014).
- In the next PSUR, the MAH should provide detailed analyses of cases of cardiac failure taking into account the different indications for use of ivabradine, coronary artery disorders, cardiac and cardio-respiratory arrest and conduction disorders other than atrioventricular block (AVB) and QT prolongation. In addition, the MAH should further review cases of vomiting, tremor and renal failure/impairment and discuss the need to update the product information as warranted.

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

6.1.7. Modified vaccinia ankara virus – IMVANEX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002596/PSUV/0007
MAH(s): Bavarian Nordic A/S

Background

Imvanex is a modified vaccinia Ankara virus-containing vaccine indicated for active immunisation against smallpox in adults.

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

[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.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Imvanex (modified vaccinia Ankara virus) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add angioedema with a frequency rare. Therefore the current terms of the marketing authorisation(s) should be varied[26].

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. Pixantrone – PIXUVRI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002055/PSUV/0015 (with RMP version 6.0)
MAH(s): CTI Life Sciences Limited

Background

Pixantrone is a cytotoxic aza-anthracenedione indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell Lymphomas (NHL).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Pixuvri, a centrally authorised medicine containing pixantrone, 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 Pixuvri (pixantrone) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the current warning on the risk of development of secondary malignancies (specifically acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS)). In addition, secondary malignancy should be added to the product information as an undesirable effect with a frequency uncommon. Therefore the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide an update on the invalidated case of tumour lysis syndrome which is subject to ongoing follow-up and should continue to closely monitor cases of cardiotoxic events.

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

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

- Evaluation of a PSUR procedure

[26] 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.
[27] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion.

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

Administrative details:
Procedure number(s): EMEA/H/C/000674/PSUV/0069
MAH(s): Sanofi Pasteur MSD, SNC

Background

Zostavax is a shingles (herpes zoster) vaccine (live) indicated for the prevention of herpes zoster ("zoster" or shingles) and herpes zoster-related post-herpetic neuralgia (PHN).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zostavax, a centrally authorised shingles vaccine, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Zostavax (shingles (herpes zoster) vaccine (live)) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a more detailed analysis of zoster cases in relation to time to onset after vaccination. The MAH should provide also a revised RMP concerning herpes zoster/herpes zoster-like and varicella/varicella-like rash as an important identified risk. In addition, the MAH should amend its proposed passive surveillance and should provide a more active analysis of the quantitative risk of zoster development and its characterization caused by vaccination.

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

6.1.10. Toremifene – **FARESTON** (CAP), NAP

- Evaluation of a PSUSA[28] procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002999/201309
MAH(s): Orion Corporation

Background

Toremifene is a nonsteroidal triphenylethylene derivative indicated as a first line hormone treatment of hormone-dependent metastatic breast cancer in postmenopausal patients.

Based on the assessment of the individual PSURs part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of toremifene-containing products and issued a recommendation on their marketing authorisation(s).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of toremifene-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the current warning on haematological disorders and to add anaemia, leukopenia and thrombocytopenia as undesirable effects with a frequency unknown. Therefore the current terms of the marketing authorisation should be varied[29].
- In the next PSURs for all toremifene-containing products, MAHs should provide further data, in particular, detailed reviews of cases of hepatobiliary disorders, cases of cerebrovascular disorders and cases of interstitial lung disease. MAHs should also comment on the risk for clinically relevant drug-drug interaction with toremifene as an enzyme inhibitor, based on the *in vitro* data compared with clinical exposure data as well as clinical experience.

The frequency of PSUR submission should be revised from three-yearly to yearly and the next PSUR should be submitted to the EMA within 70 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.

6.2. Follow-up to PSUR procedures[30]

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

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002211/LEG 006.1, EMEA/H/C/002706/LEG 006.1
Procedure scope: MAH's response to LEG 006 adopted in January 2014
MAH(s): Almirall S.A.

Background

Following the evaluation of the most recently submitted PSUR-related discussion for the above mentioned medicines, the PRAC requested the MAH to submit further data (see PRAC Minutes September 2013 and PRAC Minutes January 2014). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of recommendation(s) and conclusions

Based on the conclusion of the PRAC rapporteur, the PRAC considered that the outstanding issues were resolved and the RMP was satisfactorily updated to include more information on product quality issues to date and the distribution of demo kits. The MAH should submit to EMA a revised version of the follow-up questionnaire for all reports of medication errors and/or use of device errors.

See also 5.2.1.

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

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[31]

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

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur:

Administrative details:
Procedure scope: PASS protocol of EURAS-CORA
MAH(s): Bayer (Apleek)

Background

A protocol for a study entitled European Active Surveillance Study COmparing Regimens of Application (EURAS-CORA) was submitted for assessment by the PRAC by the MAHs for a transdermal patch containing ethinylestradiol and gestodene in accordance to the EC decision Annex IV conditions to the marketing authorisation of the concluded Art.31 referral procedure for combined hormonal contraceptives.

Conclusion

The PRAC appointed Isabelle Robine (FR) as Rapporteur for the assessment of the protocol and adopted a timetable for review of the protocol for PRAC decision in July 2014.

7.1.2. **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: 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)

Background

A protocol for a multicentre European observational drug utilisation study (DUS) to assess utilisation of sodium, magnesium, potassium sulphates for bowel preparation in the real life setting in a representative sample of the European target population was submitted by the MAH of the nationally authorised products Eziclen and Izinova as part of the of their post-authorisation commitments.

Conclusion

The PRAC appointed Isabelle Robine (FR) as Rapporteur for the assessment of the protocol and adopted a timetable for review of the protocol for PRAC decision in July 2014.

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

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

See Annex 16.2

7.3. Results of PASS imposed in the marketing authorisation(s)[33]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[34]

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[35]

7.5.1. **Rufinamide – INOVELON** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000660/MEA 011.9
Procedure scope: Submission of the fifth annual interim report for Inovelon registry study
MAH(s): Eisai Ltd

Background

Inovelon (rufinamide) is a centrally authorised antiepileptic medicine, indicated as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 4 years and older. A post marketing registry (European LGS Registry) study to collect further safety data on long term exposure to rufinamide and more specifically data on status epilepticus, hypersensitivity, common adverse events identified with antiepileptic drugs and the potential for developmental and maturation impairment in children and adolescents is ongoing and the MAH presented an interim analysis report that was assessed by the Rapporteur. Together with the interim report the MAH notified their intent to terminate the European LGS Registry.

