



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 09-12 February 2015

Chair: June Raine – Vice-Chair: Almath Spooner

Health and Safety Information

In accordance with the Agency's Health and Safety policy, delegates are to be briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

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

Note on access to documents

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



Explanatory notes

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

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures

(Items 2 and 3 of the PRAC agenda)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC agenda)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC agenda)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects.

RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC agenda)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC agenda)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC agenda)

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

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

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1. Introduction

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

The Chairperson opened the 9-12 February 2015 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Jana Nováková, replacing Anna Mareková, as the new alternate for Slovakia as well as Artūras Kažemekaitis, replacing Rita Dzetaveckiene as the new alternate for Lithuania.

1.2. Adoption of agenda of the meeting of 09-12 February 2015

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

1.3. Minutes of the previous PRAC meeting on 06-09 January 2015

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 6-9 January 2015 were published on the EMA website on 27 February 2015 (EMA/PRAC/54777/2015).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

3.3.1. Codeine (NAP)

- Review of the benefit-risk balance of codeine indicated for the treatment of cough in paediatric patients following the notification by Germany of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Martin Huber (DE)

Administrative details:

Procedure number: EMEA/H/A-31/1394
MAH(s): various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for codeine-containing medicines (see [PRAC Minutes November 2014](#)), relating to their indication for the treatment of cough in paediatric patients.

Following receipt of an opinion from the Paediatric Committee (PDCO) and response from the Healthcare Professionals' organisations (HCPOs) to a list of questions adopted in November 2014, as well as the MAHs' responses to a list of outstanding issues, the Rapporteurs prepared an assessment report for discussion at the meeting.

Summary of recommendation(s)/conclusions

The PRAC discussed aspects relating to paediatric use of these products based on the advice provided by the PDCO, report from HCPOs and the evaluation of the MAHs' responses to the first list of outstanding issues. The PRAC agreed a second list of outstanding issues (LoOI) to be addressed by the MAHs, together with a revised timetable for the procedure ([EMA/PRAC/180087/2014 Rev.2](#)).

3.3.2. Hydroxyzine (NAP)

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

Regulatory details:

PRAC Rapporteur: Arnaud Batz (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 for hydroxyzine-containing medicines (see [PRAC Minutes June 2014](#)) is to be concluded.

Following receipt of an opinion from the Paediatric Committee (PDCO) and a report from the Geriatric Expert Group (GEG), as well as the MAHs' responses to the list of outstanding issues, a final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs together with the available evidence on the risk for developing QT interval prolongation and Torsades de Pointes (TdP) after exposure to hydroxyzine as well as aspects relating to paediatric and geriatric use of these medicinal products taking into account the opinion provided by the PDCO and the GEG report.

Based on the available non-clinical data, the PRAC concluded that hydroxyzine has the potential to block human ether-a-go-go related-gene (hERG) channels and other types of cardiac channels, resulting in a potential risk of QT interval prolongation and cardiac arrhythmia events, as confirmed by clinical and post-marketing data. The PRAC agreed that the potential risk of QT interval prolongation and TdP can be adequately minimised through appropriate risk minimisation measures targeting the identified risk factors and restricting the use of hydroxyzine, in particular in the at-risk populations.

The PRAC considered that the efficacy data did not raise any new concerns. To minimise the risks, the PRAC recommended restricting the maximum daily dose to 100 mg per day in adults, and based on pharmacokinetic data corresponding changes in the paediatric and elderly populations. The PRAC also recommended that the treatment duration should be as short as possible. Hydroxyzine should be contra-indicated in patients with a known acquired or congenital QT interval prolongation as well as in patients with a known risk factor for QT interval prolongation and with concomitant use with drugs known to prolong the QT interval and/or to induce TdP. In addition, further changes to the product information were recommended including a warning that use in the elderly is not recommended due to the anticholinergic effects of hydroxyzine. The PRAC agreed that a Direct Healthcare Professional Communication (DHPC) should be sent and that the risks of QT interval prolongation, TdP, ventricular arrhythmia, sudden death and cardiac arrest should continue to be monitored, and the effectiveness of the risk minimisation measures should be assessed.

The PRAC concluded that the benefit-risk of the hydroxyzine-containing products remains positive, provided that the agreed changes to the product information and the additional risk minimisation measures are implemented.

Summary of recommendation(s)/conclusions

The PRAC adopted by consensus a recommendation, to be considered by the CMDh, to vary the marketing authorisations for hydroxyzine-containing medicines – see 'PRAC recommends new measures to minimise known heart risks of hydroxyzine-containing medicines' [EMA/85678/2015](#). A DHPC and communication plan was also agreed.

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

None

3.5. Others

None

4. Signals assessment and prioritisation¹

4.1. New signals detected from EU spontaneous reporting systems

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

- Signal of severe hyponatraemia leading to neurological symptoms

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:

EPITT 18212 – New signal

MAH(s): Novartis Europharm Ltd

Lead MS: IT

Background

Aliskiren is a selective direct inhibitor of human renin, indicated in the treatment of essential hypertension in adults. The recommended daily dose of aliskiren is 150 mg; the dose may be increased to 300 mg once daily.

The exposure for Rasilez a centrally authorised medicine containing aliskiren, is estimated to have been more than 3,428,623 patients-years worldwide, in the period from first authorisation in 2007 up to September 2014. The exposure for Rasilez HCT a centrally authorised medicine containing aliskiren and hydrochlorothiazide (HCT), is estimated to have been more than 886,703 patient-years worldwide, in the period from first authorisation in 2009 up to September 2014. The exposure for Rasilamlo a centrally authorised medicine containing aliskiren and amlodipine, is estimated to have been more than 32,586 patient-years worldwide, in the period from first authorisation in 2011 up to September 2014. The cumulative exposure for aliskiren is estimated to have been more than 4,354,149 patient-years worldwide up to September 2014. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of severe hyponatraemia leading to neurological symptoms and requested a cumulative review of all hyponatraemia events in association with aliskiren with a view to amending the product information for aliskiren-containing medicines as appropriate.

¹ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

Summary of recommendation(s)

- The MAH for Rasilez, Rasilez HCT and Rasilamlo (aliskiren and combinations) should submit to the EMA, with their submission of supplementary information for aliskiren, aliskiren/amlodipine, aliskiren/hydrochlorothiazide (PSUSA/0000089/201409) due by 11/03/2015, a cumulative review of cases of hyponatraemia associated with aliskiren using the narrow SMQ hyponatremia/syndrome of inappropriate antidiuretic hormone secretion (SIADH) along with a review of all laboratory data reports of hyponatraemia, while taking into account confounding medications such as hyponatraemia inducing drugs and clinical symptoms associated with hyponatraemia such as brain oedema and convulsion. Potential confounders such as underlying diseases associated with hyponatremia should be also taken into account.

4.1.2. Everolimus – AFINITOR (CAP), VOTUBIA (CAP), NAP

- Signal of lymphoedema

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Administrative details:

EPITT 18197 – New signal

MAH(s): Novartis Europharm Ltd, various

Lead MS: DE

Background

Everolimus is a protein kinase inhibitor indicated in the treatment of hormone receptor-positive advanced breast cancer, neuroendocrine tumours of pancreatic origin, renal cell carcinoma, renal angiomyolipoma associated with tuberous sclerosis complex (TSC), subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) and prevention of organ rejection in kidney and liver transplantation under certain conditions.

The exposure for Afinitor, a centrally authorised medicine containing everolimus (oncology indications), is estimated to have been more than 29,496 patient-treatment-years worldwide, in the period from first authorisation in 2009 until March 2014. The exposure for Votubia a centrally authorised medicine containing everolimus (TSC indications), is estimated to have been more than 2,670 patient-treatment-years worldwide, in the period from first authorisation in 2011 until March 2014.

During routine signal detection activities, a signal of lymphoedema was identified by Spain, based on 6 cases retrieved in the Spanish safety database. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of lymphoedema and requested a cumulative review of cases of lymphoedema in association with everolimus with a view to amending the product information for everolimus-containing medicines as appropriate.

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

Summary of recommendation(s)

- The MAH for Afinitor and Votubia (everolimus) should submit to the EMA, in the next PSUR (DLP: 31/03/2015), a cumulative review of cases of lymphoedema in association with everolimus, also addressing the potential causal association with Certican (NAP) in the transplant setting and including a discussion of all cases of lymphoedema, elephantiasis nostras verrucosa, Morbihan disease and associated terms (post-marketing and clinical trials). A literature search and a discussion of this topic should be provided by the MAH and an update of the product information and/or RMPs should be discussed.

4.1.3. Teriparatide – FORSTEO (CAP)

- Signal of angina pectoris

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

EPITT 18203 – New signal

MAH(s): Eli Lilly Nederland B.V.

Lead MS: UK

Background

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

The exposure for Forsteo a centrally authorised medicine containing teriparatide, is estimated to have been more than 1.5 million patients worldwide, in the period from first authorisation in 2003 until 2014.

During routine signal detection activities, a signal of angina pectoris was identified by Italy, based on 2 reported cases in their national database. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information from the cases reported in the Italian database and also further data from EudraVigilance and requested a cumulative review of angina pectoris with a view to amending the product information for teriparatide-containing medicines as appropriate.

Summary of recommendation(s)

- The MAH for Forsteo (teriparatide) should submit to the EMA, within 60 days, a cumulative review of available data from clinical trials and post-marketing cases of angina pectoris, including cases of chest pain and other associated terms. The MAH should review any literature relevant to teriparatide and cardiac pathophysiology, and discuss whether there is any plausible mechanism by which teriparatide could induce myocardial ischaemia. The MAH should also consider the role of known adverse reactions of teriparatide (hypotension, tachycardia) in the development of angina. The MAH should discuss the need for any updates to the product information or new risk minimisation measures as appropriate.

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

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Amiodarone (NAP)

- Signal of syndrome of inappropriate antidiuretic hormone (SIADH)

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

EPITT 18091 – Follow-up October 2014

MAH(s): various

Background

For background information see [PRAC Minutes October 2014](#). The MAH replied to the request for information on the signal of syndrome of inappropriate antidiuretic hormone (SIADH) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review of cases of syndrome of inappropriate antidiuretic hormone (SIADH) in association with amiodarone with a focus on the intravenous (IV) formulation. Twenty-five cases of SIADH in relation to IV administration of amiodarone were retrieved from the MAH's database. Ten cases suggested a strong association (chronological plausibility, positive dechallenge, lack of alternative explanations) and for 7 additional cases a contributory role of amiodarone could not be ruled out. The MAH concluded that the cumulative evidence is sufficient to support a causal association between amiodarone solution for injection and SIADH.

Based on the available data and considering the accepted association between SIADH and amiodarone for the oral formulation, the PRAC concluded that this adverse drug reaction should be also reflected in the product information of amiodarone IV formulations.

Summary of recommendation(s)

- The MAHs for amiodarone-containing products² for intravenous use should submit a variation within 60 days to the national competent authorities (NCAs) of the EU Member States to

² 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

update the product information regarding syndrome of inappropriate antidiuretic hormone (SIADH)³.

For the full PRAC recommendations, see [EMA/PRAC/107418/2015](https://www.ema.europa.eu/en/PRAC/107418/2015) published on the EMA website.

4.3.2. Aripiprazole – ABILIFY (CAP), ABILIFY MAINTENA (CAP)

- Signal of hyperprolactinaemia

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:

EPITT 18086 – Follow-up October 2014

MAH(s): Otsuka Pharmaceutical Europe Ltd

Background

For background information see [PRAC Minutes October 2014](#). The MAH replied to the request for information on the signal of hyperprolactinaemia and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review of all cases reported with aripiprazole under the MedDRA preferred terms (PTs) 'hyperprolactinaemia' or 'blood prolactin increased' and the MAH's literature and clinical trials review as well as the MAH's comments on the frequency, intensity, and the clinical course following aripiprazole dechallenge, both in terms of prolactin levels and the underlying psychiatric disorder. Fifty eight cases of hyperprolactinaemia were retrieved by the MAH in its clinical trials database and 192 (179 confirmed by health care professionals) from post-marketing reporting. Seventeen cases were clearly associated with aripiprazole. Of these seventeen cases, two had positive rechallenge and eleven positive dechallenge. It is considered noteworthy that three cases of hyperprolactinaemia had been reported with aripiprazole powder and solvent for prolonged-release suspension for injection (Abilify Maintena), considering that it was authorised relatively recently. Disproportionality analyses also show a possible relationship between aripiprazole and increase in prolactin levels.

Given the information available, the PRAC considered that users should be aware of the risk of increase in prolactin levels in patients taking aripiprazole. In clinical trials, the number of cases of high prolactin levels was small. However, these could have been masked by low prolactin samples, since there are also low prolactin samples, the mean and median was around normal levels. The risk of hypoprolactinaemia is already stated in the product information, the risk of hyperprolactinaemia should also be included with additional information regarding the studies. The reported consequences were in general mild to moderate in all but one case. Nevertheless, the PRAC agreed that it was important to inform HCPs and patients of this risk in view of the possible effects of hyperprolactinaemia.

