10 April 2015
EMA/PRAC/257790/2015
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 09-12 March 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).

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

Explanatory notes

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table of contents

1. Introduction

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

The Chairperson opened the 9-12 March 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 noted that Andis Lacis had stepped down as member for Latvia and thanked him on behalf of the committee for his contribution to the work of the PRAC since its establishment.

1.2. Adoption of agenda of the meeting of 09-12 March 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 09-12 February 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 9-12 February 2015 were published on the EMA website on 27 March 2015 (EMA/PRAC/209591/2015).

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

3.2.1. **Dexibuprofen** (NAP); **ibuprofen** (NAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/A-31/1401
MAH(s): various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for ibuprofen (and for the dextrorotatory enantiomer of ibuprofen, dexibuprofen)-containing medicines (see PRAC Minutes December 2014).

Following receipt of a response from the Coxib and traditional NSAID Trialists' (CNT) Collaboration to a list of questions adopted in December 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 cardiovascular risk of ibuprofen/dexibuprofen at high doses (≥ 2400 mg/day for ibuprofen, ≥ 1200 mg/day for dexibuprofen) and the potential interaction with low dose aspirin including the evaluation of the MAHs' responses to the first list of outstanding issues and the response from the CNT Collaboration. 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/332908/2014 Rev.2).

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 for codeine-containing medicines (see PRAC Minutes February 2015), when used for the treatment of cough and/or cold in paediatric patients, is to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs together with the available evidence on the risk of opioid toxicity after exposure to codeine when used in the treatment of cough and/or cold in paediatric patients. The opinion from the Paediatric Committee (PDCO) and responses from the Healthcare Professionals' organisations (HCPOs), consulted during the procedure, were also taken into account.

Based on the available data, the PRAC considered that the use of codeine in pain relief could be associated with serious adverse events of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine and that children below 12 years are at risk of life-threatening respiratory depression and those who are ultra-rapid metabolisers are at special risk.

The PRAC also noted that there was limited evidence supporting the efficacy of codeine in cough and cold and that these were generally self-limiting conditions in children. Treatment guidelines recommend treatment of persistent chronic cough in paediatric patients based on aetiology. Having considered the available evidence, the PRAC concluded that the use of codeine-containing medicinal products for the treatment of cough and/or cold in the paediatric population is not recommended due to the nature of the conditions and the views of clinical experts. The PRAC considered that the current evidence suggested that children below 12 years with ultra-rapid metaboliser status are at special risk of life-threatening respiratory depression and therefore, concluded that the use of codeine-containing medicinal products for the treatment of cough and/or cold is contraindicated in children below 12 years. The PRAC further considered that the use of codeine is not recommended in children aged 12 years to 18 years with compromised respiratory function. In line with the restrictions introduced as an outcome of the Article 31 referral procedure for codeine used for pain relief in children (EMA/350259/2013), the PRAC also concluded that all codeine-containing medicinal products for the treatment of cough and/or cold should be contraindicated in women when breastfeeding, as well as in patients known to be CYP2D6[1] ultra-rapid metabolisers.
As a consequence, the PRAC concluded that the benefit-risk balance of the medicinal products containing codeine for cough and/or cold remains favourable, subject to the inclusion of the restrictions, warnings and other agreed changes to the product information relating to use in children.

Summary of recommendation(s)/conclusions

The PRAC adopted by consensus a recommendation, to be considered by the CMDh, to vary the marketing authorisations for codeine-containing medicines indicated for the treatment of cough in

[1] Cytochrome P450 2D6

paediatric patients – see 'PRAC recommends restrictions on the use of codeine for cough and cold in children' EMA/163792/2015. Key elements for national communication plan were 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 prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Bisphosphonates: alendronic acid (NAP); **alendronic acid, colecalciferol - ADROVANCE** (CAP), **FOSAVANCE** (CAP), **VANTAVO** (CAP); **etidronic acid** (NAP); **ibandronic acid – BONDRONAT** (CAP), **BONVIVA** (CAP), **neridronic acid** (NAP); **pamidronic acid** (NAP); **risedronic acid** (NAP); **tiludronic acid** (NAP); **zoledronic acid – ACLASTA** (CAP), **ZOMETA** (CAP), **and denosumab – PROLIA** (CAP), **XGEVA** (CAP)

- Signal of osteonecrosis of the external auditory canal

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 18256 – New signal
MAH(s): various
Lead MS: UK

Background

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

The worldwide exposure of bisphosphonates containing medicinal products is estimated to have been very large with over 190 million prescriptions.
The exposure for Prolia, a centrally authorised medicine containing denosumab (indicated for bone resorption, osteoporosis and postmenopausal), is estimated to have been more than 2,455,929 patient treatment years worldwide, in the post-marketing setting in the period from first authorisation in 2010 up to September 2014. The exposure for Xgeva, a centrally authorised medicine containing denosumab (indicated in fractures, bone metastases), is estimated to have been more than 278,170 patient treatment years worldwide in the post-marketing setting, in the period from first authorisation in 2011 up to September 2014.