Summary of recommendation(s) and conclusions

The PRAC commented that the adverse events (AEs) reported in the rufinamide group were consistent with the known safety profile of rufinamide and that long-term data on the safety profile in rufinamide-treated patients or other AEs were accumulated in the LGS registry over 6 years.

The PRAC noted the recruitment challenges of the registry despite the previous extension of the recruitment time and the introduction of some additional measures. It was accepted that further extension of the recruitment time is unlikely to achieve the expected study size.

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

The MAH proposal to initiate the termination of the European LGS registry was accepted, providing that some actions are undertaken, including that all prescribers of the registry are fully informed, a final clinical study report is submitted and the RMP is revised to include a proposal for an appropriate strategy for the management of all the potential and identified risks that were subject to follow up in the registry.

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

See Annex 17

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. On-going or concluded pharmacovigilance inspection

None

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. Epoetin beta – NEORECORMON (CAP)

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

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000116/II/083
Procedure scope: Submission of measures to minimise the potential risk of retinopathy of prematurity (RoP) as requested in the PSUR procedure covering the period 2007-2010
MAH(s): Roche Registration Ltd

Background

Epoetin beta is a human erythropoietin manufactured by recombinant DNA technology. Following assessment of the PSUR covering the period 2007-2010, the MAH was requested to consider measures to minimise the potential risk of retinopathy of prematurity (RoP) and to submit revised product information as well as an updated RMP. A proposal for amendment of the product information was submitted and was assessed as part of this variation.
Based on the important new safety relevant information and change of product information a DHPC was also requested by the CHMP, for which advice from the PRAC was sought.

Summary of recommendation(s) and conclusions

The PRAC agreed on the content of the DHPC and considered that the communication plan should target dissemination to neonatologists and other relevant healthcare professionals.

The PRAC also reiterated that the RMP should be updated to include the increased risk of RoP as an important potential risk. The possibility of additional pharmacovigilance activities to address this issue, e.g. updated meta-analyses at specific points in time, should be explored in this update.

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); **cobicistat – TYBOST** (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); **enfuvirtide – FUZEON** (CAP); **etravirine – INTELENCE** (CAP); **fosamprenavir – TELZIR** (CAP); **indinavir – CRIXIVAN** (CAP); **lamivudine – EPIVIR** (CAP); **lamivudine, zidovudine – COMBIVIR** (CAP); **lopinavir, ritonavir – KALETRA** (CAP); **maraviroc – CELSENTRI** (CAP); **nevirapine – VIRAMUNE** (CAP); **raltegravir – ISENTRESS** (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, Tybost, Viread), Janssen-Cilag International N.V.(Edurant, Intelence, Prezista), Merck Sharp & Dohme Ltd (Crixivan, Isentress, Stocrin), Roche Registration Ltd. (Fuzeon, Invirase), ViiV Healthcare UK Limited (Celsentri, Combivir, Epivir, Kivexa, Telzir, Trizivir, Ziagen)

Background

The CHMP requested the advice of the PRAC on a proposal to review the current wording of product information of relevant antiretroviral medicines with respect to mitochondrial toxicity, lactic acidosis and lipodystrophy. The review was considered necessary based on the need to revaluate previous regulatory positions to take into account new evidence.

Summary of recommendation(s) and conclusions

The PRAC agreed on the need to carry out a review. Qun-Ying Yue (SE) was appointed as overall Rapporteur to assess the evidence, together with Isabelle Robine (FR) and Julie Williams (UK) as Co-

Rapporteurs, and to coordinate the regulatory approach consisting of a number of synchronised post-authorisation measures. A list of questions for the various MAHs will be discussed in July 2014.

10.3.2. **Dabigatran - PRADAXA** (CAP)

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

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/LEG 0042.1
Procedure scope: Assessment of MAH's response to request for supplementary information (RSI) adopted by the CHMP in April 2014
MAH(s): Boehringer Ingelheim International GmbH

Background

The CHMP is evaluating the choice of the fatal bleeding events definition from the RE-LY study and assessing a targeted re-analysis of selected RE-LY data. This re-analysis was performed to determine whether there were any previously uncategorized major bleeding events and how they were distributed. Following an initial assessment, further data and analysis had been requested to the MAH. The MAH had fulfilled this request, provided re-calculated results and the advice of the PRAC was requested on the interpretation of the findings.

Summary of recommendation(s) and conclusions

The PRAC agreed with the interpretation of the definitions of the major bleeding events used in the RE-LY trial and emphasised on alternative resources such as registries (e.g. GLORIA-AF) or health care databases as more appropriate means of monitoring of post-marketing rates of adverse drug reactions. In addition, in relation to the targeted review of selected RE-LY data, the PRAC indicated that the product information may needed to be updated in line with the re-calculated results.
However, whilst updated frequency estimates and hazard ratios will reflect more precisely the dataset, PRAC agreed that they overall did not change the current understanding of the risk of bleeding. Management of the communication of these changes to the scientific community was considered important and should be enhanced to facilitate appropriate interpretation, providing a full background and rationale for the changes.

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

11.1. Safety related variations of the marketing authorisation

11.1.1. **Aceclofenac** (NAP)

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

Regulatory details:
Lead member: Dolores Montero Corominas (ES)

Administrative details:
Procedure number(s): ES/H/XXXX/WS/001
Procedure scope: Update the product information of systemic aceclofenac-containing medicinal products in accordance with the outcome of the referral procedure for diclofenac, DHPC

MAH(s): Almirall, S.A., Temis Farma, S.L., Ivowen Ltd. (Airtal and associated names)

Background

At its September 2013 meeting, the PRAC was notified of the intention of the MAH for the innovator of the aceclofenac-containing medicines to submit a variation to update the product information regarding cardiovascular risk, in line with the PRAC recommendations for diclofenac as agreed in PRAC minutes 10-13 June 2013. A proposal for updating the product information was submitted at national level together with a DHPC and ES requested PRAC advice on this variation and on the related communication.