Based on the available data from clinical trials and post-marketing indicating that hyperprolactinaemia may occur in association with aripiprazole, the PRAC concluded that this adverse drug reaction should be reflected in the product information with an uncommon frequency.

³ SmPC section 4.8 and package leaflet

Summary of recommendation(s)

- The MAHs for aripiprazole-containing medicinal products should submit variations, within 60 days, to the EMA to update the product information regarding hyperprolactinaemia. Following the variation of the marketing authorisations for these products, MAHs for any medicinal products containing the same active substance should submit a respective variation application to the NCAs of the EU Member States.

For the full PRAC recommendations see [EMA/PRAC/107418/2015](#) published on the EMA website.

4.3.3. Paliperidone – INVEGA (CAP)

- Signal of accidental exposure of children to oral formulations

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

EPITT 18069 – Follow-up September 2014

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

Background

For background information, see [PRAC Minutes September 2014](#). The MAH replied to the request for information on the signal of accidental exposure of children to oral formulations and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review of cases reported under the PT 'accidental exposure to product by child' and other possibly related PTs and the root cause analysis (RCA) provided by the MAH in order to assess the risk and any aspects of risk minimisation. Sixteen cases were reported under the PT 'accidental exposure to product by child' and two cases under the PT 'accidental overdose' in patients who received paliperidone. No pattern was observed with regard to product packaging in the limited cases (n = 2) in which the product packaging was described. The reporting rate seemed to be relatively low when the number of cases retrieved by the MAH was compared to the number of cases in the publication of *Tsay et al*⁴, pointing to underreporting. The amount of paliperidone ingested that led to toxicity in the identified cases is not available. Even a few tablets were enough to lead to toxicity in the cases with available narratives; a higher reported dose was associated with serious toxicity in children less than 6 years according to the publication of *Tsay et al*. Based on the cumulative review of cases and root cause analysis, it was not possible to identify a specific cause for the accidental exposure.

The PRAC acknowledged that there are regional differences concerning the packaging. The existing packaging options (bottles and blisters) should be evaluated for their appropriateness concerning the potential serious intoxication risk in children.

The PRAC concluded that the MAH should consider cases of accidental exposure in the context of overdose management in children and provide a proposal for updating the product information and if appropriate, the risk management plan, within the next regulatory procedure. Regarding the MAH's

⁴ Tsay ME, Klein-Schwartz W, Anderson B. Toxicity and Clinical Outcomes of Paliperidone Exposures Reported to US Poison Centers. *Clin Toxicol*. 2014;52 (3):207-213

commitment to explore improved packaging solutions in terms of child-resistance, a detailed plan with estimated timeframes for the different steps should be provided with the next PSUR.

Summary of recommendation(s)

- The MAH for Invega (paliperidone)⁵ should consider cases of accidental exposure in the context of overdose management in children and provide a proposal for updating the product information and if appropriate the risk management plan, within the next regulatory procedure. Regarding the MAH's commitment to explore improved packaging solutions in terms of child-resistance, a detailed plan with estimated timeframes for the different steps should be provided with the next PSUR (DLP: 30/06/2015).

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

- Signal of cardiovascular events

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

EPITT 17931 – Follow-up October 2014

MAH: various

Background

For background information, see [PRAC Minutes April 2014](#) and [PRAC Minutes September 2014](#).

Following the request of the PRAC, the Paediatric Committee (PDCO) provided input regarding age-related intake thresholds of sodium.

Discussion

The PRAC discussed the revised draft questions and answers (Q&A) document drafted by the Excipient Guideline Working Group. The draft Q&A, once endorsed by the PRAC and the CHMP, will be released for public consultation. The PRAC also discussed the feedback from the PDCO consultation. The PDCO agreed that labelling of sodium in medicines should be updated in line with adults and provided advice on appropriate thresholds. The PRAC noted that the PDCO had highlighted that neonates were a particular high risk group and this should be acknowledged in the warnings and recommendations for medicines authorised for use in children.

The PRAC discussed the scope of the procedure and the wording proposed by the PRAC Rapporteur for updating the product information, the labelling and the package leaflet.

The PRAC recommended that further clarification was required in a number of areas including the evidence supporting the thresholds, the scope of procedure and the proposed implementation of the regulatory actions. It was recommended that an updated proposal which more fully addresses these aspects is brought back to the March 2015 PRAC meeting.

⁵ 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

Summary of recommendation(s)

- The PRAC reviewed the revised draft Q&A document from the Excipient Guideline Working Group, the thresholds proposed by the Paediatric Committee (PDCO) and the proposed wordings and regulatory implementation of the labelling updates and recommended further work should be performed to allow for an amended informed proposal.

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/Committees>CHMP>Agendas, minutes and highlights>).

See also ANNEX I Risk Management Plans

5.1.1. Betulae cortex dry extract

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

Administrative details:

Product number(s): EMEA/H/C/003938

Intended indication(s): Treatment of partial thickness wounds

5.1.2. 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(s): Radiolabelling of carrier molecules

5.1.3. Pemetrexed

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

Administrative details:

Product number(s): EMEA/H/C/003788, *Generic*

Intended indication(s): Treatment of malignant pleural mesothelioma and non-small cell lung cancer

5.1.4. Pemetrexed

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

Administrative details:

Product number(s): EMEA/H/C/003970, *Generic*

Intended indication(s): Treatment of malignant pleural mesothelioma and non-small cell lung cancer

5.1.5. Pemetrexed

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

Administrative details:

Product number(s): EMEA/H/C/003905, *Generic*

Intended indication(s): Treatment of malignant pleural mesothelioma and non-small cell lung cancer

5.1.6. Pemetrexed

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

Administrative details:

Product number(s): EMEA/H/C/004011, *Generic*

Intended indication(s): Treatment of malignant pleural mesothelioma and non-small cell lung cancer

5.1.7. Tolvaptan

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

Administrative details:

Product number(s): EMEA/H/C/002788, *Orphan*

Intended indication(s): Treatment of autosomal dominant polycystic kidney disease (ADPKD)

Applicant: Otsuka Pharmaceutical Europe Ltd

5.2. Medicines already authorised**RMP in the context of a variation⁶ – PRAC-led procedure**

See under ANNEX I

RMP in the context of a variation – CHMP-led procedure**5.2.1. Dimethyl fumarate – TECFIDERA (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/002601/WS0689/0011

Procedure scope: Update of SmPC sections 4.4 to add a recommendation to consider interruption of treatment in patients with low lymphocyte counts (<0.5 x 10⁹/L) persisting for more than six months and to monitor lymphocyte counts until recovery. Update of SmPC section 4.8 with information on observed low lymphocyte counts in clinical studies and progressive multifocal leukoencephalopathy (PML) occurrence in the setting of severe and prolonged lymphopenia

MAH(s): Biogen Idec Ltd

Background

Tecfidera is a centrally authorised product containing dimethyl fumarate, indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). Another product containing dimethyl fumarate (Fumaderm) authorised nationally, is indicated for the treatment of psoriasis.

The CHMP is evaluating a worksharing variation procedure for Tecfidera and Fumaderm, to update the product information to add progressive multifocal leukoencephalopathy (PML) and recommendations following previous signal evaluation (see [PRAC Minutes November 2014](#)). The PRAC is responsible for

⁶ In line with the revised variation regulation for submissions as of 4 August 2013

providing advice to the CHMP on the necessary updates to the RMP to support this variation and the related DHPC.

Summary of advice

The RMP version 6.0 for Tecfidera (and Fumaderm) was considered acceptable, in the context of the worksharing variation under CHMP's evaluation, provided an updated RMP and satisfactory responses to the request for supplementary information are submitted. Based on the evidence available so far it was recommended that PML should be added to the RMP as a separate important identified risk. In addition, the PRAC recommended requesting a joint study as part of the obligation of the marketing authorisations for Tecfidera and Fumaderm to further characterise effects on lymphocyte subsets and to explore their clinical relevance with the objective of further evaluation of the mechanism underlying lymphopenia, frequency and pattern of lymphopenia and PML, timeframe of reversibility/recovery of lymphopenia, and risk factors predisposing patients for lymphopenia and development of PML. A draft synopsis including proposals for sample size, feasibility, interim analyses, and timelines should be provided. In addition, the PRAC recommended mechanistic studies to obtain further insight into the characterisation of cellular and molecular/signalling targets for dimethyl fumarate. Moreover, the PRAC suggested disseminating a further DHPC (in addition to that in December 2014 following the signal assessment, see [PRAC minutes November 2014](#)) as a further risk minimisation measure. The MAH advised to request the MAH to submit a DHPC to be reviewed in line with the wording for inclusion in the product information as agreed by the CHMP. The PRAC also recommended obtaining further expert advice of the Scientific Advisory Group (SAG) Neurology in relation to risk minimisation measures.

5.2.2. Insulin glargine – OPTISULIN (CAP)

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

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/000309/X/0079/G

Procedure scope: Extension of the MA of Optisulin to register additional strength 300 U/ml, grouped with type IA variation to vary the invented name from Optisulin to Toujeo

MAH(s): Sanofi-aventis Deutschland GmbH

Background

For background information, see [PRAC Minutes January 2015](#).

Further information as requested by the PRAC was received and assessed by the PRAC Rapporteur.

Summary of advice

- The updated RMP version 4.4 for Optisulin (insulin glargine) in the context of a variation for a line extension under CHMP's evaluation was considered acceptable.
- The PRAC agreed the key elements for inclusion in educational materials for HCPs and for patients to address the risks of medication error (switching between 100U/mL and 300U/mL without dose adjustment).

See also medication errors under 13.1.

5.2.3. Ivacaftor – KALYDECO (CAP)

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

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:

Procedure number(s): EMEA/H/C/002494/X/0034/G

Procedure scope: Line extension for a new pharmaceutical form in two strengths (50 mg and 75 mg unit doses) to support an indication extension of Kalydeco to treat cystic fibrosis (CF) patients aged 2 to less than 6 years old. A type II variation has been submitted together to align the SmPC with the new data is grouped with the extension application

MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

Background

Kalydeco, is a centrally authorised medicine containing ivacaftor, indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older under certain conditions.

The CHMP is evaluating a line extension for Kalydeco to add a new pharmaceutical form available in two strengths (50 mg and 75 mg unit doses) to support an indication extension of Kalydeco to treat CF patients aged 2 to less than 6 years old. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation for a line extension.

Summary of advice

- The RMP version 4 for Kalydeco (ivacaftor) was considered acceptable, in the context of the line extension under CHMP's evaluation, provided an updated RMP and satisfactory responses to the request for supplementary information are submitted. In particular, the potential effects on liver function tests in children aged between two to five years should be better characterised. Moreover, the MAH should discuss the possibility to conduct a specific study as a condition of the marketing authorisation nested in an existing cystic fibrosis registry to evaluate the long-term safety and efficacy in children aged less than 6 years. The MAH should discuss the nature and frequency of data collection in the proposed data source and detail the way these will impact on the ability to investigate specific safety endpoints for ivacaftor. In particular, timing of exposure to ivacaftor in relation to liver function tests should be carefully considered.

5.2.4. Ocriplasmin – JETREA (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002381/X/0013

Procedure scope: Introduction of a ready-to-use (RTU) formulation with adjusted fill volume for Jetrea 0.375 mg/0.3 mL

MAH(s): ThromboGenics NV

Background

Ocriplasmin has a proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (VRI) and is indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with a macular hole of diameter less than or equal to 400 microns.

The CHMP is evaluating a line extension for Jetrea to add a new formulation which does not require dilution prior to injection. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation for a line extension.

Summary of advice

- The RMP version 5.2 for Jetrea (ocriplasmin) was considered acceptable, in the context of the line extension under CHMP's evaluation. The PRAC discussed some risk minimisation measures such as differentiating the labelling/packaging of the existing and new formulations. The PRAC supported and reviewed the content of a DHPC emphasising that special care is needed during the transition period to identify which formulation is used, and whether or not it requires dilution before injection.

5.2.5. Ponatinib – ICLUSIG (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002695/II/0017

Procedure scope: Update of SmPC sections 4.8 and 5.1 to update the safety information and to update pharmacology information after the availability of the updated Clinical Study report for Study AP24534-10-201 (PACE). The RMP is updated accordingly. The MAH take this opportunity to update the RMP as for the requests received during the referral procedure (EMEA/H/C/002695/A-20/0003)

MAH(s): Ariad Pharma Ltd

Background

Iclusig is a centrally authorised medicine containing ponatinib, indicated in adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) as well as indicated for patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) under certain conditions.

The CHMP is evaluating a type II variation for Iclusig, to update the product information and the RMP with the most recent safety and efficacy data from the pivotal phase II clinical study (AP24534) in patients with refractory chronic myeloid leukaemia and Ph+ acute lymphoblastic leukaemia as well as the updated protocols for several studies, updated educational material for HCPs and the updated information on evaluation of the effectiveness of the risk minimisation measures.