During routine signal detection activities, a signal of osteonecrosis of the external auditory canal was identified by the UK, based on 18 cases (including 4 cases retrieved from EudraVigilance), which were

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

mainly reported in the published literature. Two spontaneous reports of osteonecrosis of the temporal bone/auditory canal have also been identified in association with denosumab.
The UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of osteonecrosis of the external auditory canal and noted that bisphosphonate-induced osteonecrosis has previously been thought to be possibly restricted to the jaw, however there are similarities between the external ear canal and the jaw, which may potentially be reasons why the external auditory canal may also be susceptible to osteonecrosis in association with bisphosphonates. The PRAC considered that in addition to bisphosphonates, the possible risk of osteonecrosis of the external auditory canal also needs to be considered for denosumab. The PRAC recommended to request MAHs to comment on this signal with a view to amend the product information for bisphosphonates- and denosumab-containing medicines as appropriate.

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

Summary of recommendation(s)

- The MAHs for alendronic acid/colecalciferol (Merck Sharp & Dohme Ltd), for ibandronic acid (Roche Registration Limited), for zoledronic acid (Novartis Europharm Limited), for denosumab (Amgen Europe B.V.), for clodronic acid (Bioprojet Europe), for etidronic acid (Warner Chilcott), for neridronic acid (Abiogen Pharma), for pamidronic acid (Hospira UK), for risedronic acid and for tiludronic acid (Sanofi-Aventis) should submit to the EMA, within 60 days, details of any additional clinical trial, spontaneous or literature reports of osteonecrosis of the external auditory canal in association with bisphosphonates and/or denosumab that have not been identified in the reviewed literature (*Polizzotto et al., 2005, Froelich et al., 2011, Bast et al., 2012, Salzman et al., 2013, and Wickham et al., 2013*), the reviewed abstract cases reports (*Amiraraghi et al., 2014*), and the report in the SWEDIS database (*Kharazmi et al., 2013*) and discuss the possible mechanisms involved in osteonecrosis of the external auditory canal in association with bisphosphonates and/or denosumab. Based on the above, the MAHs should propose updates to the product information for bisphosphonates and/or denosumab to inform healthcare professionals and patients about the risk of osteonecrosis of the external auditory canal in association with these medicinal products.
- 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

4.2.1. **Adalimumab - HUMIRA** (CAP)

- Signal of convulsions

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

Administrative details:
EPITT 18211 – New signal
MAH(s): AbbVie Ltd.
Lead MS: SE

Background

Adalimumab is a selective immunosuppressive agent indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, axial spondyloarthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis.

The exposure for Humira a centrally authorised medicine containing adalimumab, is estimated to have been more than 2.9 million patient-years worldwide in the post-marketing setting, in the period from first authorisation in 2003 up to December 2013.

During routine signal detection activities, a signal of convulsions was identified by the UK, based on 35 cases from a national review. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of convulsions and requested a cumulative review of all reported cases of convulsions (retrieved at the level of the high level group term (HLGT) 'seizures'), in association with adalimumab with a view to amend the product information for adalimumab-containing medicines.

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should submit to the EMA, within 60 days, a cumulative review of all reported cases of convulsions, in association with adalimumab. The review should include reports from post-marketing and clinical trials. Cases with known history of epilepsy should also be provided and medically confirmed convulsions (not necessarily witnessed, but regarded as at least probable by healthcare professionals, e.g. by observation of post-ictal confusion or electroencephalogram changes) should be analysed separately. If applicable, the MAH should make a proposal for a change to the product information and/or to the risk management plan.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Amiodarone (NAP)

- Signal of pancreatitis

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

Administrative details:
EPITT 18216 – New signal
MAH(s): Sanofi
Lead MS: NL

Background

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

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

During routine signal detection activities, a signal of pancreatitis was identified by Spain, based on 8 cases retrieved in the Spanish safety database. The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of pancreatitis and requested a cumulative review of all cases concerning pancreatitis associated with amiodarone with a view to amend the product information for amiodarone-containing medicines.

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

Summary of recommendation(s)

- The MAH for the innovator medicinal product containing amiodarone (Sanofi) should submit to the EMA, within 60 days, a cumulative review of all cases concerning pancreatitis associated with amiodarone, both from clinical trials and spontaneous sources in order to further evaluate this signal. Also, the MAH should provide a discussion of relevant non-clinical data and scientific literature. Based on the review, the MAH should also discuss the need for an update of the product information and the necessity for any additional pharmacovigilance activities.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3. Donepezil (NAP)

- Signal of rhabdomyolysis

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 18261 – New signal
MAH(s): Eisai Ltd.
Lead MS: UK

Background

Donepezil is a specific and reversible inhibitor of acetylcholinesterase indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

The exposure for donepezil is estimated to have been more than 20,000,000 patient years worldwide, in the period from first authorisation in 1997 up to the latest PSUR (DLP: 25/11/2011).

During routine signal detection activities and following the issue of a new warning on the risk of rhabdomyolysis by Health Canada, a signal of rhabdomyolysis was identified by the UK, based on 88 cases retrieved from EudraVigilance. The UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of rhabdomyolysis and considered that this signal merited further review. Therefore, the PRAC requested a cumulative review of all cases of

rhabdomyolysis and related terms reported for donepezil with a view to amend the product information for donezepil-containing medicines.