Summary of advice

The PRAC provided recommendations for improving the wording of the product information and on the content of the DHPC.

Post meeting note: upon request of IT PRAC clarified that such recommendations are applicable to all products containing aceclofenac.

11.1.2. Olmesartan (NAP)
Olmesartan, hydrochlorothiazide (NAP)

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

Regulatory details:
Lead member: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): DE/H/xxxx/WS/068/G
Procedure scope: Work sharing variation assessing the implementation in the product information of the PRAC recommendation regarding the risk of cardiovascular mortality in patients with type II diabetes as well as the PRAC recommendation to include a warning about sprue-like enteropathy in association with the use of olmesartan
MAH(s): Daiichi Sankyo Europe GmbH (Olmetec and associated names)

Background

Following discussion in 2012 (see PRAC minutes 29-31 October 2012) new information and a recently published study data had become available on olmesartan and the risk of cardiovascular mortality in patients with type 2 diabetes. Further information, together with a proposal for updating the product information, had been submitted by the MAH in the framework of a national work-sharing variation. The PRAC had also discussed whether a meta-analysis comprising trial data from all ARBs was useful for a further evaluation of the signal of increased cardiovascular risk at the therapeutic class level.

Summary of advice

The PRAC agreed on the inclusion of a wording reflecting the imbalances in cardiovascular risk as seen in diabetic patients treated with olmesartan to be added under the 'pharmacodynamic properties' in the product information.

The PRAC also agreed that the recently published epidemiological studies aiming to evaluate the risk of mortality and cardiovascular endpoints in olmesartan users, as compared to other ARB users, were not conclusive.

The PRAC therefore agreed that there was still a need to closely monitor the signal of increased risk of cardiovascular events in diabetic patients to gain further evidence. This should be done within the

ongoing clinical trials, as well as within epidemiological studies, both for olmesartan individually and for the ARB class as a whole.

Based on the current evidence, the PRAC concluded that well-conducted pharmacoepidemiological studies might help to obtain useful information for a better characterisation of the safety concern. Such studies could benefit from public funding.
Furthermore, if and when new substantial evidence would become available, the potential added value and need for a patient-level meta-analysis with a comprehensive re-analysis of the clinical trials databases from the MAHs of all ARB containing medicines should be more carefully evaluated.

11.1.3. **Solutions for parenteral nutrition** combination, emulsion for infusion (NAP)

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

Regulatory details:
Lead member: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): SE/H/948/2-3/II/1i
Procedure scope: Evaluation of RMP within a type II variation: evaluation of the effectiveness of risk minimisation measures: survey and acceptable success threshold to indicate whether the survey participants demonstrate understanding of the DHPC and SmPC recommendations regarding the risk of hypermagnesemia and the recommendations for monitoring serum magnesium levels during product use
MAH(s): Baxter (Numeta G19%E, G16%E and associated names)

Background

Numeta (solutions for parenteral nutrition, combination, emulsion for infusion) is a nationally authorised product indicated for parenteral nutrition in paediatric patients when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Following an Article 107i Referral (EMA/564255/2013) the PRAC recommended that an updated risk management plan reflecting changes to the SmPC, the DHPC, an active surveillance scheme and a post-authorisation safety study should be submitted, through the relevant regulatory procedure, to the national competent authorities for assessment. Proposals for evaluating the effectiveness of the risk minimisation measures needed to be provided as part of the updated RMP.

The MAH submitted an updated RMP version v 3.0 which was assessed by SE including relevant proposals for assessment of risk minimisation, reflecting the requested changes to the SmPC together with a DHPC. SE requested PRAC's advice on the updated RMP.

Summary of advice

The PRAC endorsed the RMP and noted a proposed survey to evaluate if participants demonstrate understanding of the DHPC and SmPC recommendations regarding the risk of hypermagnesemia and the recommendations for monitoring serum magnesium levels during product use.
However the PRAC recommended that the MAH should present an elaborated protocol for the survey including details of how the survey will be constructed to evaluate the risk minimising effect, how it will be conducted, how prescribers will be identified, how estimate of responders and non-responders will be determined.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Work Programme

- Draft PRAC Work Programme 2014-2015

The PRAC discussed further development of the PRAC work plan and topic leaders. Further discussion to identify deliverables for 2015 will take place at the July 2014 meeting of the PRAC.

12.2. Pharmacovigilance audits and inspections

None

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

12.3.1. Union Reference Date List

- Consultation on the draft list, version June 2014

On CMDh's request, PRAC advice was sought on whether the DLP for piracetam could have been brought forward. Piracetam is a substance contained in nationally authorised products and included in the EURD list as a single substance and in combination with other active substances. During the assessment of renewals for piracetam-containing medicinal products, two Member States requested the deletion of one indication - due to lack of efficacy - and these cases have been brought to the attention of the CMDh according to the provisions of Article 107i, paragraph 1 of Directive 2001/83/EC. The PRAC advised that in order to address this issue other regulatory procedures should be explored first. Therefore it was not considered appropriate to amend the EURD list at this point in time.

The PRAC endorsed the draft revised EURD list version June 2014 reflecting the PRAC comments impacting DLP and PSUR submission frequencies of the substances/combinations.

The EMA secretariat also presented a proposal to set up a group ((granularity and periodicity advisory group (GPAG)) composed of NCA representatives from CMDh and PRAC as well as EMA to review and rationalise the EURD list. The PRAC delegates were invited to express their interests in participating in this group by 7 July 2014.

Post-meeting note: following the PRAC meeting in June 2014, the updated EURD list was adopted by the CHMP at its June 2014 meeting and published on the EMA website on 02/07/2014 (see: Home>Regulatory>Human medicines>Pharmacovigilance>EU reference date and PSUR submission).

12.4. Signal Management

12.4.1. Signal Management

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

The SMART Working Group discussed various topics including the updated signal assessment template and improvement in the format and details of the PRAC recommendations for signals as transmitted to MAHs.