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 11 for Iclusig (ponatinib) in the context of the variation under CHMP's evaluation was considered in line with the requests made in the concluded Article 20 referral procedure ([EMEA/H/C/2695/A20/0003](https://www.ema.europa.eu/en/medicines/human/EPAR/clusig/clusig.htm)) and was considered acceptable, provided an updated

RMP and satisfactory responses to the request for supplementary information are submitted. In particular, the MAH should implement some updates to the proposed educational material and provide further clarifications regarding the planned dose-ranging phase II study.

RMP evaluated in the context of a PSUR procedure

None

RMP evaluated in the context of PASS results

See also Elvitegravir – VITEKTA 16.1.12. , Ivacaftor – KALYDECO 16.1.16. , Lamivudine, zidovudine – COMBIVIR 16.1.17.

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

See Annex 14.1

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

None

Others

Bisphosphonates, denosumab and risk of osteonecrosis of the jaw (ONJ): consultation with Scientific Advisory Group (SAG) Oncology and action plan for implementation, see under 12.14.4.

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures⁷

6.1.1. Acridinium bromide – BRETARIS GENUAIR (CAP), EKLIRA GENUAIR (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002706/PSUSA/09005/201407,
EMEA/H/C/002211/PSUSA/09005/201407
MAH(s): Almirall S.A

Background

Acridinium bromide is an anticholinergic indicated for the treatment of chronic obstructive pulmonary disease (COPD).

⁷ Where a regulatory action is recommended (variation, suspension or revocation of the terms of Marketing Authorisation(s)), the assessment report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion. Where PRAC recommends the maintenance of the terms of the marketing authorisation(s), the procedure finishes at the PRAC level

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bretaris Genuair and Eklira Genuair (acridinium bromide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include reference to a sensation of a grainy texture in the mouth after inhalation, to include as undesirable effects dizziness and stomatitis with an uncommon frequency and nausea with a common frequency. In addition, the product information should reflect that dizziness may affect the ability to drive and use machinery. Therefore the current terms of the marketing authorisation(s) should be varied⁸.
- In the next PSUR, the MAH should provide further details about the cases and any further reports received of atrial fibrillation, medication errors, and intentional drug misuse. The MAH should also consider how further information on any product quality issues and medication errors can be collected and provided in the next PSUR. In addition, the MAH should provide more details on the reported cases of eye pain in case these relate to undiagnosed glaucoma. Moreover, the MAH should provide a further cumulative review of cases of tremor and propose to update product information as necessary. Finally, the MAH should discuss the reported cases of oral mucosal disorders.
- The MAH should update the RMP with regard to expanding the information relating to dizziness, nausea and stomatitis as class effects in the next regulatory procedure affecting the RMP.

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

6.1.2. Aripiprazole – ABILIFY (CAP), ABILIFY MAINTENA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:

Procedure number(s): EMEA/H/C/000471/PSUSA/00234/201407,

EMEA/H/C/002755/PSUSA/00234/201407

MAH(s): Otsuka Pharmaceutical Europe Ltd

Background

Aripiprazole is an antipsychotic indicated for the treatment of schizophrenia, moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode under certain conditions. The solution for injection is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in bipolar I disorder, when oral therapy

⁸ Update of SmPC sections 4.2, 4.7 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

is not appropriate. The suspension for injection pharmaceutical form is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Abilify and Abilify Maintena (aripiprazole) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include hypersexuality as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied⁹.
- In the next PSUR, the MAH should review reported cases of 'off-label use', analyse the possible reasons and discuss risk minimisation measures to address the increased number of 'off-label use' reports. The MAH should also review reported cases of 'injury, poisoning and procedural complications' to evaluate whether there is a trend for increased adverse drug reactions. If applicable, risk minimisation measures should be proposed by the MAH. The MAH should review reported cases of interaction between aripiprazole and other antipsychotics, including a discussion on a potential pharmacodynamic interaction and the possibility to conduct a study to further investigate this.
- The MAH should review the list of important risks according to the definitions of [GVP Module V](#), the wording of some potential risks, and the need for inclusion of diplopia in the RMP for all formulations at the next regulatory opportunity affecting the RMP.

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

6.1.3. Botulinum toxin type B – NEUROBLOC (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Magda Pedro (PT)

Administrative details:

Procedure number(s): EMEA/H/C/000301/PSUSA/00428/201406

MAH(s): Eisai Ltd

Background Background

Botulinum toxin type B is a muscle relaxant (peripherally acting agent) indicated for the treatment of cervical dystonia (torticollis).

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

⁹ 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 NeuroBloc (botulinum toxin type B) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 60 days a detailed discussion on the available evidence to support the effectiveness of the educational materials for botulinum toxin B and the need to keep these educational materials as a condition to the marketing authorisation, based on the available evidence of their effectiveness.
- In the next PSUR, the MAH should provide a detailed analysis of cases of glaucoma and rectal abscess.

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. Collagenase clostridium histolyticum – XIAPEX (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Administrative details:

Procedure number(s): EMEA/H/C/002048/PSUSA/00871/201402

MAH(s): Swedish Orphan Biovitrum AB (publ)

Background

Collagenase clostridium histolyticum is a drug for disorders of the musculo-skeletal system indicated for the treatment of Dupuytren's contracture. The indication has recently been extended to include the treatment of Peyronie's disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xiapex, a centrally authorised medicine containing collagenase clostridium histolyticum, 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 Xiapex (collagenase clostridium histolyticum) in the approved indications remains favourable.
- The product information should be updated to include a warning on the higher risk of tendon/ligament damage for patients who have had surgical repair, prior tendon or ligament injury or skin friability at the palpable cord intended to be injected, particularly on the fifth finger. Additionally, a warning on skin laceration should be added. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁰.
- In the next PSUR, the MAH should further monitor cases of tendon rupture with regard to prior damage of the tendon. The MAH should comment on the increase in the number of

¹⁰ Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

reported cases of 'drug ineffective' along with a proposal for appropriate measures if needed. The MAH should explain the discrepancy in the number of medication errors stated in different parts of the PSUR.

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. Dapagliflozin, metformin – XIGDUO (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002672/PSUSA/10294/201407

MAH(s): AstraZeneca AB

Background

Dapagliflozin is a sodium-dependent glucose co-transporter (SGLT)-2 inhibitor and metformin is a biguanide with anti-hyperglycaemic effects. The combination of dapagliflozin and metformin is indicated in the treatment of type 2 diabetes mellitus under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xigduo, a centrally authorised medicine containing dapagliflozin and metformin, 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 Xigduo (dapagliflozin/metformin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a detailed analysis of the potential risk of hypersensitivity using all data available up to the data lock point of the PSUR and consider updating the RMP.

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

6.1.6. Diphtheria (D), tetanus (T), pertussis (whole cell) (PW) and hepatitis b (rDNA) (HBV) vaccine (adsorbed) – TRITANRIX HB (Art 58¹¹)

- Evaluation of a PSUR procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Administrative details:

Procedure number(s): EMEA/H/W/003838/PSUV/0007

¹¹ Article 58 of Regulation (EC) No 726/2004 allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO), on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

Scientific Opinion Holder(s) (SOH): GlaxoSmithKline Biologicals S.A.

Background

Diphtheria, tetanus, pertussis (whole cell) and hepatitis b (rDNA) vaccine (adsorbed) (DTPW-HBV) is indicated for active immunisation against diphtheria, tetanus, pertussis and hepatitis B (HBV) in infants from 6 weeks onwards. Tritanrix HB is exclusively intended for markets outside the European Union.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tritanrix HB, a medicine containing diphtheria (D), tetanus (T), pertussis (whole cell) (PW) and hepatitis b (rDNA) (HBV) vaccine (adsorbed), and issued a recommendation on its scientific opinion.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Tritanrix HB (DTPw-HBV) in the approved indication(s) remains favourable for markets outside the European Union.
- Nevertheless, Annex II should be updated to reflect the next PSUR submission. Therefore the current terms of the scientific opinion should be varied¹².
- In the next PSUR, the SOH should continue to carefully monitor all neurological adverse events, particularly convulsions, encephalopathy, gaze palsy and hypotonia and discuss these safety topics in future PSURs. The SOH should discuss cases of circulatory collapse in the signal section in the next PSUR.

It is recommended that the PSURs are submitted in parallel of PSURs for 'diphtheria, tetanus, pertussis (acellular, component), haemophilus type b conjugate vaccine (adsorbed)' containing products authorised in the European Union as defined in the updated list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. 'Diphtheria, tetanus, pertussis (acellular, component), haemophilus type b conjugate vaccine (adsorbed)' containing products in the EU currently have a 5-yearly PSUR submission with a next DLP of 13/01/2018. The next PSUR should be submitted within 90 days of the data lock point.

6.1.7. Dolutegravir – TIVICAY (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002753/PSUSA/10075/201407

MAH(s): ViiV Healthcare

Background

Dolutegravir is an antiviral for systemic use indicated for the treatment of human immunodeficiency virus (HIV) infected patients under certain conditions.

¹² Update of Annex II. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tivicay, a centrally authorised medicine containing dolutegravir, 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 Tivicay (dolutegravir) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include as undesirable effects depression with a common frequency and suicidal ideation or suicide attempt with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied¹³.

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

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002778/PSUSA/10106/201407,
EMEA/H/C/002576/PSUSA/10106/201407
MAH(s): Hospira UK Limited, Celltrion Healthcare Hungary Kft.

Background

Infliximab is a tumour necrosis factor alpha (TNF α) inhibitor indicated for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Inflectra and Remsima, centrally authorised medicines containing infliximab (biosimilars), and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

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

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

The PRAC agreed to request the MAH for Remicade (infliximab) to submit to EMA within 60 days further information on the effect of infliximab on weight changes (weight gain and loss) following the

¹³ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

publication of data suggesting weight gain in patients treated with infliximab in a variety of therapeutic settings.

6.1.9. Saxagliptin – ONGLYZA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/001039/PSUSA/02685/201407

MAH(s): AstraZeneca AB

Background

Saxagliptin is a dipeptidyl peptidase-4 (DPP4) inhibitor indicated for the treatment of type 2 diabetes, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Onglyza, a centrally authorised medicine containing saxagliptin, 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 Onglyza (saxagliptin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include as undesirable effect constipation with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied¹⁴.
- In the next PSUR, the MAH should present new information on the risk of pancreatic cancer, which is included in the RMP as a potential risk, only in the section 'evaluation of the risks and new information' of the PSUR.

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

6.2. Follow-up to PSUR procedures¹⁵

6.2.1. Agomelatine – THYMANAX (CAP), VALDOXAN (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Ingebjørg Buajordet (NO)

Administrative details:

Procedure number(s): EMEA/H/C/000915/LEG 025, EMEA/H/C/000916/MEA 025

¹⁴ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

¹⁵ Follow-up as per the conclusions of the previous PSUR procedure, assessed outside of the next PSUR procedure

Procedure scope: Follow up to PSUV/0021 and PSUV/0023 [PSUR#7] as adopted in September 2014
MAH(s): Les Laboratoires Servier, Servier (Ireland) Industries Ltd.

Background

Following the most recent assessment of a PSUR for the above mentioned medicines, the PRAC requested the MAH to provide a detailed review of cases of overdose and to consider updating the product information accordingly, to provide additional data for further analysis of signals on palpitations, tachycardia, vertigo, amnesia/memory impairment and delirium. In addition, the MAH was requested to submit narratives for all cases with positive dechallenge or rechallenge, as well as cases resolving despite continued agomelatine treatment. With regard to tachycardia, the MAH was requested to provide a detailed analysis of the publication by *Comte et al*¹⁶ (see [PRAC Minutes September 2014](#)). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

Based on the review of the data submitted by the MAH, the PRAC agreed that there was no need to update the product information section on overdose, in the light of the cumulative review of all cases provided by the MAH, and that the signal of vertigo could be refuted and closed. However, the MAH should submit within the next PSUR detailed reviews of any further relevant cases of tachycardia and palpitations, amnesia/memory impairment and delirium.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)¹⁷

7.1.1. Hydroxyethyl starch (HES) (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

Procedure number(s): EMEA/H/N/PSP/J/0014.1

Procedure scope: Evaluation of a revised PASS protocol (drug utilisation study) to assess the effectiveness of the risk minimisation taken following the European Commission decision dated 19 December 2013 for the referral procedure EMEA/H/A-107I/1376

MAH(s): B. Braun Melsungen AG (Tetraspan, Venofundin), Fresenius Kabi Deutschland GmbH (Volulyte, Voluven Fresenius, Voluven, HyperHAES, HAES-steril), Serumwerk Bernburg AG (VitaHES, Vitafusal, Plasma Volume Redibag, PlasmaHES Redibag, Hesra, Hesra infusioneste)

Background

For background, see [PRAC Minutes July 2014](#) and [PRAC Minutes October 2014](#). The Rapporteur assessed the draft protocol submitted in accordance with the agreed timetable.