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

Summary of recommendation(s)

- The MAH for Aricept (donezepil) should submit to the EMA, within 60 days, a cumulative review of all cases of rhabdomyolysis and related terms reported for donepezil. The review should include reports in the MAH's clinical trial and post-marketing safety databases and the published literature. If applicable, the MAH should make a proposal to update the product information.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.4. Fingolimod - GILENYA (CAP)

- Signal of progressive multifocal leukoencephalopathy (PML)

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
EPITT 18241– New signal
MAH(s): Novartis Europharm Ltd
Lead MS: FR

Background

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

The exposure for Gilenya a centrally authorised medicine containing fingolimod, is estimated to have been more than 135,800 patient years worldwide, in the period from first authorisation in 2011 up to February 2014.

During routine signal detection activities, a signal of progressive multifocal leukoencephalopathy (PML) was identified by France, based on a spontaneous report of PML in a patient treated with fingolimod for multiple sclerosis for 4 years in Germany. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the newly reported case of PML associated with long-term treatment with fingolimod. The diagnosis was confirmed and based on magnetic resonance imaging (MRI) findings and John Cunningham virus (JCV) DNA polymerase chain reaction (PCR) results. It was notable that the patient experienced weakness but no clinical sign or symptoms related to PML. The lack of previous immunosuppressive treatment further pointed towards a possible causal association with Gilenya . The PRAC also discussed twelve other cases of PML with fingolimod reported in the last PSUR (DLP: 28/02/2014). Among these, no case was previously reported without a history of natalizumab or another immunosuppressant treatment. Only one patient had no prior history of natalizumab use but was treated with another immunosuppressant. PML is currently included as an important potential risk in the fingolimod Risk Management Plan.

Taking into account this first report of asymptomatic case of PML after long-term treatment with fingolimod without prior immunosuppressive treatment and considering the seriousness of PML, the PRAC agreed that a direct healthcare professional communication (DHPC) should be circulated promptly and additional information on this signal is requested from the MAH. The PRAC also considered that seeking expert advice from the Scientific Advisory Group (SAG) Neurology would be helpful.

Summary of recommendation(s)

- The PRAC agreed that the MAH for Gilenya (fingolimod) should distribute a DHPC according to the text and communication plan agreed with the PRAC and CHMP.
- The MAH for Gilenya should provide,by 06/04/2015 an estimate of total patient exposure (i.e. from both trials and non-study use) stratified by duration of exposure to fingolimod along with an estimate of the risk of PML according to the number of patients at risk, assuming that PML associated with fingolimod has a long latency period of at least several years (over four years in the index case).
  The MAH should provide any new follow-up information on the case as soon as this is available, especially confirmation of whether or not there was an immune reconstitution inflammatory syndrome (IRIS)-type response in this patient after fingolimod withdrawal and whether or not the MRI lesions are receding. The MAH should discuss the absence of overt clinical symptoms in this case.
  In addition, the MAH should discuss whether studies FTY20D2403 and FTY20D2406 are of sufficient duration and size to adequately characterise the risk of PML with long-term fingolimod therapy, especially when the index case had a time to onset of more than four years.
  The MAH should provide an updated cumulative review of data from all sources (including previous cases) with the view of elucidating the mechanisms of action in relation to the risk of PML for fingolimod, including any identifiable or potential risk factors (with and without prior immunosuppressant treatments) that could inform implementation of risk minimisation measures, or that would warrant further study.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.5. Palifermin - KEPIVANCE (CAP)

- Signal of increased mortality associated with unlicensed use in acute lung injury

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
EPITT 18160 – New signal
MAH(s): Swedish Orphan Biovitrum AB (publ)
Lead MS: UK

Background

Palifermin is a human keratinocyte growth factor (KGF) indicated to decrease the incidence, duration and severity of oral mucositis in adult patients with haematological malignancies under certain conditions.

The exposure for Kepivance, a centrally authorised medicine containing palifermin, is estimated to have been more than 17,287 patients worldwide, in the period from first authorisation in 2005 up to January 2012.

A signal of increased mortality associated with the unlicensed use of palifermin in acute lung injury was identified by EMA, based on the results of the recently completed keratinocyte growth factor in acute lung injury to reduce pulmonary dysfunction (KARE) study. The MAH provided EMA with a summary of the results of this investigator-sponsored randomised placebo-controlled study in patients with acute lung injury conducted in Northern Ireland. The study results showed that intensive care unit (ICU) and 28-day survival were significantly lower in the palifermin group compared to placebo. In addition, the palifermin group had a longer duration of ventilator use, ICU stay and hospital stay. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information provided by the MAH on the KARE study and noted that the approved indication and the KARE study differ in terms of patient population, conditions treated and posology. Randomised clinical trials, observational studies and spontaneous reports in patients with haematological malignancies have not raised a signal of increased mortality or pulmonary events with palifermin. Pulmonary events, both infectious and non-infectious, are currently included as an important potential risk in the RMP. The PRAC agreed that no regulatory action was necessary based on this study report and that the MAH should continue to closely monitor pulmonary adverse events including fatal cases in future PSURs. The PRAC considered that the investigator should be encouraged to promptly publish the results in a suitable peer reviewed publication of the KARE study.