At the organisational matters teleconference held on 26 June 2014, the EMA secretariat presented

plans to provide advance notification of signals on the PRAC agenda to relevant MAHs. EMA clarified this will be done for information only and MAHs must not contact PRAC members and/or the European Medicines Agency with regards to the signals listed when they receive the advance notification in this.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

- Guidance on EudraVigilance analysis to support community procedures

The EMA secretariat presented a draft paper that provides guidance on how to conduct the analyses of EudraVigilance data to evaluate safety concerns in the framework of Union procedures and describing EMA secretariat support in the analyses. Members commented on different aspects concerning the interface of EudraVigilance with the type of review performed during a referral procedure and made some recommendations that will be taken into account once analyses are performed.

12.5.2. List of Product under Additional Monitoring

- Consultation on the draft list, version June 2014

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

Post-meeting note: The updated additional monitoring list was published on 25/06/2014 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.6. EudraVigilance Database

None

12.7. Risk Management Plans and Effectiveness of risk Minimisations

12.7.1. Risk Management Systems

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

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

Following the circulation of documents after the presentation to PRAC in May 2014, members were asked to comment on the PML labelling initiative. A brief follow-up discussion took place at the current meeting after which it was agreed to commence a 1 year long pilot, applicable proactively only, to products with PML ADR(s). This initiative proposes a systematic approach to deal with SMPC and RMP handling of PML related information. The experience with this approach will be reviewed in July 2015.

12.8. Post-authorisation Safety Studies

12.8.1. Post-Authorisation Safety Studies

- Imposed PASS protocol workflow

At the organisational matters teleconference held on 26 June 2014, the EMA secretariat presented a revised procedure for handling imposed non-interventional PASS protocols as well as a revised assessment report template, following a similar structure to the PSUR assessment report template. The

EMA secretariat also made a proposal to assign procedure numbers to such protocols concerning nationally approved products. The PRAC delegates were invited to send comments by 8 July 2014.

12.9. Community Procedures

None

12.10. Risk communication and Transparency

None

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

At the organisational matters teleconference held on 26 June 2014, the EMA secretariat presented the draft list of withdrawn products provided for in Article 123(4) of the Directive 2001/83/EC. The scope of the list focuses on the actions related to centrally and non-centrally authorised medicinal products initiated since 28 October 2013 (date of entry into force of Directive 2012/26/EU amending Directive 201/83/EC) on grounds provided in Articles 116 and 117 of the Directive.

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Paediatric Committee (PDCO)

- EMA Extrapolation Group: call for expert nominations

At the organisational matters teleconference held on 26 June 2014, the EMA Secretariat presented a call for interest for the creation of an EMA extrapolation group (see EMA/129698/2012 Concept paper on extrapolation of efficacy and safety in medicine development). The group will also include two contributors from the PRAC. PRAC delegates were invited to express their interest in participating.

12.12.2. Pharmacovigilance Inspectors Working Group (PhV IWG)

- Organisation of training course

At the organisational matters teleconference held on 26 June 2014, the EMA Secretariat presented the draft agenda for the 2014 PhV IWG training course due to take place in October 2014.

12.13. Interaction within the EU regulatory network

None

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

12.14.1. International Organisation for Standardisation (ISO) - Identification of Medicinal Products (IDMP) standards

- EU Task Force

The EMA Secretariat gave an update on the ISO IDMP standards on the identification of medicinal products covering both authorised medicinal products and investigational medicinal products and the current work of the EU task force. The PRAC delegates were invited to send any questions they may have on this topic to relevant EMA colleagues.

13. Any other business

13.1. EMA move in 2014 to new building

The PRAC received a status update from the EMA secretariat on the preparation of the EMA's move to a new building in July 2014.

13.2. EMA reorganisation

- New organisational model: changes in the operation of processing Type II variations

The EMA secretariat presented a proposal for changes in the assessment process for type II variations, including a proposed function for a rolling timetable to be applied to processing such procedures at the level of the EMA and National Competent Authorities. The EMA Secretariat also presented a draft new template for the assessment report to be applied to all type II variations (quality and (non-)clinical). The PRAC delegates were invited to send comments by 15 July 2014.
EMA secretariat also launched a call for PRAC representatives to participate in revision of current process for evaluation of initial marketing authorisation application. The PRAC delegates were invited to express their interest in participating in the review process.

13.3. Procedural Advice on CHMP/CAT/PRAC Rapporteur/Co-Rapporteur appointment principles, objective criteria and methodology

- Proposed revision to existing procedural advice document

At the organisational matters teleconference held on 26 June 2014, the EMA secretariat presented a proposal to amend the existing procedural advice to cover the principles, objective criteria and methodologies for rapporteurship appointments as they relate to the PRAC. The PRAC delegates were invited to send comments by 4 July 2014.
In this context, the EMA secretariat also presented a proposal for the appointment of Member States for PSUR single assessment for substances in Nationally Approved Products only. The PRAC delegates were invited to send comments by 18 July 2014.

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.

14.1.1. Clopidogrel, acetylsalicylic acid

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

Administrative details:
Product number(s): EMEA/H/C/002272
Intended indication: Prevention of atherothrombotic events

14.1.2. Daclatasvir

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

Administrative details:
Product number(s): EMEA/H/C/003768
Intended indication: Treatment of chronic hepatitis C virus (HCV)

14.1.3. Darunavir, cobicistat

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

Administrative details:
Product number(s): EMEA/H/C/002819
Intended indication: Treatment of patients with human immunodeficiency virus (HIV-1) in: 1) antiretroviral therapy (ART) naïve adults; 2) Antiretroviral therapy (ART)-experienced adults with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l

14.1.4. Edoxaban

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

Administrative details:
Product number(s): EMEA/H/C/002629
Intended indication: Prevention of stroke and systemic embolism and treatment of venous thromboembolism

14.1.5. Flutemetamol F-18

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

Administrative details:
Product number(s): EMEA/H/C/002557
Intended indication: Visual detection of amyloid-beta neuritic plaques in the brains

14.1.6. Lutetium, isotope of mass 177

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

Administrative details:
Product number(s): EMEA/H/C/002749
Intended indication: Radiolabelling of carrier molecules

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

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

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

14.1.8. Naloxegol

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

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

14.1.9. Ramucirumab

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

Administrative details:
Product number(s): EMEA/H/C/002829, *Orphan*
Intended indication: Treatment of gastric cancer

14.1.10. Tedizolid

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

Administrative details:
Product number(s): EMEA/H/C/002846
Intended indication: Treatment of complicated skin and soft tissue infections (cSSTI) in adults

Medicines already authorised

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

RMP in the context of a variation[36] – PRAC-led procedure

14.1.11. Adalimumab – HUMIRA (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/000481/II/0130
Procedure scope: Update of the RMP (version 11.1)

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

MAH(s): AbbVie Ltd.