¹⁶ Comte H, Auffret M, Lelièvre B, Béné J, Steen P, Gautier S. Tachycardia and precordial pain with agomelatine: a case report. *Thérapie* 2013;68(5):324-325

¹⁷ In accordance with Article 107n of Directive 2001/83/EC

Endorsement/Refusal of the protocol

The PRAC, having considered the joint draft protocol version 1.3 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for the above listed medicinal products.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)¹⁸

See Annex 16

7.3. Results of PASS imposed in the marketing authorisation(s)¹⁹

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)²⁰

See Annex 16

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variations regulation²¹

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

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:

Procedure number(s): EMEA/H/C/000966/MEA 032, EMEA/H/C/000957/MEA 032

Procedure scope: Enhanced safety surveillance for NH 2014-2015 campaign (intermediate results interventional studies/GID47 final report)

MAH(s): Sanofi Pasteur, Sanofi Pasteur MSD SNC

Background

Idflu and Intanza, centrally authorised medicines, are influenza vaccines (split virion, inactivated) indicated for the prophylaxis of influenza in adults up to 59 years of age, especially in those who run an increased risk of associated complications.

As part of the RMP for Idflu and Intanza, there was a post-authorisation safety study (PASS) to meet the interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU ([EMA/PRAC/222346/2014](#)).

The MAH submitted interim results from interventional study GID47: safety assessment of the trivalent influenza vaccine (split-virion, inactivated), northern hemisphere 2014-2015 formulation (intradermal route).

¹⁸ 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

¹⁹ In accordance with Article 107p-q of Directive 2001/83/EC

²⁰ 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

²¹ In line with the revised variations regulation for any submission before 4 August 2013

Summary of advice

The PRAC discussed the review of expedited summary safety reports and concurred with the MAHs' overall conclusions. No significant change in the reactogenicity profile was observed and no changes to the product information were considered necessary at the present time. The MAHs' proposal to conduct a follow-up of the adverse event frequency during the 2015-2016 enhanced safety surveillance is endorsed by the PRAC. Nevertheless, the MAHs should provide some clarifications. The MAHs should also provide a stratified analysis by medication use, clarify the discrepancies in the number of cases of pruritus and rash and provide a detailed description of any actions to be taken as applicable. A discussion about the strengths and limitations of this active enhanced surveillance is missing and the MAHs' strategy for the next season should be clarified.

See also Seasonal influenza vaccines under 12.14.3.

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

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/000758/LEG 050

Procedure scope: Report on an enhanced safety surveillance following the annual strain update as laid down in the interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU

MAH(s): Novartis Vaccines and Diagnostics GmbH

Background

Optaflu, a centrally authorised medicine, is an influenza vaccine (surface antigen, inactivated, prepared in cell cultures) indicated for the prophylaxis of influenza for adults, especially in those who are at an increased risk of influenza-associated complications.

The MAH submitted an expedited summary report of their enhanced safety surveillance (study V58_400B) to meet the interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU ([EMA/PRAC/222346/2014](http://ema.europa.eu/PRAC/222346/2014)). The MAH also submitted their responses to the three post-approval commitments related to the MAH's proposal for the enhanced safety surveillance for season 2014-2015 evaluated as part of variation EMEA/H/C/000758/II/0069.

Summary of advice

The PRAC discussed the MAH's expedited summary safety report and concluded that overall the reporting frequency of adverse events (including adverse events of interest (AEIs)) following Optaflu vaccination during the surveillance period was low. The limitations and challenges of the current enhanced passive approach raised by the MAH were acknowledged (limited market share, low absolute number of reports, different methods in the calculation of the denominator between EU countries, lack of brand specific uptake data across age groups on a national level, change in reporting behaviour). Consequently, the results presented should be interpreted with caution. Nevertheless, based on the reporting rates and medical review of the individual reports, the PRAC concluded that the available data does not raise any new safety concern. The MAH has taken on board the PRAC's suggestions to improve accuracy of denominator/exposure information using a supply distribution model. The refinement of estimating exposure is considered valuable and should be taken into account for the

future seasons. The MAH is requested to confirm that no serious adverse events have been reported and to comment on a discrepancy between the estimated number of subjects eligible for Optaflu vaccination and the total number of Optaflu doses distributed.

See also Seasonal influenza vaccines under 12.14.3.

7.5.3. Mannitol – BRONCHITOL (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/001252/ANX 002.4

Procedure scope: Fourth interim analysis of the cystic fibrosis (CF) study

MAH(s): Pharmaxis Pharmaceuticals Limited

Background

Bronchitol is a centrally authorised medicine containing mannitol, indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.

The MAH had committed to perform an interventional PASS to be conducted over 5 years in the UK Cystic Fibrosis Registry according to the conditions included in the Annex II of the marketing authorisation.

Interim results of a PASS examining the rates of identified and potential risks of Bronchitol in CF by comparing mannitol exposed versus unexposed patients in a matched cohort from the CF registry, were assessed by the Rapporteur for PRAC review.

Summary of advice

The PRAC discussed the fourth interim summary report of the CF registry study. The PRAC noted that these further interim results highlighted a consistent signal of increased incidence of new pulmonary infections and/or exacerbation with Bronchitol treatment compared with matched unexposed patients. Additionally, as with the previous interim analysis, there is also a suggestion that 'forced expiratory volume in one second' (FEV₁) declined in patients treated with Bronchitol compared with matched unexposed patients. The PRAC noted the limitations of this registry study, however, given the trends towards decreasing efficacy and increased harm for several endpoints in this study, the PRAC recommended that the MAH should be requested to consider how they might obtain further data to inform considerations relating to the benefit-risk balance of this medicinal product.

The PRAC also noted that the use in patients under 18 years of age is still low (9 patients only to date) but out of the 9 patients aged below 18, 2 had discontinued treatment due to haemoptysis (versus 1 out of 82 adults) and this may suggest a higher incidence of this adverse drug reaction in children compared to adults. Mannitol is currently not recommended in patients below 18 years of age as clinical trial data suggest very little benefit in FEV₁ compared to adult patients. Of note, an efficacy study in children is currently ongoing. The MAH is requested by the PRAC to review all available data from clinical trials, including ongoing study DPM-CF-304 if possible, and provide a discussion of the incidence of haemoptysis amongst the paediatric, adolescent and adult populations, including seriousness and outcomes and whether there is any evidence from clinical studies of an increased incidence of haemoptysis in younger compared with older patients. Based on the available data, the MAH should also discuss the overall balance of benefits and risks of mannitol in children and

adolescents and make proposals for risk minimisation as necessary. The MAH should address the above request within 60 days.

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 inspections

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

9.3. Others

None

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. Albiglutide – EPERZAN (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002735/II/009

Procedure scope: Update of SmPC section 4.8 with information on appendicitis/pancreatitis. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to correct some information in SmPC sections 5.1 and 6.6, Annex III.A and package leaflet

MAH(s): GlaxoSmithKline Trading Services

Background

Albiglutide is a glucagon-like peptide (GLP)-1 receptor agonist indicated for the treatment of type 2 diabetes mellitus in adults to improve glycaemic control under certain conditions.

The MAH submitted a type II variation to include appendicitis as an undesirable effect to the product information. The CHMP requested advice from the PRAC on the assessment of this variation.

Summary of advice

Based on the review of the available information from clinical trials and the current lack of a plausible mechanism, the PRAC agreed that a causal association between albiglutide and the occurrence of appendicitis could not be established. Therefore, the PRAC considered that proposed addition of appendicitis to the product information was not currently approvable. The PRAC however supported the proposals for further evaluation of the risk of appendicitis with albiglutide treatment as an adverse event of special interest in the planned phase IV cardiovascular outcome PASS study, which will compare patients on standard anti-hyperglycaemic treatment with albiglutide or placebo. In addition, the PRAC recommended that appendicitis is evaluated as an adverse event of special interest in the next PSURs (DLP for next PSUR: 21 March 2015) and supported requesting the MAH to submit a meta-analysis of all available controlled clinical trial to further examine this risk.

10.1.2. Ambrisentan – VOLIBRIS (CAP)

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

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:

Procedure number(s): EMEA/H/C/000389/0039

Procedure scope: Update of SmPC section 4.4 in relation to the current recommendations for liver function and SmPC section 5.1 with data on aminotransferase abnormalities from an analysis of the clinical study report (CSR) for PASS 'AMB110094 (VOLT)'. The current 'healthcare professional information' in Annex II has been updated accordingly as well as the package leaflet and RMP (version 6)

MAH(s): Glaxo Group Ltd

Background

Ambrisentan is an endothelin receptor antagonist indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO²² functional class II and III.

The MAH submitted a type II variation, following the completion of the observational surveillance programme VOLT²³ and the review of the liver safety profile of ambrisentan, proposing to remove the requirement for monthly aminotransferase monitoring by implementing monitoring as clinically indicated, considering that the observed increases in alanine transaminase (ALT) and aminotransferase (AST) >3 times the upper limit of normal (ULN) are not higher than expected in this population. The CHMP requested advice from the PRAC on the assessment of this variation.

Summary of advice

Based on the review of the available information and the results of the VOLT study, the PRAC noted its limitations, including the inability to provide compliance data at patient level and the inclusion of a high proportion of ambrisentan-experienced patients that started treatment before entering the study, without data on treatment duration. The inclusion of the latter will underestimate the incidence of transaminase increases in the studied population and undermine the ability of the study to provide a firm basis for recommending changes to liver function monitoring. Furthermore, the fact that a significant proportion of patients were not monitored while in a study (non-compliance) is of concern in

²² World Health Organisation

²³ VOLT (VOL-ibris Tracking): open label, observational, post-marketing surveillance programme to better characterise the safety profile of ambrisentan when used in clinical practice

itself, and also because liver outcomes for those patients were not provided, which argues against relaxing monitoring instructions in the product information. Therefore, the PRAC did not support the proposed changes from monthly liver function testing to 'monitoring as clinically indicated'. The PRAC discussed the possibility of moving to monthly monitoring during the 6 months of treatment and as clinically indicated afterwards. However, the PRAC did not consider the results sufficiently powered given the limited number of naïve patients to support such a conclusion. Finally, the PRAC noted that the recommendation for monitoring 'as clinically indicated' would suggest that testing is conducted only after clinical signs or symptoms of hepatotoxicity have appeared, by which time significant hepatic injury may have already occurred.

On the basis of the available evidence, the PRAC recommended not to remove the requirement for monthly aminotransferase monitoring for ambrisentan nor replacing monthly monitoring with the provision for monitoring as clinically indicated.

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

None

10.3. Other requests

10.3.1. Dabigatran – PRADAXA (CAP)

- PRAC consultation on a post-authorisation measure, upon CHMP request

Regulatory details:

PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:

Procedure number(s): EMA/H/C/000829/LEG/043.1

Procedure scope: MAH's response to LEG-043 as adopted by CHMP on 29 September 2014, pertaining to four publications from the BMJ

MAH(s): Boehringer Ingelheim International GmbH

Background

Dabigatran is a direct thrombin inhibitor indicated for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) under certain conditions and the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

In July and September 2014, the CHMP addressed lists of questions to the MAH that focussed, amongst other aspects, on the possible identification of a therapeutic concentration interval for dabigatran and whether routine monitoring of dabigatran concentrations may provide increased benefits and lower risks for patients. In particular, the MAH was requested to comment on recent publications from the BMJ (British Medical Journal) and to provide information about its current and planned activities with regard to investigating the relationship between dabigatran exposure and clinical efficacy and safety in the authorised indications as well as the utility of monitoring dabigatran anticoagulant activity on a more regular basis. The CHMP requested advice from the PRAC on the assessment of this post-authorisation measure.

Summary of advice

Based on the review of the available information, the PRAC agreed that currently there was no strong evidence for a general recommendation of regular therapeutic drug monitoring (TDM) in patients treated with dabigatran in the authorised indications. However, further questions were proposed to be put forward to the MAH to explore the benefits for limited therapeutic monitoring in certain specific circumstances. The PRAC agreed that the current advice in the product information regarding options for monitoring the anticoagulant effect of Pradaxa (such as use of activated partial thromboplastin time aPTT) could be clarified and a wider communication to HCPs could be considered.