Summary of recommendation(s)

- No regulatory action was considered necessary based on this study report; however the MAH should continue to closely monitor pulmonary adverse events including fatal cases in future PSURs.

4.2.6. Warfarin (NAP)

- Signal of bone density decrease

Regulatory details:
PRAC Rapporteur: Torbjörn Callreus (DK)

Administrative details:
EPITT 18173 – New signal
MAH(s): various
Lead MS: DK

Background

Warfarin is an oral anticoagulant used for short and long term prevention of thrombo-embolic disorders, including treatment and prevention of deep venous thrombosis and pulmonary embolism, secondary prevention of myocardial infarction and prevention of thromboembolic complications (stroke or systemic embolism) after myocardial infarction, and prevention of thromboembolic complications in patients with atrial fibrillation, cardiac valvular disease and or prosthetic heart valves.

The worldwide exposure for medicines containing warfarin is estimated to have been very large, since the medicine has been extensively prescribed since its first authorisation in the mid-1950s.

During routine signal detection activities, a signal of bone density decrease was identified by EMA, based on four cases reported in the literature. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results of the published study by *Monagle et al.*[3] in which four patients showed reduced bone mineral density in at least one site as well as the results of the published study by *Barnes et al.*[4], a case control study which examined the effect of long-term warfarin treatment in children and a possible association with decreased bone density. The PRAC acknowledged that a number of confounding factors such as the underlying disease, concomitant medication and diet must be considered. Having considered the available evidence, the PRAC agreed to seek the Paediatric Committee's (PDCO) views in order to obtain advice on the need to further assess the potential effect on bone density in children treated with warfarin.
The PRAC appointed Torbjörn Callreus (DK) as Rapporteur for the signal.

Summary of recommendation(s)

- Taking into account the limitations of the studies by *Barnes et al.*[4] and *Monagle et al.*[2] (including the possible confounding effects by indications), the PDCO's view is sought on the clinical relevance of the magnitude of the decreased bone mineral density described in these studies in children treated with warfarin, and whether this should warrant further investigation by PRAC.

4.3. Signals follow-up and prioritisation

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

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

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
EPITT 18112 – Follow-up October 2014
Procedure number(s): EMEA/H/C/002392/SDA/012
MAH(s): Bayer Pharma AG

Background

For background information, see PRAC Minutes October 2014. The MAH replied to the request for information on the signal of higher systemic exposure compared to ranibizumab after intravitreal injection and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the re-analysis of the data from the VIEW-1 (study VGFT-OD-0605) and VIEW-2 (study 311523) studies (which compared aflibercept to ranibizumab, focusing on cerebrovascular

[3] Monagle K., Jones S, King I et al. Anticoagulation of cardiomyopathy in children. Thrombosis research. May 10, 2014; 134:255-258.
[4] Barnes C, Newall F, Ignajatovic V, et al. reduced bone density in children on long-term warfarin. Pediatric Res 2005; 57:578-581.

events in elderly patients) and the complete review and discussion of pre-clinical and clinical data available on the risks associated with the systemic exposure to anti-vascular-endothelial-growth-factor, including pharmacokinetic data, provided by the MAH. Based on the available data, the PRAC concluded that higher systemic exposure of aflibercept compared to ranibizumab after intravitreal injection cannot be excluded but that the current data does support any specific conclusion on its clinical consequences.

Summary of recommendation(s)

- To better assess the clinical consequences (cardiovascular and cerebrovascular risk), these should be investigated in the post-authorisation safety study 15971 LIBRA (Long-term Investigation and risk-Benefit analysis of the Real-life utilisation of Aflibercept in macular disease), which is an additional pharmacovigilance measure in the Eylea EU risk management plan. The MAH of Eylea should submit within four months a study protocol suited to address this signal and its clinical consequences.
- The PRAC will assess the protocol within a 60 day timetable.

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

- Signal of aggression and related events

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:
EPITT 18127 – Follow-up November 2014
Procedure number(s): EMEA/H/C/000471/SDA/072
MAH(s): Otsuka Pharmaceutical Europe Ltd

Background

For background information, see PRAC Minutes November 2014. The MAH replied to the request for information on the signal of aggression and related events and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review of the signal of aggression and related events provided by the MAH and acknowledged that the indications for which aripiprazole is approved may be associated with aggressive / violent thinking or behaviour. As such, lack of drug treatment effect or the cycling nature of the underlying disorder may induce or exacerbate aggression or related events. It was also acknowledged that some of the patients treated with aripiprazole have been co-treated with other agents for which the risk of aggressive behaviour has been shown. However, there was evidence that in patients with no previously known aggressive behaviour, aripiprazole treatment was associated with the development of this behaviour. Most aggression and related behaviours are serious adverse events. The PRAC considered that based on the available evidence the product information for aripiprazole-containing medicinal products should be updated to include 'aggression' and that the MAH for Abilify and Abilify Maintena should cumulatively review in the next PSUR the overdose associated risk of aggression and related events.

Summary of recommendation(s)

- The MAHs of aripiprazole-containing medicinal products should submit a variation within 60 days to include 'aggression' [5] as an undesirable effect with an unknown frequency in the product information.
- The MAH for Abilify and Abilify Maintena should submit in the next PSUR (DLP: 16/07/2015), a cumulative review of aripiprazole overdose and the risk of aggression and related events.