14.1.12. Dabigatran – PRADAXA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/II/0058
Procedure scope: Changes in the agreed study protocol for 1160.136 (SPAF MEA 025), a global Registry Program GLORIA-AF investigating patients with newly diagnosed non-valvular atrial fibrillation at risk for stroke receiving dabigatran. Consequent changes were done to the RMP (version 28.3)
MAH(s): Boehringer Ingelheim International GmbH

14.1.13. Everolimus – VOTUBIA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002311/II/0021
Procedure scope: Update of the RMP (version 8.0)
MAH(s): Novartis Europharm Ltd

14.1.14. Fondaparinux – ARIXTRA (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/000403/II/0061
Procedure scope: Update of the RMP (version 1.9) including an update of the current timeline for completion of the superficial vein thrombosis post-marketing observational study from December 2013 to December 2014
MAH(s): Glaxo Group Ltd

14.1.15. Insulin glulisine – APIDRA (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/000557/II/0054
Procedure scope: Update of RMP (version 6.0)
MAH(s): Sanofi-aventis Deutschland GmbH

14.1.16. Prucalopride – RESOLOR (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001012/II/0030
Procedure scope: Revised RMP (version 11.0) and updated study protocol of a study specified in the pharmacovigilance plan, following a request from the PRAC based on the review of the PRAC on PSUR 006 (EMEA/H/C/001012/PSU/012) and RMP vs. 10 (EMEA/H/C/1012 RMP 020) as adopted by CHMP in May 2013. This includes an update of the safety concerns and of the study due dates in section III. 4.3 of the RMP
MAH(s): Shire Pharmaceuticals Ireland

14.1.17. Sildenafil – REVATIO (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000638/II/0061
Procedure scope: Update of the RMP (version 6) and consequential update to Annex II
MAH(s): Pfizer Limited

14.1.18. Strontium ranelate – OSSEOR (CAP), **PROTELOS** (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/000561/II/0038, EMEA/H/C/000560/II/0043
Procedure scope: Update of the RMP (version 14) to include all the measures agreed during the recent Article 20 procedure
MAH(s): Les Laboratoires Servier

14.1.19. Telmisartan – KINZALMONO (CAP), **MICARDIS** (CAP), **PRITOR** (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000211/WS0570/0099, EMEA/H/C/000209/WS0570/0103, EMEA/H/C/000210/WS0570/0112
Procedure scope: Submission of updated RMPs (version 6.0)
MAH(s): Bayer Pharma AG (Kinzalmono, Pritor), Boehringer Ingelheim (Micardis)

14.1.20. Telmisartan, hydrochlorothiazide – KINZALKOMB (CAP), **MICARDISPLUS** (CAP), **PRITORPLUS** (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000415/WS0569, EMEA/H/C/000413/WS0569, EMEA/H/C/000414/WS0569
Procedure scope: Submission of updated RMPs (version 9.0)
MAH(s): Bayer Pharma AG (Kinzalkomb, PritorPlus), Boehringer Ingelheim (MicardisPlus)

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

14.1.21. Abatacept – ORENCIA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

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

14.1.22. Aflibercept – EYLEA (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/002392/II/0009
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. SmPC section 4.8 was furthermore updated to introduce a single table of adverse drug reactions
MAH(s): Bayer Pharma AG

14.1.23. Apixaban – ELIQUIS (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/002148/II/0014/G
Procedure scope: Grouping of 2 variations including a type II extension of indication to include treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults and a type IA variation to add a new pack size of 28 film coated tablets for Eliquis 5mg strength
MAH(s): Bristol-Myers Squibb / Pfizer EEIG

14.1.24. Bevacizumab – AVASTIN (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000582/II/0063
Procedure scope: Extension of indication to include the use of Avastin in combination with chemotherapy (paclitaxel, topotecan or pegylated liposomal doxorubicin) in patients with recurrent, platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube carcinoma based on the results of study MO22224 (AURELIA)

MAH(s): Roche Registration Ltd

14.1.25. Cetuximab – ERBITUX (CAP)

- Evaluation of an RMP in the context of a variation

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

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

14.1.26. Darunavir – PREZISTA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

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

14.1.27. 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 tear off section after the package leaflet
MAH(s): Allergan Pharmaceuticals Ireland

14.1.28. Eslicarbazepine – ZEBINIX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

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

14.1.29. Etanercept – ENBREL (CAP)

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000262/II/0167
Procedure scope: Extension of indication to treatment of adults with severe non-radiographic axial spondyloarthritis (nr-AxSpA)
MAH(s): Pfizer Limited

14.1.30. Fidaxomicin – DIFICLIR (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/002087/II/0016
Procedure scope: Update of SmPC sections 4.5 and 5.2 with results from study 2819-CL-2003, assessing the effect of multiple doses of fidaxomicin on the pharmacokinetics of a single dose of rosuvastatin in healthy male subjects. With respect to missing information on the impact of fidaxomicin on intestinal efflux transporters (BCRP, MRP2, OAP2B1), a corresponding deletion from the RMP is proposed
MAH(s): Astellas Pharma Europe B.V.