10.3.2. Epoetins:

Darbepoetin alfa – ARANESP (CAP);

Epoetin alfa – ABSEAMED (CAP), BINOCRIT (CAP), EPOETIN ALFA HEXAL (CAP);

Epoetin beta – MIRCERA (CAP), NEORECORMON (CAP);

Epoetin theta – BIOPOIN (CAP), EPORATIO (CAP);

Epoetin zeta – RETACRIT (CAP), SILAPO (CAP)

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

Regulatory details:

PRAC Rapporteur (overall): Valerie Strassmann (DE)

PRAC Co-Rapporteurs: Arnaud Batz (FR), Dolores Montero Corominas (ES)

Administrative details:

Procedure scope: Erythropoiesis-stimulating agents: outcome of statistical analysis of clinical trial data in chronic kidney disease (CKD) patients on dialysis/not on dialysis (treatment of anaemia)

Procedure number(s): EMEA/H/C/000332/LEG 083.4 (Aranesp), EMEA/H/C/000727/LEG 023.4 (Abseamed), EMEA/H/C/000725/LEG 022.4 (Binocrit), EMEA/H/C/000726/LEG 023.4 (Epoetin Alfa Hexal), EMEA/H/C/000739 LEG 032.4 (Mircera), EMEA/H/C/000116/LEG 049.4 (NeoRecormon), EMEA/H/C/001036/LEG 019.4 (Biopoin), EMEA/H/C/001033/LEG 019.4 (Eporatio), EMEA/H/C/000872/LEG 036.4 (Retacrit), EMEA/H/C/000760/LEG 035.4 (Silapo)

Scope: Erythropoiesis-stimulating agents (ESA): Evaluation of the outcome of statistical analysis of clinical trial data in chronic kidney disease (CKD) patients on dialysis/not on dialysis (treatment of anaemia)

MAH(s): Amgen Europe B.V. (Aranesp), Medice Arzneimittel Pütter GmbH & Co. KG (Abseamed), Sandoz GmbH (Binocrit), Hexal AG (Epoetin Alfa Hexal), Roche Registration Ltd (Mircera, NeoRecormon), CT Arzneimittel GmbH (Biopoin), Ratiopharm GmbH (Eporatio)

Background

For background, see [PRAC Minutes July 2014](#). Previously, the MAHs of erythropoiesis-stimulating agents (ESA) were requested to provide specific statistical analysis plans (SAP) and common core elements of an analysis plan (CCE) from a re-analysis of their clinical trial data in order to evaluate the risk of cardiovascular events associated with epoetins administered to obtain haemoglobin (Hb) levels of 11g/dL or higher in chronic kidney disease (CKD) patients (on dialysis or not on dialysis) for the treatment of anaemia. In July 2014, based on the results of the analysis, the PRAC and CHMP agreed to request MAHs to respond to a request for supplementary information, including commenting on proposed product information revisions aiming at better individualised treatment and to warrant caution with regard to dose escalation in patients with a poor initial response to ESA therapy.

Summary of advice and conclusion(s)

The PRAC discussed the MAHs' responses to the request for supplementary information, including the companies' comments on proposed amendments to their product information on the increased risk of mortality, serious cardiovascular and cerebrovascular events with cumulative high ESA doses. Overall,

the PRAC agreed with the MAH's proposed amendments, however, the Committee advised some further changes. Moreover, the PRAC supported requesting MAHs' to provide a proposal for a draft DHPC to inform relevant HCPs that the recommendation on target haemoglobin (Hb) levels remains unchanged (up to 12g/dl), however, particular attention should be given to poor responders. This DHPC should reflect the need to avoid dose escalation in patients with an inadequate response to ESA, and the need to use only the lowest effective dose. In addition, the proposed DHPC should warn about an increased risk of mortality, serious cardiovascular and cerebrovascular events which could be associated with cumulative high ESA doses. Finally, the PRAC noted that further MAHs' analyses were submitted to the EMA in January 2015. Further discussion will be scheduled at the March 2015 PRAC meeting once the further data are assessed.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Renewals of the marketing authorisation

None

12.2. Mandate and organisation of the PRAC

None

12.3. Pharmacovigilance audits and inspections

12.3.1. Pharmacovigilance Systems and their Quality Systems

None

12.3.2. Pharmacovigilance inspections

None

12.3.3. Pharmacovigilance audits

12.3.3.1. Pharmacovigilance Audit Facilitation Group (PAFG)

- Nomination of PRAC representatives

At the organisational matters teleconference held on 26 February 2015, the EMA Secretariat presented a call for interest to join the Pharmacovigilance Audit Facilitation Group (PAFG). PRAC delegates were invited to express their interest by 20 March 2015.

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

12.4.1. Periodic Safety Update Reports

- PSUR Single Assessment (PSUSA) procedure numbers

In order to prepare appropriately for the introduction of the PSURs repository, all EU PSUR single-assessment procedures starting from October 2014 include the acronym 'PSUSA' in their procedure numbers and procedure numbers are published in the EURD list in advance of any PSUR submissions. This principle applies to substances covered in procedures for CAPs only, procedures for CAPs/NAPs as well as procedures for NAPs only.

12.4.2. PSURs repository

- PSURs repository implementation plan: update

The EMA Secretariat gave an update on the deployment of the PSUR repository, with proposed detailed timelines for its full implementation, from the pilot phase, the switch-on phase followed by its mandatory use. Follow-up discussion will take place at the March 2015 PRAC meeting. Several measures are put in place to ensure the smooth transition to the PSURs repository and relevant training will be given as well as relevant updated documents published. Regular bulletins are circulated to PRAC as of January 2015.

12.4.3. Union Reference Date List

- Consultation on the draft list, version February 2015
- Feedback from the Granularity and Periodicity Advisory Group (GPAG)

The PRAC was updated on the activities of the GPAG, composed of PRAC delegates and EMA staff members, focussing on harmonising and streamlining the EURD list.

The PRAC endorsed the draft revised EURD list version February 2015 reflecting the PRAC comments impacting on the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC Minutes April 2013](#)).

Post-meeting note: following the PRAC meeting in February 2015, the updated EURD list was adopted by the CHMP and CMDh at their February 2015 meeting and published on the EMA website on 05/02/2015, see:

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

12.5. Signal Management

12.5.1. Signal Management

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

The PRAC was updated on the outcome of the February 2015 SMART Working Group meeting, where the EudraVigilance annual report for 2014 was discussed. The document will be presented to PRAC in March 2015. Furthermore, SMART reviewed the draft guideline on screening drug-event combinations that will be further discussed at PRAC once a consolidated version is available. Finally, the publication

of PRAC recommendations on signals for update of the product information in all EU languages started for the January 2015 relevant signals, see:

[Home>Human regulatory>Pharmacovigilance>Signal management>PRAC recommendations](#)

12.6. Adverse Drug Reactions reporting and additional monitoring

12.6.1. Management and reporting of adverse reactions to medicinal products

12.6.1.1. Collection of off-label information without suspected adverse reaction

- EMA questions and answers document on recording and reporting of off-label use

Status: *for discussion*

At the organisational matters teleconference held on 26 February 2015, the EMA Secretariat presented the draft EMA question and answer (Q&A) document on recording and reporting of off-label use. This document is planned to be published as part of the Q&A document to support the implementation of the pharmacovigilance legislation ([EMA/228816/2012 - v.3](#)) and the information integrated in the context of the next GVP modules V, VI and VII update. In view of comments raised by the PRAC, further consideration will be given to the wording and a revised version will be presented to the PRAC for endorsement in the coming months.

12.6.1.2. Monitoring of medical literature

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

Status: *for discussion*

At the organisational matters teleconference held on 26 February 2015, the EMA Secretariat presented the detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency following public consultation. The final guide was adopted by the PRAC via written procedure on 3 March 2015.

12.6.2. Additional monitoring

12.6.2.1. List of products under additional monitoring

- Consultation on the draft list, version February 2015

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

Post-meeting note: The updated additional monitoring list was published on 29/02/2015 on the EMA website (see: [Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#))

- Guidance on the maintenance of the list of products under additional monitoring

At the organisational matters teleconference held on 26 February 2015, the EMA Secretariat presented the draft of the guideline on maintenance of the additional monitoring list. The PRAC was invited to send comments in writing by 13 March 2015.

12.7. EudraVigilance database

12.7.1. Activities related to the confirmation of full functionality

None

12.8. Risk Management Plans and effectiveness of risk minimisations

12.8.1. Risk Management Systems

None

12.8.2. Tools, Educational Materials and effectiveness measurement for risk minimisations

- Guideline on good pharmacovigilance practices (GVP) Module XVI: Addendum I on educational materials

At the organisational matters teleconference held on 26 February 2015, the PRAC lead member presented the draft guideline on good pharmacovigilance practices (GVP) Module XVI addendum I on educational materials. Numerous written comments were raised by PRAC members reflecting the great interest in this issue. The draft addendum was endorsed by the PRAC. Regarding the next steps, it will be circulated to the CHMP and CMDh for adoption prior to release for public consultation.

12.9. Post-authorisation Safety Studies

12.9.1. Post-authorisation Safety Studies

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

Following previous discussion in December 2014, the PRAC discussed a revised proposal for the assessment and regulatory handling of protocols for non-imposed, non-interventional PASS with collaboration of the Scientific Advice Working Party (SAWP). As part of the revised process, the PRAC will be invited to provide comments on the protocol and ultimately, SAWP advice will be endorsed by the PRAC. The PRAC noted the start of a pilot phase in May 2015. Stakeholders will be informed of the arrangements accordingly.

12.10. Community procedures

12.10.1. Referral procedures for safety reasons

None

12.11. Renewals, conditional renewals, annual reassessments

None

12.12. Risk communication and transparency

12.12.1. Public participation in pharmacovigilance

None

12.12.2. Safety communication

None

12.13. Continuous pharmacovigilance

12.13.1. Incident Management

None

12.14. Interaction with EMA Committees and Working Parties

12.14.1. Committees

None

12.14.2. Blood Products Working Party (BPWP)

- Guideline on clinical investigation of recombinant and human plasma-derived factor IX products

The PRAC was invited to provide written comments on the draft revised guideline on clinical investigation of recombinant and human plasma-derived factor IX products, updated in line with the outcome of the 2013 EMA/European Directorate for the Quality of Medicines (EDQM) workshop on potency assays by 27 February 2015.

12.14.3. Vaccine Working Party (VWP)

- Seasonal influenza vaccines: Manufacturers' proposal for passive enhanced safety surveillance for the 2015-2016 season

The PRAC discussed Vaccines Europe's collaborative proposal for a passive enhanced surveillance system for the 2015-2016 season and onwards. The proposal was found to be within the requirements described in the 'interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU'. While recognising the challenges raised in relation to the implementation of such a system (e.g. concerns that the system described would not be feasible in all EU MSs and that aspects of the proposed enhanced monitoring will occur outside the responsibilities of NCAs), the PRAC supported the collaborative approach aimed at setting up a sustainable system able to deliver adequate enhanced surveillance for seasonal influenza vaccines in EU. The PRAC thus encouraged the MAHs of seasonal flu vaccines to continue the development and the implementation of a system as outlined in Vaccines Europe's preliminary proposal dated 3 February 2015.

12.14.4. Scientific Advisory Group (SAG) Oncology

- Bisphosphonates, denosumab: effectiveness of risk minimisation measures: consultation of the SAG oncology on the risk of osteonecrosis of the jaw (ONJ) and action plan for implementation

As agreed in December 2014, the PRAC discussed a draft detailed action plan for the implementation of the enhanced risk minimisation measures regarding the risk of osteonecrosis of the jaw (ONJ) with bisphosphonates and denosumab. This included a proposal for key safety messages to be reflected in the product information for these products, as well as a proposal for a patient reminder card, giving details in the benefit of treatment as well as of precautions to take to minimise the risk for ONJ. The PRAC supported the introduction of the patient reminder card and agreed on the core wording for both product information and patient reminder card. However, the PRAC considered that further refinement

may be needed with regard to the detailed wording of the revised product information and the patient reminder card. The PRAC agreed to finalise the action plan at the March 2015 plenary meeting.

12.15. Interaction within the EU regulatory network

None

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

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

None

12.16.2. Others

12.16.2.1. International Society for Pharmaceutical Engineering (ISPE)

- Analysis of patient and healthcare professional input in EMA oral contraceptive communication, following the symposium, October 2014

The topic was deferred to the March 2015 PRAC meeting.

13. Any other business

13.1. Medication errors

- Guidance on medication errors following PRAC and Patient Safety and Quality of Care Working Group (PSQCWG)'s consultation

The EMA Secretariat presented a revised version of the draft guidance on medication errors after consultation with PRAC, the EC's Patient Safety Quality of Care Working Group (PSQCWG) and experts from the EMA's Patients' and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Party (HCPWP). PRAC members were invited to provide advice in particular on aspects concerning regulatory definitions, coding of medication errors, signal detection methods and the draft risk minimisation strategy for new high strength/ fixed combination insulin products.

The PRAC emphasised the importance of consistency across regulatory guidelines including with MedDRA points to consider and acknowledgement in guidance of the multifactorial nature of medication errors.

The PRAC welcomed in principal the EMA proposal of a service to NCAs where collated medication error reports from EudraVigilance would be made available via the EudraVigilance Data Analysis System (EVDAS) in line with the revised EudraVigilance Access Policy, but considered that further details were required to assess the benefits of such a service. NCAs could use those reports e.g. to combine EU wide ICSR data on medication errors with data from other national sources on medication errors (for example national patient safety reporting systems) to support NCA signal detection activities. The PRAC SMART working group was mandated to further elaborate on the technicalities and implementation of such reports for signal detection purposes in line with the timelines for the revised EudraVigilance Access Policy.

With regard to the draft risk minimisation strategy for medication errors with novel high strength/ fixed combination insulin products developed by a dedicated PRAC drafting group, the PRAC agreed that further reflection and discussion of the current proposal is warranted with a view to stakeholder communication and consultation, and the drafting group was mandated to present a corresponding proposal at the PRAC in March 2015.

The PRAC also agreed on the consultation of the amended draft guidance with the Implementation Group (IG) of Member States and EMA governance structure and the EU regulatory network, and to seek European Risk Management Strategy Facilitation Group (ERMS-FG) approval of the final draft for public consultation scheduled in Q2 2015.

13.2. Pharmacovigilance programme and revised implementation governance

The PRAC received a further update on the revised implementation governance of the pharmacovigilance legislation and the pharmacovigilance programme.