For the full PRAC recommendations, see EMA/PRAC/176901/2015 published on the EMA website.

4.3.3. Infliximab – **INFLECTRA** (CAP), **REMICADE** (CAP), **REMSIMA** (CAP)

- Signal of rhabdomyolysis

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

Administrative details:
EPITT 18129 – Follow-up November 2014
Procedure number(s): EMEA/H/C/002778/SDA/020, EMEA/H/C/000240/SDA/152, EMEA/H/C/002576/SDA/019
MAH(s): Hospira UK Limited (Inflectra), Janssen Biologics B.V. (Remicade), Celltrion Healthcare Hungary Kft. (Remsima)

Background

For background information, see PRAC Minutes November 2014. The MAH replied to the request for information on the signal of rhabdomyolysis and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review of the signal of rhabdomyolysis provided by the MAH. Three cases of possible rhabdomyolysis were reported from clinical trials in infliximab treated subjects, versus one case reported among placebo treated patients. Regarding the 53 post marketing reported cases, no clear sentinel case was identified. For one case from Japan, a positive rechallenge was reported. However, the information regarding relationship timing of the first dose of infliximab in relation to the event, and concomitant administration of ciprofloxacin contradicts a causal relationship. In total, six patients treated with infliximab in registries were reported to experience rhabdomyolysis. It is not known if these cases were confounded. Due to the time frame for responding, no rheumatoid arthritis registry data were included in the review provided. No relevant cases were described in the literature. Based on the available evidence, the PRAC considered that there is insufficient evidence at present to add rhabdomyolysis to the product information of infliximab-containing medicinal products. However further clarifications from the MAH are required to address this signal fully.

Summary of recommendation(s)

- The MAH for Remicade should submit to EMA, within 60 days, the rationale for classifying an event of rhabdomyolysis emerging in a clinical trial as an adverse drug reaction (ADR), clarification whether the cases retrieved from the clinical trials represent verified cases of rhabdomyolysis, and what criteria were used to identify these, considering the medical coding

[5] Section 4.8 of the Summary of Product Characteristics

applied and finally the MAH should provide with further information on the case described above.

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

4.3.4. Recombinant Factor VIII:
Antihemophilic factor (recombinant) (NAP)
Moroctocog alfa – REFACTO AF (CAP)
Octocog alfa – ADVATE (CAP), **HELIXATE NEXGEN** (CAP), **KOGENATE** (CAP)

- Signal of inhibitor development in previously untreated patients

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

Administrative details:
EPITT 18134 – Follow-up January 2015
MAH(s): Baxter AG (Advate, Recombinate), Bayer Pharma AG (Kogenate, Helixate NexGen), Pfizer Limited (ReFacto AF), various

Background

For background information, see PRAC Minutes November 2014, PRAC Minutes December 2014 and PRAC Minutes January 2015.
The PRAC Rapporteur presented a draft protocol for the analysis of the data from three published studies[6].

Discussion

The PRAC discussed the draft protocol for the analysis of the data from three published studies and recommended some amendments. The updated protocol will be discussed with the study authors and PRAC Rapporteurs in a dedicated meeting to be held at EMA in March 2015. During this meeting, clarification will be obtained as to whether or not individual patient level data will be available for analysis. A revised protocol will be then discussed at the PRAC.

Summary of recommendation(s)

- The PRAC discussed the draft protocol for the analysis of the data from three published studies and recommended some amendments (e.g. clarifications of the specified aims and objectives of the study, criteria for inclusion, statistical methods to be specified, pre-specification of the assessment of bias).
- The updated protocol will be discussed with the study authors and PRAC Rapporteurs in a dedicated meeting to be held at EMA in March 2015. A revised protocol will be then discussed at the PRAC.

[6] Gouw SC, et al. PedNet and RODIN Study Group. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013;368:231-9
Calvez T et al. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A, Blood. 2014 Sep 24. pii: blood-2014-07-586347
Collins PW et al. Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe haemophilia A, 2000-2011. Blood. 2014 Oct 22. pii: blood-2014-07-580498

4.3.5. 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 February 2015
MAH: various

Background

For background information, see PRAC Minutes April 2014, PRAC Minutes September 2014 and PRAC Minutes February 2015.
Following the request of the PRAC, further clarifications were provided by the PRAC Rapporteur on the scope of the procedure in terms of products and duration of use, the evidence supporting the thresholds for daily intake of sodium, and the proposed regulatory approach to implementation of improved labelling information.

Discussion

The PRAC agreed on a revised scope for this procedure: medicinal products high in sodium excipient content with chronic or regular use. It was anticipated that the majority of the medicines that fall within this scope would be effervescent or soluble formulations. The PRAC recommended that it was appropriate to use ≥ 17 mmol of sodium as the threshold for defining products as being high in sodium as this was excipient content driven by dietary sodium intake recommendations for adults and was equivalent to ≥20% of the WHO maximum recommended daily intake for sodium for an adult.