14.1.31. Ivacaftor – KALYDECO (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/002494/II/0009
Procedure scope: Update of SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 to extend the indication of Kalydeco in the treatment of cystic fibrosis to patients aged 6 years and older who have other gating (class III) mutation in the CFTR gene than G551D
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

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

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

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

14.1.33. Lixisenatide – LYXUMIA (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/002445/II/0003
Procedure scope: Update of SmPC section 4.4 in order to implement the recommendations of the recent Article 5(3) procedure on GLP-1-based therapies and pancreatic safety
MAH(s): Sanofi-Aventis Groupe

14.1.34. Ibandronic acid – IBANDRONIC ACID ACCORD (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002638/X/0006
Procedure scope: Addition of a new strength/potency and a new pharmaceutical form 3 mg solution for injection
MAH(s): Accord Healthcare Limited

14.1.35. Methylnaltrexone – RELISTOR (CAP)

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

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000870/II/0030
Procedure scope: Extension of indication for the treatment of opioid induced constipation in adult non cancer pain patients. Consequently, the MAH proposed the update of SmPC sections 4.1, 4.2, 4.4 and 5.1
MAH(s): TMC Pharma Services Ltd

14.1.36. Nilotinib – TASIGNA (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/000798/II/0067
Procedure scope: Update of SmPC sections 4.2, 4.4, 4.8 and 5.1 further to 60 month data analysis from the phase III multicentre, open-label, randomised study CAMN107A2303 of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia in chronic phase (CML-CP) (ANX 40.3)
MAH(s): Novartis Europharm Ltd

14.1.37. Palivizumab – SYNAGIS (CAP)

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

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Product number(s): EMEA/H/C/000257/X/0095

Procedure scope: Introduction of a new pharmaceutical form: 100 mg/ml solution for injection presented in vials containing 0.5 ml and 1 ml
MAH(s): AbbVie Ltd.

14.1.38. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – ADJUPANRIX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001206/II/0034
Procedure scope: Update of SmPC section 4.4 to include a statement regarding the observed increased risk of narcolepsy following vaccination with Pandemrix, the MAH's ASO3 adjuvanted H1N1 influenza vaccine, based on a review of epidemiologic or post-marketing surveillance
MAH(s): GlaxoSmithKline Biologicals S.A.

14.1.39. Pneumococcal polysaccharide conjugate vaccine (adsorbed) – SYNFLORIX (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/000973/II/0079
Procedure scope: Update of SmPC section 5.1 to reflect the results of the phase III/IV clinical trial (Finnish Invasive Pneumococcal disease vaccine) to evaluate the effectiveness of Synflorix (against reduction of hospital-diagnosed pneumonia, and impact on tympanostomy tube placements and outpatient antimicrobial prescriptions) to address a post-authorisation measure
MAH(s): GlaxoSmithKline Biologicals S.A.

14.1.40. Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – PREPANDRIX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000822/II/0051
Procedure scope: Update of SmPC to include a statement regarding the observed increased risk of narcolepsy following vaccination with Pandemrix, the MAH's ASO3 adjuvanted H1N1 influenza vaccine, based on a review of epidemiologic or post-marketing surveillance
MAH(s): GlaxoSmithKline Biologicals S.A.

14.1.41. Pyronaridine, artesunate – PYRAMAX (Art 58)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/W/002319/II/0002
Procedure scope: Changes to SmPC section 4.1 to remove restrictions on repeated course of treatment in any individual and use only in areas of low transmission with evidence of artesmisinin resistance, based on further clinical experience. Consequent changes in SmPC sections 4.2, 4.4, 4.8. Change is

also made to SmPC Section 4.2 in relation to dosing in mild to moderate renal impairment. A minor editorial adjustment is proposed to SmPC section 5.1
Scientific Opinion Holder(s): Shin Poong Pharmaceutical Co., Ltd.

14.1.42. Regorafenib – STIVARGA (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

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

14.1.43. Saxagliptin – ONGLYZA (CAP)
saxagliptin, metformin – **KOMBOGLYZE** (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/001039/WS0528/0025, EMEA/H/C/002059/WS0528/0015
Procedure scope: Update of SmPC section 4.4 in order to implement the recommendations of an Article 5(3) procedure on GLP-1-based therapies and pancreatic safety
MAH(s): Bristol-Myers Squibb / AstraZeneca EEIG

14.1.44. Temsirolimus – TORISEL (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

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

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

14.1.45. Lamivudine, abacavir – KIVEXA (CAP)

- PRAC consultation on a renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000581/R/0051 (with RMP version 2.0)
MAH(s): ViiV Healthcare

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

14.1.46. Atosiban – TRACTOCILE (CAP)

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

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000253/RMP 015.2
MAH(s): Ferring Pharmaceuticals A/S

14.1.47. Oseltamivir – TAMIFLU (CAP)

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

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000253/RMP 096.2
MAH(s): Roche Registration Ltd

14.1.48. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – ADJUPANRIX (CAP), **PUMARIX** (CAP)

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001206/RMP 035.1, EMEA/H/C/001212/RMP 030.1
MAH(s): GlaxoSmithKline Biologicals S.A.

14.1.49. Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – PREPANDRIX (CAP)

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

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000822/RMP 057.1
MAH(s): GlaxoSmithKline Biologicals S.A.

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. Alogliptin – VIPIDIA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002182/PSUV/0004
MAH(s): Takeda Pharma A/S

15.1.2. Alogliptin, metformin – VIPDOMET (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002654/PSUV/0005
MAH(s): Takeda Pharma A/S

15.1.3. Alogliptin, pioglitazone – INCRESYNC (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002178/PSUV/0005
MAH(s): Takeda Pharma A/S

15.1.4. Apixaban – ELIQUIS (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002148/PSUV/0018
MAH(s): Bristol-Myers Squibb / Pfizer EEIG

15.1.5. Bosentan – STAYVEER (CAP), TRACLEER (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002644/PSUV/0006, EMEA/H/C/000401/PSUV/0065
MAH(s): Marklas Nederlands BV (Stayveer), Actelion Registration Ltd. (Tracleer)

15.1.6. Bromfenac – YELLOX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001198/PSUV/0007
MAH(s): Croma-Pharma GmbH

15.1.7. Conestat alfa – RUCONEST (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001223/PSUV/0014
MAH(s): Pharming Group N.V

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

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002136/PSUV/0001
MAH(s): Sparkle Srl

15.1.9. Eribulin – HALAVEN (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002084/PSUV/0018 (with RMP version 3.0)
MAH(s): Eisai Europe Ltd.

15.1.10. Erlotinib – TARCEVA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000618/PSUV/0036 (with RMP version 4.0)
MAH(s): Roche Registration Ltd

15.1.11. Fidaxomicin – DIFICLIR (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002087/PSUV/0017
MAH(s): Astellas Pharma Europe B.V.