At the organisational matters teleconference held on 26 February 2015, the EMA Secretariat presented a proposal to change the governance for a number of deliverables of the new pharmacovigilance legislation from Project and Maintenance Groups to the PRAC for decision-making as organisational matters topics.

13.3. Feedback from the Scientific Coordination Board

At the organisational matters teleconference held on 26 February 2015, the PRAC Chair provided to the PRAC some feedback on the Scientific Coordination Board meeting which took place on 29 January 2015. As the Scientific Coordination Board, which meets 3-4 times a year, is aimed to foster cross-committee collaboration on key strategic issues, the PRAC agreed to receive regular feedback from the Chair.

13.4. EU Medicines Agencies Network Strategy to 2020

At the organisational matters teleconference held on 26 February 2015, the PRAC Chair presented the draft EMA/Heads of Medicines Agencies (HMA) EU Medicines Agencies Network Strategy to 2020 document that will be discussed at the upcoming EMA Management Board meeting.

14. ANNEX I - Risk Management Plans

14.1. Medicines in the pre-authorisation phase

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

14.1.1. Aripiprazole

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

Administrative details:

Product number(s): EMEA/H/C/003803, *Generic*

Intended indication(s): Treatment of schizophrenia and prevention of manic episodes in bipolar I disorder

14.1.2. Aripiprazole

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

Administrative details:

Product number(s): EMEA/H/C/003899, *Generic*

Intended indication(s): Treatment of schizophrenia and prevention of manic episodes in bipolar I disorder

14.1.3. Blinatumomab

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

Administrative details:

Product number(s): EMEA/H/C/003731, *Orphan*

Intended indication(s): Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia

Applicant: Amgen Europe B.V.

14.1.4. Ceritinib

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

Administrative details:

Product number(s): EMEA/H/C/003819

Intended indication(s): Treatment of non-small cell lung cancer (NSCLC)

14.1.5. 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(s): Prevention of stroke, embolism and treatment of venous thromboembolism

14.1.6. Efmoroctocog alfa

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

Administrative details:

Product number(s): EMEA/H/C/003964, *Orphan*

Intended indication(s): Treatment of haemophilia A

Applicant: Biogen Idec Ltd

14.1.7. Human fibrinogen, human thrombin

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

Administrative details:

Product number(s): EMEA/H/C/003914

Intended indication(s): Supportive treatment for improvement of haemostasis and as a suture support in vascular surgery

14.1.8. Idebenone

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

Administrative details:

Product number(s): EMEA/H/C/003834, *Orphan*

Intended indication(s): Treatment of Leber's hereditary optic neuropathy (LHON)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

14.1.9. Pegfilgrastim

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

Administrative details:

Product number(s): EMEA/H/C/003910

Intended indication(s): Treatment of neutropenia

14.1.10. Pregabalin

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

Administrative details:

Product number(s): EMEA/H/C/003962

Intended indication(s): Treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD)

14.1.11. Pregabalin

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

Administrative details:

Product number(s): EMEA/H/C/004078

Intended indication(s): Treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD)

14.1.12. Tasimelteon

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

Administrative details:

Product number(s): EMEA/H/C/003870, *Orphan*

Intended indication(s): Treatment of non-24-hour sleep-wake disorder (non-24)

Applicant: Vanda Pharmaceuticals Ltd

14.2. Medicines already authorised

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

RMP in the context of a variation²⁴ – PRAC-led procedure

14.2.1. Alglucosidase alfa – MYOZYME (CAP)

- Evaluation of an RMP in the context of a variation

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

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/000636/II/0052

Procedure scope: Revised RMP (version 7.2) to update the physician guide: safety information packet (version 8.1) following the conclusion of PSUV/0049 procedure in May 2014

MAH(s): Genzyme Europe BV

14.2.2. Crizotinib – XALKORI (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/002489/II/0025/G

Procedure scope: Grouped variations of a type II and a type IB variation: submission of a revised RMP (version 6.0) to change the CYP3A inhibitor from ketoconazole to itraconazole in study A8081001; and to change the due date for completion of MEA 009

MAH(s): Pfizer Limited

14.2.3. Interferon beta 1B – BETAFERON (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/000081/II/0100

Procedure scope: To introduce the RMP for Betaferon following a signal assessment on thrombotic microangiopathy (TMA) covering the entire class of interferon beta. The RMP for Extavia, informed consent of Betaferon, has already been assessed. This follows variation EMEA/H/C/000081/II/0095

MAH(s): Bayer Pharma AG

14.2.4. Memantine – AXURA (CAP), EBIXA (CAP), MEMANTINE MERZ (CP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:

Procedure number(s): EMEA/H/C/000378/WS0668/0067, EMEA/H/C/000463/WS0668/0083, EMEA/H/C/002711/WS0668/0004

Procedure scope: Revised RMP (version 7.1) to include the interim results of the prostate cancer study, 4 finalised studies. In addition, this RMP update also introduces changes to the required additional pharmacovigilance activity regarding the identified potential risk of prostate cancer by adjusting the due dates of agreed milestones

MAH(s): Merz Pharmaceuticals GmbH (Axura, Memantine Merz), H. Lundbeck A/S (Ebixa)

14.2.5. Pegfilgrastim – NEULASTA (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/000420/II/0082

Procedure scope: Revised RMP (version 3) to address the PRAC recommendation concerning capillary leak syndrome and cytokine release syndrome

MAH(s): Amgen Europe B.V.

14.2.6. Tenofovir disoproxil – VIREAD (CAP)

Tenofovir disoproxil, emtricitabine – EVIPLERA (CAP), TRUVADA (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/000419/WS0598/0141/G, EMEA/H/C/002312/WS0598/0048/G, EMEA/H/C/000594/WS0598/0107/G

Procedure scope: Worksharing variation to: 1) update the RMP to remove study 174-0127 on renal safety; add references to studies previously submitted, add intermediate results for APR and MITOC studies and correct the classification from category 3 to 4 of the 7 studies (in the RMP for Eviplera and Truvada); 2) update the deadline for the final submission of study 104-0423 in the RMP

MAH(s): Gilead Sciences International Ltd

14.2.7. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000955/II/0046

Procedure scope: Revised RMP (version 16.3) with information from the final clinical study report (CSR) of study WA 19926 (FUNCTION)

MAH(s): Roche Registration Limited

14.2.8. Vildagliptin – GALVUS (CAP), JALRA (CAP), XILIARX (CAP)

vildagliptin, metformin – EUCREAS (CAP), ICANDRA (CAP), ZOMARIST (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/000771/WS0696/0040, EMEA/H/C/001048/WS0696/0039, EMEA/H/C/001051/WS0696/0038

EMEA/H/C/000807/WS/0695, EMEA/H/C/001050/WS/0695, EMEA/H/C/001049/WS/0695

Procedure scope: Revised RMP (version 12.1) to change of the due date of the final clinical study report (CSR) for study CLAF237A2401 from 'Q4 2014' to 'Q2 2015'

MAH(s): Novartis Europharm Ltd

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

14.2.9. Adalimumab – HUMIRA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/000481/II/0137

Procedure scope: Extension of indication to the paediatric population of the treatment of active moderate to severe hidradenitis suppurativa (acne inversa), including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas. Consequential changes to SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 and to the package leaflet

MAH(s): AbbVie Ltd

14.2.10. Adalimumab – HUMIRA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/000481/II/0134

Procedure scope: Extension of indication to add the treatment of chronic plaque psoriasis in children and adolescents from 4 years of age, based on data from study M04-717 'multicentre, randomised, double-dummy, double-blind study evaluating two doses of adalimumab versus methotrexate in paediatric subjects with chronic plaque psoriasis.' As a consequence SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 and the package leaflet have been updated accordingly. In addition, the MAH proposed minor editorial changes in the SmPC and package leaflet

MAH(s): AbbVie Ltd

14.2.11. Ambrisentan – VOLIBRIS (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:

Procedure number(s): EMEA/H/C/000839/II/0039

Procedure scope: Update of SmPC section 4.4 in relation to the current recommendations for liver function and section 5.1 with data on aminotransferase abnormalities from an analysis of the clinical safety report (CSR) for PASS AMB110094 (VOLT). The current healthcare professional information in Annex II has been updated accordingly as well as the package leaflet and RMP (version 6)

MAH(s): Glaxo Group Ltd

14.2.12. Bevacizumab – AVASTIN (CAP)

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

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Administrative details:

Procedure number(s): EMEA/H/C/000582/II/0072

Procedure scope: Extension of indication for the use of Avastin in combination with paclitaxel and cisplatin or paclitaxel and topotecan in patient with persistent, recurrent, or metastatic carcinoma of the cervix. Consequently, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 and package leaflet are updated
MAH(s): Roche Registration Ltd

14.2.13. Bevacizumab – AVASTIN (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/000582/II/0080

Procedure scope: Update of SmPC sections 4.6, 4.8 and 5.3 to update the safety information regarding a contraindication during pregnancy and the potential for foetal abnormalities based on post-marketing data showing that foetal malformations have been observed in children of pregnant patients treated with bevacizumab in combination with embryotoxic chemotherapeutics

MAH(s): Roche Registration Ltd

14.2.14. Caffeine – PEYONA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Jan Neuhauser (AT)

Administrative details:

Procedure number(s): EMEA/H/C/001014/II/0013

Procedure scope: Update of SmPC section 4.8 to reflect the results of a European non-interventional post-authorisation study to assess the drug utilisation and safety of caffeine citrate in the treatment of premature infants affected by apnoea. The package leaflet is updated accordingly

MAH(s): Chiesi Farmaceutici S.p.A.

14.2.15. Darbepoetin alfa – ARANESP (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000332/II/0130

Procedure scope: Update of SmPC section 4.2 to incorporate dosing recommendations for paediatric patients from 1 to < 11 years of age and include updates to SmPC sections 4.8, 5.1 and 5.2 to reflect the available data in the paediatric population. The package leaflet is updated accordingly

MAH(s): Amgen Europe B.V.

14.2.16. Deferiprone – FERRIPROX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/000236/II/0089/G

Procedure scope: Update of SmPC section 4.5 regarding combination of deferiprone with other iron chelators further to request of the PRAC in the assessment of the PSUR (PSUV/083). Update of SmPC section 5.1 and the RMP with the results of study LA37-111 conducted to evaluate the effect of deferiprone on cardiac QT and QTc interval duration. The package leaflet is updated accordingly
MAH(s): Apotex Europe BV

14.2.17. Efavirenz – SUSTIVA (CAP)

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

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:

Procedure number(s): EMEA/H/C/000249/II/0126/G

Procedure scope: Grouped variation consisting of two consequential variations: 1) type II variation to extend the therapeutic indication to include children 3 months of age to less than 3 year of age and weighing at least 3.5kg; 2) type IB variation, consequential to this update, to remove the oral solution pharmaceutical form for Sustiva (efavirenz) and as such upgrade the already approved 'capsule sprinkle' dosing method as primary means of dosing for young patients and those that cannot swallow capsules and/or tablets

MAH(s): Bristol-Myers Squibb Pharma EEIG

14.2.18. Eltrombopag – REVOLADE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:

Procedure number(s): EMEA/H/C/001110/II/0020

Procedure scope: Update of SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 to add a new indication on the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy. The package leaflet is updated accordingly

MAH(s): GlaxoSmithKline Trading Services

14.2.19. Empagliflozin – JARDIANCE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Miguel Angel Macia (ES)

Administrative details:

Procedure number(s): EMEA/H/C/002677/II/0005 (with RMP)

Procedure scope: Submission of an updated environmental risk assessment (ERA) and final study report for a toxicity study on a sediment dwelling organism (OECD 218) performed as a post-approval measure

MAH(s): Boehringer Ingelheim International GmbH

14.2.20. Enzalutamide – XTANDI (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:

Procedure number(s): EMEA/H/C/002639/II/0015

Procedure scope: Update of SmPC sections 4.2, 4.4 and 5.2 to update the safety and pharmacokinetic information on hepatic impairment after finalisation of the study 9785-CL-0404. The package leaflet is updated accordingly

MAH(s): Astellas Pharma Europe B.V.

14.2.21. Fentanyl – INSTANYL (CAP)

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

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/000959/X/0030G

Procedure scope: Grouped variation including the 1) addition of a new strength of 400 micrograms/dose in a multi-dose nasal spray in pack size of 10, 20, 30 and 40 doses; 2) replacement of the current multi-dose nasal spray by a new improved child resistant multi-dose nasal spray; 3) addition of a new pack size of 30 doses for each current strength (50 micrograms/dose, 100 micrograms/dose & 200 micrograms/dose); 4) tightening of the assay release limit of the multi-dose finished product to 98.0%-102.0%; 5) reduction of the shelf life of all strengths of the multi-dose finished product to 24 months

MAH(s): Takeda Pharma A/S

14.2.22. Febuxostat – ADENURIC (CAP)

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

Regulatory details:

PRAC Rapporteur: Jan Neuhauser (AT)

Administrative details:

Procedure number(s): EMEA/H/C/000777/II/0037

Procedure scope: Update of SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 for the 120 mg strength further to the introduction of a new indication for prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of tumour lysis syndrome (TLS). The package leaflet is updated accordingly

MAH(s): Menarini International Operations Luxembourg S.A.