The PRAC discussed and agreed the aim of product information changes as well as the proposed wording. It was agreed that implementation should be through a PRAC recommendation and it was considered important that further consideration be given to the most appropriate approach to implementation in order to facilitate identification of products that would be within the scope and for which the product information would need to be varied. For that purpose, the PRAC agreed that prior to adopting a formal recommendation on implementation, engagement with the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on this topic should be pursued.

Summary of recommendation(s)

- The PRAC noted and broadly supported the proposals for the revised scope, the threshold for defining products as high in sodium excipient content and also the proposed product information updates. Before final PRAC recommendations are adopted it was considered that engagement with CMDh should be pursued in order to develop a plan to facilitate implementation of the final PRAC recommendation.

4.3.6. Sorafenib – NEXAVAR (CAP)

- Signal of acute generalised exanthematous pustulosis (AGEP)

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

Administrative details:
EPITT 18109 – Follow-up November 2014
Procedure number(s): EMEA/H/C/000690/SDA/033
MAH(s): Bayer Pharma AG

Background

For background information, see PRAC Minutes November 2014. The MAH replied to the request for information on the signal of acute generalised exanthematous pustulosis (AGEP) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review of the signal of AGEP provided by the MAH. One case of AGEP referring to a publication by *Pretel et al.* (2014) was not typical as there was no fever, but was accepted as confirmed. Causality in relation to sorafenib, however, may be questioned due to negative patch tests and the longer than expected duration of exposure to sorafenib prior to the event. Further search in clinical studies, databases and the literature revealed one case of clinically diagnosed, atypical case of AGEP not confirmed by biopsy. Having considered the responses provided by the MAH for Nexavar, the PRAC considered that the number of possible cases of AGEP with a temporal relationship to sorafenib is very small and that the likelihood of a causal relationship between treatment with sorafenib and AGEP is not sufficiently strong to warrant changes in the product information at this stage. Nevertheless, the MAH should continue to monitor these events as part of routine safety surveillance. Furthermore, the PRAC considered that the RMP should be updated at the next regulatory opportunity to include a form to collect information on potential cases of AGEP, similar to its approach for other severe cutaneous adverse reactions.

Summary of recommendation(s)

- The MAH for Nexavar should continue to monitor cases of acute generalised exanthematous pustulosis (AGEP) as part of routine safety surveillance. Furthermore, the MAH should update the RMP at the next regulatory opportunity to include a form to collect information on potential cases of AGEP, similar to its approach for other severe cutaneous adverse reactions.

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).

5.1.1. Allogeneic cells genetically modified to express suicide gene

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

Administrative details:
Product number(s): EMEA/H/C/002801, *Orphan, ATMP*

Intended indication(s): Treatment in haploidentical haematopoietic stem cell transplantation
Applicant: MolMed SpA

5.1.2. Asfotase alfa

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

Administrative details:
Product number(s): EMEA/H/C/003794, *Orphan*
Intended indication(s): Treatment of paediatric-onset hypophosphatasia
Applicant: Alexion Europe SAS

5.1.3. Bortezomib

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

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

5.1.4. Dexamethasone

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

Administrative details:
Product number(s): EMEA/H/C/004071, *Orphan, Hybrid*
Intended indication(s): Treatment of symptomatic multiple myeloma in combination with other medicinal products
Applicant: Laboratoires CTRS

5.1.5. Duloxetine

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

Administrative details:
Product number(s): EMEA/H/C/003981, *Generic*
Intended indication(s): Treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder

5.1.6. Empagliflozin, metformin

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

Administrative details:
Product number(s): EMEA/H/C/003770
Intended indication(s): Treatment of type II diabetes

5.1.7. Human papillomavirus [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed)

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

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

5.1.8. Lenvatinib

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

Administrative details:
Product number(s): EMEA/H/C/003727, *Orphan*
Intended indication(s): Treatment of papillary thyroid cancer, treatment of follicular thyroid cancer
Applicant: Eisai Ltd

5.1.9. Levodopa, carbidopa

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

Administrative details:
Product number(s): EMEA/H/C/002611
Intended indication(s): Treatment of Parkinson's disease

5.1.10. Mepolizumab

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

Administrative details:
Product number(s): EMEA/H/C/003860
Intended indication(s): Treatment of asthma

5.1.11. Nivolumab

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

Administrative details:
Product number(s): EMEA/H/C/003985
Intended indication(s): Treatment of advanced (unresectable or metastatic) melanoma in adults

5.1.12. Panobinostat

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

Administrative details:
Product number(s): EMEA/H/C/003725, *Orphan*
Intended indication(s): Treatment of multiple myeloma
Applicant: Novartis Pharmaceuticals UK Limited

5.2. Medicines already authorised

RMP in the context of a variation[7] – PRAC-led procedure

5.2.1. Oseltamivir – TAMIFLU (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000402/II/0114

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

Procedure scope: Proposal for a new and alternative study BV29684 'assessing the safety of prenatal exposure to oseltamivir' as category 3 study (MEA 099) to replace the agreed 2-year extension of the Danish-Swedish registry (NV25577)
MAH(s): Roche Registration Ltd

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 RMP version 12 for Tamiflu (oseltamivir), replacing the two year-extension of study NV25577 (2-year extension of the Danish-Swedish registry assessing the safety of oseltamivir exposure in pregnant women in Denmark and Sweden) with the proposed new study BV 29684 (assessing the safety of prenatal exposure to oseltamivir), was not considered acceptable as it was not a suitable replacement for the requested extension of study NV 25577. The MAH should provide further justification for not performing study NV25577. In addition, the MAH should address the remaining PRAC questions and further justify how the new proposed study BV 29684 overcomes the limitations previously raised and how it better addresses the scientific question investigated. A request for further information to be addressed by the MAH was agreed before the procedure is concluded.