15.1.12. Human normal immunoglobulin – HYQVIA (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002491/PSUV/0004
MAH(s): Baxter Innovations GmbH

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

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000721/PSUV/0055
MAH(s): GlaxoSmithKline Biologicals S.A.

15.1.14. Hydroxocobalamin – CYANOKIT (CAP), NAP

- Evaluation of a PSUSA[37] procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001690/201311
MAH(s): Merck Santé S.A.S.

15.1.15. Indacaterol – HIROBRIZ BREEZHALER (CAP), ONBREZ BREEZHALER (CAP), OSLIF BREEZHALER (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callréus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001211/PSUV/0031, EMEA/H/C/001114/PSUV/0030, EMEA/H/C/001210/PSUV/0030
MAH(s): Novartis Europharm Ltd

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

15.1.16. Irbesartan, hydrochlorothiazide – COAPROVEL (CAP), **KARVEZIDE** (CAP), **IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA** (CAP), NAP

- Evaluation of a PSUSA[38] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00001653/201309
MAH(s): Sanofi Clir SNC (CoAprovel), Sanofi-Aventis Groupe (Karvizide, Irbesartan hydrochlorothiazide Zentiva), various

15.1.17. Linaclotide – CONSTELLA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002490/PSUV/0010
MAH(s): Almirall S.A.

15.1.18. Pandemic influenza vaccine (H1N1) (whole virion, inactivated, prepared in cell culture) – CELVAPAN (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000982/PSUV/0027
MAH(s): Baxter AG

15.1.19. Pegvisomant – SOMAVERT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000409/PSUV/0070
MAH(s): Pfizer Limited

15.1.20. Piperaquine, dihydroartemisinin – EURARTESIM (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001199/PSUV/0011
MAH(s): Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.

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

15.1.21. Radium-223 – XOFIGO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002653/PSUV/0002
MAH(s): Bayer Pharma AG

15.1.22. Rilpivirine – EDURANT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002264/PSUV/0012
MAH(s): Janssen-Cilag International N.V.

15.1.23. Rituximab – MABTHERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000165/PSUV/0093
MAH(s): Roche Registration Ltd

15.1.24. Rotavirus vaccine, live, oral – ROTATEQ (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000669/PSUV/0050 (with RMP version 6.0)
MAH(s): Sanofi Pasteur MSD, SNC

15.1.25. Sapropterin – KUVAN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000943/PSUV/0029 (with RMP version 8.0)
MAH(s): Merck Serono Europe Limited

15.1.26. Saxagliptin, metformin – KOMBOGLYZE (CAP)

- Evaluation of a PSUR procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002059/PSUV/0016
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

15.1.27. Stiripentol – DIACOMIT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000664/PSUV/0015
MAH(s): Biocodex

15.1.28. Tafamidis – VYNDAQEL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002294/PSUV/0015 (with RMP version 7.0)
MAH(s): Pfizer Limited

15.2. Follow-up to PSUR procedures[39]

15.2.1. Infliximab – REMICADE (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/000240/LEG 135.6
Procedure scope: MAH's response to LEG-135.5 following the CHMP conclusions adopted in January 2014
MAH(s): Janssen Biologics B.V.

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.

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

16.1. Protocols of PASS imposed in the marketing authorisation(s)[40]

16.1.1. **Flupirtine** (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

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

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

16.2.1. **Aliskiren – RASILEZ** (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000780/MEA 034.2
Procedure scope: MAH's response to MEA 034.1 (PASS CSPP100A2418 - colorectal cancer) as adopted in February 2014
MAH(s): Novartis Europharm Ltd

16.2.2. **Catridecacog – NOVOTHIRTEEN** (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002284/MEA 003.2
Procedure scope: MAH's response to MEA 3.1 containing amendment to PASS NN1841-3868 4
MAH(s): Novo Nordisk A/S

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

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000707/MEA 069
Procedure scope: PASS protocol to assess growth abnormalities (height) in children using Prezista in which data will be compared with data from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) or other data in children on other antiretroviral (ARV). (Category 3) - PENTA study

[40] In accordance with Article 107n of Directive 2001/83/EC
[41] 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

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

16.2.4. Eltrombopag – REVOLADE (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/001110/MEA 020.1, MEA 025.1 & MEA 026.1
Procedure scope: MAH's responses to PRAC assessment of MEA-020 as adopted in January 2014, containing an updated PASS protocol WEUSKOP7136 (study of HCV patients treated with eltrombopag: multicentre, prospective observational cohort study of thrombocytopenic HCV patients receiving eltrombopag)
MAH(s): GlaxoSmithKline Trading Services

16.2.5. Florbetaben (^{18}F) – NEURACEQ (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002553/MEA 001.1
Procedure scope: MAH's response to list of questions adopted by the PRAC (PASS Study 1 - Revision of Protocol FBB-01_02_13), dated 5 December 2013
MAH(s): Piramal Imaging Limited

16.2.6. Human coagulation factor VIII, human von Willibrand factor – VONCENTO (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002493/MEA 001.1
Procedure scope: Evaluation of two PASS protocols on 1) open-label, multi-centre PASS to assess the efficacy and safety of Voncento in male subjects with haemophilia A (CSLCT-BIO-12-78); 2) open-label, multi-centre PASS to assess the efficacy and safety of Voncento in subjects with von Willebrand disease (CSLCT-BIO-12-83)
MAH(s): CSL Behring GmbH

16.2.7. Insulin glargine – LANTUS (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/000284/MEA 051
Procedure scope: PASS protocol related to a packaging differentiation study UK SoloStar differentiation study: test in patients with Type 1 or Type 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin
MAH(s): Sanofi-aventis Deutschland GmbH

16.2.8. Insulin glulisine – APIDRA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000557/MEA 037
Procedure scope: PASS protocol related to a packaging differentiation study UK SoloStar differentiation study: test in patients with Type 1 or Type 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin
MAH(s): Sanofi-aventis Deutschland GmbH

16.2.9. Ranibizumab – LUCENTIS (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/000557/REC 0067
Procedure scope: Submission of a 3-year observation study protocol (F2401) to evaluate the long-term efficacy and safety in subjects with choroidal neovascularisation (CNV) secondary to pathologic myopia (PM)
MAH(s): Novartis Europharm Ltd

16.2.10. Sodium oxybate – XYREM (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/000593/MEA 002.4
Procedure scope: MAH's response to FUM-002.3 relating to an amendment to protocol C00302 on the reformulation of the sample size from 1,000 to 750 patients
MAH(s): UCB Pharma Ltd.