14.2.23. Golimumab – SIMPONI (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/000992/II/0061

Procedure scope: Update of SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of to add a new therapeutic indication for non-radiographic axial spondyloarthritis. The package leaflet is updated accordingly

MAH(s): Janssen Biologics B.V.

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

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Administrative details:

Procedure number(s): EMEA/H/C/000721/II/0061

Procedure scope: Update of SmPC section 4.6 on pregnancy outcomes in women exposed to the vaccine during pregnancy to reflect the outcome of study EPI-HPV-018 (an observational cohort) and other available data on safety during pregnancy. The package leaflet is amended accordingly

MAH(s): GlaxoSmithKline Biologicals

14.2.25. Ibrutinib – IMBRUVICA (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/003791/II/0001

Procedure scope: Extension of indication to the treatment of adult patients with Waldenström macroglobulinaemia (WM). Consequently, changes are proposed to SmPC sections 4.1, 4.2, 4.8 and 5.1 and to the package leaflet to incorporate all information relevant to the WM indication

MAH(s): Janssen-Cilag International NV

14.2.26. Ivacaftor – KALYDECO (CAP)

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

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:

Procedure number(s): EMEA/H/C/002494/II/0027

Procedure scope: Extension of indication to include the treatment of cystic fibrosis in patients aged 18 years and older who have a R117H mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Consequently, SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 and the package leaflet are updated

MAH(s): Vertex Pharmaceuticals (U.K.) Ltd

14.2.27. 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/0031

Procedure scope: Update of SmPC sections 4.8 and 5.1 to reflect the results of part 2 of study VX12-770-111 as fulfilment of the post-authorisation measure (PAM) MEA 007

MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

14.2.28. Lomitapide – LOJUXTA (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/002578/II/0014/G

Procedure scope: Grouping of three type II variations: 1) submission of the clinical study report (CSR) for study AEGR-733-024 undertaken to investigate the effect of atorvastatin (a weak CYP3A4 inhibitor) on the pharmacokinetics of lomitapide.; 2) submission of the CSR for study AEGR-733-029 undertaken to investigate the effect of ethinyl estradiol/norgestimate (weak CYP3A4 inhibitor) on the pharmacokinetics of lomitapide; 3) submission of the final report related to the validation of a mechanistic (PBPK) model to predict lomitapide interactions with CYP3A4 inhibitors. As a consequence SmPC sections 4.2, 4.4 and 4.5, the package leaflet and the RMP are updated accordingly
MAH(s): Aegerion Pharmaceuticals Limited

14.2.29. Nintedanib – VARGATEF (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Leonidas Klironomos (GR)

Administrative details:

Procedure number(s): EMEA/H/C/002569/II/0001

Procedure scope: Submission of the final clinical trial report for study PK140T (in vitro evaluation of the interaction of nintedanib with human OAT transporters) in order to fulfil a post-authorisation measure (MEA) included as additional activity in the RMP
MAH(s): Boehringer Ingelheim International GmbH

14.2.30. 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/0035

Procedure scope: Submission of a study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine refractory chronic lymphocytic leukemia (CLL) to address the outstanding specific obligation of the conditional MA. As a consequence the MAH proposes to change the status of the MA from conditional to a full MA. The product information and RMP are updated accordingly
MAH(s): Glaxo Group Ltd

14.2.31. Pegvisomant – SOMAVERT (CAP)

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

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/000409/X/0072

Procedure scope: Addition of 25 mg and 30 mg powder and solvent for solution for injection
MAH(s): Pfizer Limited

14.2.32. Pyronaridine phosphate, artesunate – PYRAMAX (Art 58)

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

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/W/002319/X/0008/G

Procedure scope: Line extension to add a new paediatric formulation: 60 mg/20 mg granules for oral suspension. The product information for Pyramax 180 mg/60 mg film coated tablets is updated accordingly

MAH(s): Shin Poong Pharmaceutical Co., Ltd

14.2.33. Riociguat – ADEMPAS (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002737/II/0006

Procedure scope: Submission of category 3 in vitro study to determine the substrate characteristics of riociguat and metabolite M-1 towards human transporters

MAH(s): Bayer Pharma AG

14.2.34. Rivaroxaban – XARELTO (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

Procedure number(s): EMEA/H/C/000944/II/0034

Procedure scope: Amendment of the Annex II of the marketing authorisation: as an alternative to the study imposed as specific obligation, the company proposes to extend and expand the ongoing epidemiological rivaroxaban PASS programme to fulfil the CHMP objective on the post approval programme for the acute coronary syndrome (ACS) indication

MAH(s): Bayer Pharma AG

14.2.35. Romiplostim – NPLATE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:

Procedure number(s): EMEA/H/C/000942/II/0049

Procedure scope: Update of SmPC sections 4.8 and 5.1 based on the final clinical study report (CSR) for study 20080009: a long-term open-label prospective study to assess changes in bone marrow morphology

MAH(s): Amgen Europe B.V.

14.2.36. Silodosin – SILODYX (CAP), UROREC (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/001209/WS0672/G, EMEA/H/C/001092/WS0672/G

Procedure scope: Grouping of two variations: 1) Update of SmPC sections 4.8 and 5.1 to add efficacy and safety information from a European phase IV open label clinical study undertaken in patients with benign prostate hyperplasia; 2) update of the RMP with changes requested by the PRAC in the recent renewal and PSUR procedures.

MAH(s): Recordati Ireland Ltd.

14.2.37. Telaprevir – INCIVO (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/002313/II/0035

Procedure scope: As part of the RMP commitments to address the missing information in the liver post-transplant population and based on the submission the phase 3b study report HPC3006, update of SmPC section 4.2 to provide posology information for the special population of liver transplant patients without cirrhosis and of section 4.4 to add a warning for organ transplant patients. SmPC section 4.5, 4.8 and 5.1 are also updated to reflect the new safety and clinical data of the study. The package leaflet is updated accordingly

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

14.2.38. Trastuzumab – HERCEPTIN (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000278/II/0084/G

Procedure scope: Update of SmPC sections 4.2 and 4.8 with information on switching between intravenous (IV) and subcutaneous (SC) formulations further to safety data from study MO22982. The package leaflet is updated accordingly. Update of SmPC section 4.2 with a statement regarding switching between Herceptin and biosimilars

MAH(s): Roche Registration Ltd

14.2.39. Ulipristal – ESMYA (CAP)

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

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/002041/II/0028

Procedure scope: Update of SmPC section 4.1 with subsequent updates to sections 4.2, 4.4, 4.8 and 5.1 in order to extend the current indication to long term (repeated intermittent) treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The package leaflet is updated accordingly

MAH(s): Gedeon Richter Plc.

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

14.2.40. Alendronic acid, colecalciferol – FOSAVANCE (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000619/R/0032 (with RMP)

MAH(s): Merck Sharp & Dohme Limited

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).

15.1. Evaluation of PSUR procedures

15.1.1. Aflibercept – ZALTRAP (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/002532/PSUSA/10019/201408

MAH(s): Sanofi-Aventis Groupe

15.1.2. Agalsidase alfa – REPLAGAL (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Administrative details:

Procedure number(s): EMEA/H/C/000369/PSUSA/00069/201408

MAH(s): Shire Human Genetic Therapies AB

15.1.3. Asenapine – SYCREST (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/001177/PSUSA/00256/201408

MAH(s): N.V. Organon

15.1.4. Axitinib – INLYTA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Ingebjørg Buajordet (NO)

Administrative details:

Procedure number(s): EMEA/H/C/002406/PSUSA/10022/201407

MAH(s): Pfizer Limited

15.1.5. Catridecacog – NOVOTHIRTEEN (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/002284/PSUSA/10034/201407

MAH(s): Novo Nordisk A/S

15.1.6. Colistimethate sodium – COLOBREATHE (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/001225/PSUSA/09112/201408

MAH(s): Forest Laboratories UK Limited

15.1.7. Copper (⁶⁴Cu) chloride – CUPRYMINA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002136/PSUSA/10040/201408

MAH(s): Sparkle Srl

15.1.8. Corifollitropin alfa – ELONVA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/001106/PSUSA/00875/201407

MAH(s): Merck Sharp & Dohme Limited

15.1.9. Dronedarone – MULTAQ (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/001043/PSUSA/01180/201407

MAH(s): sanofi-aventis groupe

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

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Administrative details:

Procedure number(s): EMEA/H/C/002312/PSUSA/09142/201408

MAH(s): Gilead Sciences International Ltd

15.1.11. Fampridine – FAMPYRA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Administrative details:

Procedure number(s): EMEA/H/C/002097/PSUSA/01352/201407

MAH(s): Biogen Idec Ltd.

15.1.12. Gefitinib – IRESSA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/001016/PSUSA/01518/201407

MAH(s): AstraZeneca AB

15.1.13. Idursulfase – ELAPRASE (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000700/PSUSA/01722/201407

MAH(s): Shire Human Genetic Therapies AB

15.1.14. Ingenol mebutate – PICATO (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002275/PSUSA/10035/201407
MAH(s): Leo Pharma A/S

15.1.15. Ivacaftor – KALYDECO (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:

Procedure number(s): EMEA/H/C/002494/PSUSA/09204/201407
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

15.1.16. Lipegfilgrastim – LONQUEX (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002556/PSUSA/10111/201407
MAH(s): Sicor Biotech UAB

15.1.17. Lixisenatide – LYXUMIA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

Procedure number(s): EMEA/H/C/002445/PSUSA/10017/201407
MAH(s): Sanofi-Aventis Groupe

15.1.18. Lomitapide – LOJUXTA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/002578/PSUSA/10112/201407
MAH(s): Aegerion Pharmaceuticals Limited

15.1.19. Meningococcal group B vaccine (rDNA, component, adsorbed) – BEXSERO (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

Procedure number(s): EMEA/H/C/002333/PSUSA/10043/201407

MAH(s): Novartis Vaccines and Diagnostics S.r.l.

15.1.20. Methoxy polyethylene glycol-epoetin beta – MIRCERA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:

Procedure number(s): EMEA/H/C/000739/PSUSA/02017/201407

MAH(s): Roche Registration Ltd

15.1.21. Modified vaccinia Ankara virus – IMVANEX (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002596/PSUSA/10119/201407

MAH(s): Bavarian Nordic A/S

15.1.22. Nitric oxide – INOMAX (CAP), NAP

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000337/PSUSA/02172/201406

MAH(s): Linde Healthcare AB, various

15.1.23. Palivizumab – SYNAGIS (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:

Procedure number(s): EMEA/H/C/000257/PSUSA/02267/201406

MAH(s): AbbVie Ltd.

15.1.24. Pegloticase – KRYSTEXXA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Administrative details:

Procedure number(s): EMEA/H/C/002208/PSUSA/10046/201407
MAH(s): Crelta Pharmaceuticals Ireland Limited

15.1.25. Perampanel – FYCOMPA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002434/PSUSA/09255/201407
MAH(s): Eisai Europe Ltd.

15.1.26. Ribavirin – REBETOL (CAP), RIBAVIRIN MYLAN (CAP), RIBAVIRIN TEVA (CAP), RIBAVIRIN TEVA PHARMA BV (CAP), NAP

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/000246/PSUSA/10007/201407,
EMEA/H/C/001185/PSUSA/10007/201407, EMEA/H/C/001018/PSUSA/10007/201407,
EMEA/H/C/001064/PSUSA/10007/201407
MAH(s): Merck Sharp & Dohme Limited, Generics (UK) Limited, Teva B.V., various

15.1.27. Romiplostim – NPLATE (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:

Procedure number(s): EMEA/H/C/000942/PSUSA/02660/201407
MAH(s): Amgen Europe B.V.

15.1.28. Rotavirus vaccine (live, oral) – ROTARIX (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Jean-Michel Dogné (BE)

Administrative details:

Procedure number(s): EMEA/H/C/000639/PSUSA/02665/201407
MAH(s): GlaxoSmithKline Biologicals S.A.

15.1.29. Stavudine – ZERIT (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

Procedure number(s): EMEA/H/C/000110/PSUSA/02787/201406
MAH(s): Bristol-Myers Squibb Pharma EEIG

15.1.30. Tocofersolan – VEDROP (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000920/PSUSA/02981/201407
MAH(s): Orphan Europe S.A.R.L.