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

5.2.2. Crizotinib – XALKORI (CAP)

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

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002489/II/0024
Procedure scope: Extension of indication to the first-line treatment anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) and to update SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 to include results of the pivotal Study A8081014, a multinational, multicentre, randomized, open-label, phase 3 study comparing the efficacy and safety of crizotinib to first-line chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in patients with previously untreated ALK-positive advanced non-squamous NSCLC and updated safety results from studies A8081001, A8081005 and A8081007. In addition, SmPC section 5.1 was revised to include updated overall survival data from studies A8081001 and A8081005
MAH(s): Pfizer Limited

Background

Crizotinib is a protein kinase inhibitor indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

The CHMP is evaluating an extension of the therapeutic indication for Xalkori, a centrally authorised product containing crizotinib, to extend the indication to the first-line treatment of ALK-positive advanced NSCLC. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 6.0 for Xalkori (crizotinib) submitted in the context of the extension of indication under evaluation by the CHMP was considered acceptable, provided an updated RMP and satisfactory responses to the PRAC list of questions are submitted.
- The PRAC considered that since further data are expected in relation to the overall survival (OS) analysis from randomised study A8081007, the corresponding specific obligation cannot be considered fulfilled at this stage. In addition, the MAH should maintain the additional risk minimisation measures for gastrointestinal perforation. Finally, the MAH should closely monitor QTc prolongation effects, particularly in patients with pre-existing bradycardia, who have a history of/or predisposition for QTc prolongation, taking antiarrhythmic drugs or other medicinal products that are known to prolong QT interval and in patients with relevant pre-existing cardiac disease and/or electrolyte disturbances.

5.2.3. Lenalidomide – REVLIMID (CAP)

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

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000717/II/0079
Procedure scope: Extension of indication to add treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). As a consequence, SmPC sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 as well as the package leaflet are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and package leaflet
MAH(s): Celgene Europe Limited

Background

Lenalidomide is an anti-neoplastic, anti-angiogenic, pro-erythropoietic immunomodulator indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant, and indicated in combination for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. In addition, lenalidomide is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

The CHMP is evaluating an extension of the therapeutic indication for Revlimid, a centrally authorised product containing lenalidomde, to include the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 25.0 for Revlimid (lenalidomide) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable, provided an updated RMP and satisfactory responses to the PRAC list of questions are submitted.
- The MAH should propose a post-authorisation non-interventional safety study of patients with relapsed and/or refractory mantle cell lymphoma to further investigate and characterise the

association of lenalidomide and second primary malignancies (SPM), tumour flare reaction (TFR), venous thromboembolism (VTE) and arterial thromboembolism (ATE).

5.2.4. Ritonavir – NORVIR (CAP)

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

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

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

Background

Ritonavir is a protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of two years of age and older).

The CHMP is evaluating a line extension for Norvir for a new oral powder formulation as a replacement of the currently marketed oral solution as a more suitable ritonavir formulation in the paediatric population. 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 (see PRAC Minutes October 2014).

Summary of advice

- The RMP version 6 for Norvir (ritonavir) submitted in the context of the line extension under evaluation by the CHMP was considered acceptable.
- The PRAC considered that the amendments to the instructions for use provide better guidance on how the oral powder should be reconstituted to avoid under-dosing. The PRAC noted that user testing had been conducted with a satisfactory outcome. The updated risk minimisation measures in the product information are considered adequate to minimise the risk of under-dosing in relation to the Norvir oral powder.

5.2.5. Tigecycline – TYGACIL (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/000644/II/0092
Procedure scope: Addition of a new restricted indication in children aged eight year-old and older. SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 have been updated accordingly. The package leaflet is also updated
MAH(s): Pfizer Limited

Background

Tigecycline is a glycylcycline antibiotic indicated in adults for the treatment of complicated skin and soft tissue infections, excluding diabetic foot infections and for complicated intra-abdominal infections.

The CHMP is evaluating an extension of the therapeutic indication for Tygacil, a centrally authorised product containing tigecycline, to include the treatment of complicated skin and soft tissue infections, excluding diabetic foot infections and complicated intra-abdominal infections in children of eight years- and older.

The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 12 for Tygacil (tigecycline) submitted in the context of the extension of indication variation under evaluation by the CHMP was considered acceptable, provided an updated RMP and satisfactory responses to the PRAC list of questions are submitted.
- The PRAC considered that the safety concerns identified by the MAH are appropriate (hepatotoxicity grouped, missing information in paediatrics moved to <8 years old). The PRAC considered that off-label use should not be added as an important risk. The proposed pharmacovigilance plan is sufficient to identify and characterise the risks of the product (antibiotic resistance surveillance) and the routine risk minimisation measures are adequate. A request for further information on minor aspects to be addressed by the MAH was agreed.