16.2.11. Telavancin – VIBATIV (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001240/MEA 006.3, EMEA/H/C/001240/MEA 017
Procedure scope: MEA 006.3: Revised protocol of the study of the use of intravenous telavancin in the clinical setting. MEA 017: Audit of the effectiveness of educational materials for telavancin, study no. CLIN_2014_TLV_003
MAH(s): Clinigen Healthcare Ltd

16.2.12. Tenofovir disoproxil – VIREAD (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000419/MEA 265.1
Procedure scope: MAH's response to request for information (RSI) to MEA265 (final protocol for Viread HBV PASS study GS-EU-174-1403) as adopted in October 2013
MAH(s): Gilead Sciences International Ltd

16.3. Results of PASS imposed in the marketing authorisation(s)[42]

None

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

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

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002252/II/0011 (with RMP version 11.0)
Procedure scope: Submission of the final clinical study report for study D3720C00002 (phase III, multicentre, randomised, double-blind, comparative study to evaluate the efficacy and safety of intravenous ceftaroline fosamil versus intravenous ceftriaxone in the treatment of adult hospitalised patients with community-acquired bacterial pneumonia in Asia) as requested in the RMP
MAH(s): AstraZeneca AB

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

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/001110/II/0014/G (with RMP version 23)
Procedure scope: Submission of four final study reports for the fulfilment of RMP commitments and a proposal for changes in the RMP (replacement of a study and date extensions for RMP commitments listed in section III 4.3)
MAH(s): GlaxoSmithKline Trading Services

16.4.3. **Etanercept – ENBREL** (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000262/II/0170 (without RMP)
Procedure scope: Submission of the final report for observational surveillance registry study 20040210 as listed in Part III of the RMP

[42] In accordance with Article 107p-q of Directive 2001/83/EC
[43] 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

MAH(s): Pfizer Limited

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

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000832/II/0068 (without RMP)
Procedure scope: Review of the data from the test-negative case-control analysis of a retrospective epidemiological study conducted in Quebec, Canada to evaluate the risk of narcolepsy associated with vaccination with Arepanrix and to follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects. This submission fulfils post authorisation measure ANX 115, therefore it is proposed to remove this condition from Annex II
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[44]

16.5.1. Boceprevir – **VICTRELIS** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002332/MEA 017.7
Procedure scope: MAH's response to MEA 017.5 (interim data on the observational PASS of Victrelis (boceprevir) among chronic hepatitis C patients (P08518) as adopted in February 2014
MAH(s): Merck Sharp & Dohme Limited

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

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

17.1.1. Brentuximab vedotin – **ADCETRIS** (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

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

Administrative details:
Procedure number(s): EMEA/H/C/002455/R/0017 (without RMP)
MAH(s): Takeda Pharma A/S

17.1.2. Crizotinib – XALKORI (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Isabelle Robine (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002489/R/0015 (without RMP)
MAH(s): Pfizer Limited

17.1.3. Idursulfase – ELAPRASE (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000700/S/0050 (without RMP)
MAH(s): Shire Human Genetic Therapies AB

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 10 - 13 June 2014 meeting.

PRAC member PRAC alternate	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting***	***Topics on the current Committee Agenda for which restriction applies*** ***Product/ substance***
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer reviewer for:	fluoroquinolones; telmisartan; telmisartan, hydrochlorothiazide; apixaban; regorafenib; aflibercept; radium-223; ethinylestradiol, gestodene
Veerle Verlinden	Belgium	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Marin Banovac	Croatia	Full involvement	
Nectaroula Cooper	Cyprus	Full involvement	
Eva Jirsová	Czech Republic	Full involvement	
Torbjörn Callreus	Denmark	Full involvement	
Doris Stenver	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Isabelle Robine	France	Full involvement	
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
Leonidas Klironomos	Greece	Cannot act as Rapporteur or Peer reviewer for:	bazedoxifene, estrogens conjugated; sildenafil; apixaban; etanercept; temsirolimus; pegvisomant; tafamidis; etanercept; crizotinib
Julia Pallos	Hungary	Cannot act as Rapporteur or Peer reviewer for:	irbesartan, hydrochlorothiazide
Almath Spooner	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
Ruchika Sharma	Ireland	Full involvement	
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	
Adam Przybylkowski	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Roxana Stroe	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Milena Radoha-Bergoč	Slovenia	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
June Munro Raine	Chair	Full involvement	
Julie Williams	United Kingdom	Full involvement	
Rafe Suvarna	United Kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting:**	**Topics on the current Committee Agenda for which restriction applies** ***Product/ substance***
Jane Ahlqvist Rastad	Not applicable	Cannot act as Rapporteur or Peer reviewer for:	naloxegol; olaparib; saxagliptin, metformin; ceftaroline fosamil
Marie Louise De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer reviewer for:	fondaparinux; ofatumumab; pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted); pneumococcal polysaccharide conjugate vaccine (adsorbed); prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted); human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed); eltrombopag; pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted)
Brigitte Keller-Stanislawski		Full involvement	
Hervé Le Louet		Full involvement	
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	
Marco Greco		Full involvement	
Kristen Myhr		Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (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	
Arnaud Batz	France	No restrictions were identified for the participation of European experts attending the PRAC meeting for discussion on specific agenda items
Céline Druet	France	
Martin Tribout	France	
Thomas Grüger	Germany	
Vahid Taravati	Germany	
Giuseppe Rosano	Italy	
Marjolein Willemen	Netherlands	
Sabine Leh	Norway	
César de la Fuente	Spain	
Lena Hansson	Sweden	
Karl-Mikael Kälkner	Sweden	
Inga Bellahn	United Kingdom	
Eleni Gaki	United Kingdom	
Max Lagnado	United Kingdom	
Angelika Siapkara	United Kingdom	

ANNEX III – List of abbreviations

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

www.ema.europa.eu

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