15.1.31. Vismodegib – ERIVEDGE (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/002602/PSUSA/10140/201407
MAH(s): Roche Registration Ltd

15.2. Follow-up to PSUR procedures²⁵

15.2.1. Epoetin beta – NEORECORMON (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000116/LEG 054
Procedure scope: MAH's response to PSUV/0084 [PSURs 19, 20 and 21] as adopted in September 2014
MAH(s): Roche Registration Ltd

15.2.2. Vernakalant – BRINAVESS (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

²⁵ Follow-up as per the conclusions of the previous PSUR procedure, assessed outside of the next PSUR procedure

Administrative details:

Procedure number(s): EMEA/H/C/001215/LEG 021.1

Procedure scope: MAH's response to PSUV/0019 (PSUR #5 [PSU-008]) and LEG-021 as adopted in September 2014

MAH(s): Cardiome UK Limited

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

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

16.1.1. Teicoplanin (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:

PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:

Procedure number(s): EMEA/H/N/PSP/0011.2

Procedure scope: Evaluation of a revised protocol for a prospective observational cohort, non-comparative study describing the safety profile of the higher recommended teicoplanin loading dose of 12 mg/kg twice a day

MAH(s): Sanofi-Aventis (Targocid)

16.1.2. Aflibercept – ZALTRAP (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:

Procedure number(s): EMEA/H/C/002532/MEA 003.2

Procedure scope: Revised PASS protocol for a drug utilisation study (DUS) to address potential for off-label use and particularly intravitreal off-label use (study AFLIBC06660)

MAH(s): Sanofi-Aventis Groupe

16.1.3. Aripiprazole – ABILIFY MAINTENA (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

Procedure number(s): EMEA/H/C/002755/MEA/002.1

Procedure scope: Revised PASS protocol for a non-interventional, non-imposed post-authorisation safety study related to extrapyramidal symptoms in patients treated with Abilify Maintena: cohort study with a 2-year follow-up using European automated healthcare databases (study 15893N)

MAH(s): Otsuka Pharmaceutical Europe Ltd

16.1.4. Delamanid – DELTYBA (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002552/MEA/002.1

Procedure scope: MAH's response to MEA-002 (revised PASS protocol for study 242-120402) adopted in September 2014

MAH(s): Otsuka Novel Products GmbH

16.1.5. Follitropin alfa – OVALEAP (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/002608/MEA 002.1

Procedure scope: Revised PASS protocol XM17-WH-50005: non-interventional study of a prospective observational study to assess the safety of Ovaleap compared to Gonal-f in one treatment cycle with respect to the incidence rates of ovarian hyperstimulation syndrome (OHSS) in infertile women undergoing superovulation for assisted reproductive technologies (ART), as requested during the assessment of the marketing authorisation application for Ovaleap

MAH(s): Teva B.V.

16.1.6. Ipilimumab – YERVOY (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Sabine Straus (NL)

Administrative details:

Procedure number(s): EMEA/H/C/002213/MEA 027.2

Procedure scope: Revised protocol for study CA184242ST (survey protocol for effectiveness assessment of the risk minimisation plan)

MAH(s): Bristol-Myers Squibb Pharma EEIG

16.1.7. Mixture of polynuclear iron(III)-oxyhydroxide , sucrose and starches – VELPHORO (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002705/MEA 002

Procedure scope: PASS study VFMCRP-MEAF-PA21-01-EU: feasibility to evaluate the nature of diarrhoea with adjunct local gastrointestinal inflammatory markers in patients with chronic kidney disease on dialysis treated with Velphoro

MAH(s): Vifor Fresenius Medical Care Renal Pharma France

16.1.8. Nilotinib – TASIGNA (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Doris Stenver (DK)

Administrative details:

Procedure number(s): EMEA/H/C/000798/MEA 038.2

Procedure scope: Request for the termination of the Tasigna and Glivec pregnancy registry for imatinib and nilotinib (CSTI571A2403)

MAH(s): Novartis Europharm Ltd

16.1.9. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of a PASS protocol

Regulatory details:

PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000955/MEA 045.2

Procedure scope: Revised PASS protocol for a UK BSR rheumatoid arthritis registry of tocilizumab treated patients and prospective surveillance study for adverse events

MAH(s): Roche Registration Limited

16.1.10. Aliskiren – RASILEZ (CAP)

aliskiren, amlodipine – RASILAMLO (CAP)

aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP)

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:

Procedure number(s): EMEA/H/C/000780/WS0581/0093, EMEA/H/C/002073/WS0581/0094, EMEA/H/C/000964/WS0581/0063 (without RMP)

Procedure scope: Submission of the final study report for the non- interventional study CSPP100A2414: cohort study to assess various safety outcomes in aliskiren initiators using US claims data

MAH(s): Novartis Europharm Ltd

16.1.11. Bivalirudin – ANGIOX (CAP)

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000562/II/0058 (without RMP)

Procedure scope: Submission of the study report for the study 'exposure and adverse event assessment (EAEA) for Angiomax protocol TMC-BIV-07-01 bivalirudin (Angiomax) as a procedural anticoagulant in the paediatric population undergoing intravascular procedures for congenital heart disease''

MAH(s): The Medicines Company UK Ltd.

16.1.12. Elvitegravir – VITEKTA (CAP)

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002577/II/0011 (with RMP)

Procedure scope: Submission of the final clinical study report for study GS-US-183-1004, a phase 1, multiple-dose study to evaluate the pharmacokinetics of cobicistat-boosted elvitegravir (EVG) in subjects with decreased UGT1A1 activity (study included as a category 3 additional pharmacovigilance study/activity in the RMP), in order to address post-authorisation measure MEA 006. A revised RMP version 1.0 has been provided as part of the application

MAH(s): Gilead Sciences International Ltd

For adoption: PRAC AR

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

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002574/II/0039 (without RMP)

Procedure scope: Submission of the final study report for study GS-US-183-1004, phase I, multiple-dose study to evaluate the pharmacokinetics of cobicistat-boosted elvitegravir in subjects with decreased UGT1A1 activity

MAH(s): Gilead Sciences International Ltd

16.1.14. Etanercept – ENBREL (CAP)

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000262/II/0176 (without RMP)

Procedure scope: Submission of the final report for study B1801130 as listed in RMP Part III

MAH(s): Pfizer Limited

16.1.15. Etanercept – ENBREL (CAP)

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000262/II/0177

Procedure scope: Submission of the final report for study B1801130 as listed in RMP Part III

MAH(s): Pfizer Limited

16.1.16. Ivacaftor – KALYDECO (CAP)

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:

Procedure number(s): EMEA/H/C/002494/II/0035 (with RMP)

Procedure scope: Submission of the final study VX08-770-105 clinical study report (CSR) to fulfil the post-authorisation measure (PAM) ANX 002

MAH(s): Vertex Pharmaceuticals (U.K.) Ltd

16.1.17. Lamivudine, zidovudine – COMBIVIR (CAP)

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/000190/II/0078 (with RMP)

Procedure scope: Variation to fulfil the obligations to provide the final study report for an observational multi-cohort study on the use and safety of Combivir scored tablets among HIV-infected children and adolescent using the EPPICC data as mentioned in version 4 of Combivir EU RMP

MAH(s): ViiV Healthcare UK Limited

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

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:

Procedure number(s): EMEA/H/C/001104/II/0116 (without RMP)

Procedure scope: Submission of a final report for post-authorisation observational safety study of 13-valent pneumococcal conjugate vaccine (13vPnC) administered in routine use to infants and toddlers

MAH(s): Pfizer Limited

16.1.19. Tolvaptan – SAMSCA (CAP)

- Evaluation of PASS results

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000980/II/0020 (without RMP)

Procedure scope: Submission of the final study report for Samsca post-authorisation safety study (FUM 004)

MAH(s): Otsuka Pharmaceutical Europe Ltd

16.1.20. Efavirenz – SUSTIVA (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:

Procedure number(s): EMEA/H/C/000249/MEA 079.1

Procedure scope: Annual report on malignant events and MAH's response to MEA-079 (annual periodic update report for malignant events) as adopted in September 2014

MAH(s): Bristol-Myers Squibb Pharma EEIG

16.1.21. Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Martin Huber (DE)

Administrative details:

Procedure number(s): EMEA/H/C/000797/MEA 039.1

Procedure scope: MAH's response to MEA-039 (annual periodic update report for malignant events) as adopted in September 2014

MAH(s): Bristol-Myers Squibb and Gilead Sciences Ltd.

16.1.22. Emtricitabine, tenofovir disoproxil – TRUVADA (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000594/MEA 041.2

Procedure scope: MAH's response to MEA-041.1 (week 144 interim report for clinical study GS-US-236-0103] as adopted in September 2014

MAH(s): Gilead Sciences International Ltd

16.1.23. Filgrastim – BIOGRASTIM (CAP), RATIOGRASTIM (CAP), TEVAGRASTIM (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:

Procedure number(s): EMEA/H/C/000826/MEA 019.1, EMEA/H/C/000825/MEA 019.1, EMEA/H/C/000827/MEA 019.1

Procedure scope: Second annual report consisting of adverse drug reaction data from all sources including spontaneous reports and reports from the severe chronic neutropenia international registry (SCNIR)

MAH(s): AbZ Pharma GmbH, Ratiopharm GmbH, Teva GmbH

16.1.24. Infliximab – INFLECTRA (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002778/MEA 019

Procedure scope: Annual report of adverse events of special interest (tuberculosis and other serious infections) with the relevant PSUR submissions. It summarises the safety data received by the MAH, from worldwide interventional, registries and observational clinical trials, between 10 September 2013 and 10 September 2014

MAH(s): Hospira UK Limited

16.1.25. Oseltamivir – TAMIFLU (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:

Procedure number(s): EMEA/H/C/000402/LEG 087.2

Procedure scope: Annual review on the pregnancy data

MAH(s): Roche Registration

16.1.26. Raltegravir – ISENTRESS (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/000860/MEA 048.4

Procedure scope: Fourth (and final) annual report for a post-authorisation safety study in a US managed care network

MAH(s): Merck Sharp & Dohme Limited

16.1.27. Tenofovir disoproxil – VIREAD (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/000419/MEA 268.2

Procedure scope: MAH's response to MEA-268.1 (week 144 interim report for clinical study GS-US-236-0103) as adopted in October 2014

MAH(s): Gilead Sciences International Ltd

16.1.28. Ticagrelor – BRILIQUE (CAP)

- Evaluation of interim PASS results

Regulatory details:

PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:

Procedure number(s): EMEA/H/C/001241/MEA 008.4

Procedure scope: Fourth annual progress report on a drug utilisation study D5130N00010A: pharmacoepidemiological study to examine patient characteristics, drug utilization pattern and crude incidence rates of selected outcomes in new users of ticagrelor, clopidogrel and prasugrel in national Swedish registries

MAH(s): AstraZeneca AB

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. Anagrelide – XAGRID (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:

Procedure number(s): EMEA/H/C/000480/S/0064 (without RMP)

MAH(s): Shire Pharmaceutical Contracts Ltd

17.1.2. Histamine dihydrochloride – CEPLENE (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Administrative details:

Procedure number(s): EMEA/H/C/000796/S/0022 (without RMP)

MAH(s): Meda AB

17.1.3. Trabectedin – YONDELIS (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:

PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:

Procedure number(s): EMEA/H/C/000773/S/0042 (without RMP)

MAH(s): Pharma Mar, S.A.

18. ANNEX II - List of participants

including any restrictions with respect to involvement of members/alternates /experts following evaluation of declared interests for the 9-12 February 2015 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to meetings	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Viola Macolić Šarinić	Member	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
Eva Jirsová	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Arnaud Batz	Member	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Ruchika Sharma	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Andis Lacis	Member	Latvia	No restrictions applicable to this meeting	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Ingebjørg Buajordet	Member	Norway	No interests declared	Full involvement
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Magda Pedro	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Alternate	Romania	No interests declared	Full involvement
Jana Nováková	Alternate	Slovakia	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Miguel-Angel Macia	Alternate	Spain	No interests declared	Full involvement
Qun-Ying Yue	Member	Sweden	No interests declared	Full involvement
Ulla Wändel Liminga	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Jane Ahlqvist Rastad	Member	Independent scientific expert	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No restrictions applicable to meetings	Full involvement
Brigitte Keller-Stanislowski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Filip Babylon	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Marianne Lunzer	Expert - in person*	Austria	No interests declared	Full involvement
Jens Heisterberg	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Corinne Fechant	Expert - in person*	France	No interests declared	Full involvement
Catherine Deguines	Expert - in person*	France	No interests declared	Full involvement
Melanie Leplay	Expert - in person*	France	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Camille Schurtz	Expert - via telephone*	France	No interests declared	Full involvement
Wilma Fischer-Barth	Expert - via telephone*	Germany	No interests declared	Full involvement
Jutta Krappweis	Expert - via telephone*	Germany	No interests declared	Full involvement
Walburga Lütkehermölle	Expert - via telephone*	Germany	No interests declared	Full involvement
Jens Rotthauwe	Expert - via telephone*	Germany	No interests declared	Full involvement
Zane Neikena	Expert - via telephone*	Latvia	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeberg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Juliana Min	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Alison Banner-Simpson	Expert - in person*	United Kingdom	No interests declared	Full involvement
Patrick Batty	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Phil Bryan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Claire Doe	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Kathryn Ord	Expert - in person*	United Kingdom	No interests declared	Full involvement
Angelika Siapkara	Expert - in person*	United Kingdom	No interests declared	Full involvement
Karen Slevin	Expert - in person*	United Kingdom	No interests declared	Full involvement

A representative from the European Commission attended the meeting

Meeting run with support from relevant EMA staff

* Experts were only evaluated against the product(s) they have been invited to participate in