RMP evaluated in the context of a PSUR procedure

None

RMP evaluated in the context of PASS results

See also Dabigatran – PRADAXA 16.1.12. ; Dolutegravir – TIVICAY 16.1.13. , 16.1.14. ; 7.4.7. Human papillomavirus vaccine – GARDASIL, SILGARD 16.1.17. ; Human rotavirus, live attenuated – ROTARIX 7.4.1.

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

See ANNEX I

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

None

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[8]

6.1.1. **Bexarotene – TARGRETIN** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000326/PSUSA/00404/201409
MAH(s): Eisai Ltd

Background

Bexarotene is an antineoplastic agent indicated for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) in adult patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Targretin, a centrally authorised medicine containing bexarotene, 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 Tagretin (bexarotene) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to also include in the appropriate section of the product information that bexarotene may potentially enhance the action of insulin, agents enhancing insulin secretion or insulin –sensitisers thus causing hypoglycaemia. Therefore the current terms of the marketing authorisation(s) should be varied[9].
- In the next PSUR, the MAH should review cumulatively cases of second primary malignancies including Hodgkin's disease and non-Hodgkin's lymphoma. This review should include cases reported spontaneously and those collected from clinical trials. A literature review should also be performed. The MAH should discuss the final results from the European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force phase III randomised clinical trial entitled 'efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides' (*Whittaker S et al*, Br J Dermatol. 2012 Sep;167(3):678-87) and continue to closely monitor reports of suspected drug-drug interactions observed with bexarotene, including interactions with vitamin K antagonists.

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.

[8] 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

[9] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.2. Brimonidine – MIRVASO (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002642/PSUSA/10093/201408
MAH(s): Galderma International

Background

Brimonidine is a selective alpha2-adrenergic receptor agonist (dermatological agent) indicated for the symptomatic treatment of facial erythema of rosacea in adult patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mirvaso, a centrally authorised medicine containing brimonidine, 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 Mirvaso (brimonidine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new warning that cases of aggravated erythema, flushing and skin burning sensation have been reported during the post-marketing period. In addition, symptoms of allergic reaction including urticaria and facial swelling should be included as undesirable effects with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should include as new important identified risk 'condition aggravated (erythema, flushing, skin burning sensation)' and upgrade the safety concern 'allergic reactions' from an important potential to an important identified risk in a revised RMP. The MAH should also provide an evidence-based review of the value of recommending that a small test dose of Mirvaso should be applied to test tolerability prior to initiation of treatment, taking into account the time to onset of aggravated symptoms and a consideration of whether any of the excipients (as well as the active ingredient) might be involved. An appropriate duration for the test period should be proposed. The MAH should discuss how patient exposure could be better estimated, given that many patients are likely to be receiving long-term treatment with Mirvaso.
- Regarding the use of a targeted questionnaire for follow-up of cases of aggravated erythema and flushing, it would be helpful for this to incorporate a question on any treatment given, and its effectiveness. The MAH should include a mock-up of the questionnaire in the revised RMP. Finally the MAH should specifically follow-up adverse event reports suggestive of a haemodynamic effect for blood pressure measurements where appropriate, and should carefully review cases of dizziness taking into account the time to onset from first dose of Mirvaso and the possible effects of other drugs.

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

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. Duloxetine – **ARICLAIM** (CAP), **CYMBALTA** (CAP), **XERISTAR** (CAP), **YENTREVE** (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000552/PSUSA/01187/201408, EMEA/H/C/000573/PSUSA/01187/201408, EMEA/H/C/000572/PSUSA/01187/201408, EMEA/H/C/000545/PSUSA/01187/201408
MAH(s): Eli Lilly Nederland B.V.

Background

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor (antidepressant) indicated for the treatment of major depressive disorder, diabetic peripheral neuropathic pain, generalised anxiety disorder and of moderate to severe stress urinary incontinence in women.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ariclaim, Cymbalta, Xeristair and Yentreve, centrally authorised medicines containing duloxetine, 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 Ariclaim, Cymbalta, Xeristair and Yentreve (duloxetine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include cutaneous vasculitis as an undesirable effect with a very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide an update on the pregnancy registry. The MAH should monitor the following specific topics: QT prolongation, myocardial infarction, homicidal ideation, safety in the paediatric population and provide an analysis. A detailed narrative of the cases supporting a safety signal should be provided.
- The MAH should update the RMP at the next regulatory opportunity to include as important identified risks: hepatic risks, suicidality, hyperglycaemia, Stevens-Johnson syndrome, gastrointestinal tract bleeding, as important potential risks: cardiovascular events including those with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) (including myocardial infarction, heart failure and stroke) and renal failure, as missing information: prospective data about potential risks of exposure to duloxetine during pregnancy and use of duloxetine 120 mg in elderly patients.

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

[11] Update of SmPC 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

6.1.4. Enzalutamide – XTANDI (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002639/PSUSA/10095/201408
MAH(s): Astellas Pharma Europe B.V.

Background

Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway indicated for the treatment of prostate cancer under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xtandi, a centrally authorised medicine containing enzalutamide, 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 Xtandi (enzalutamide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include hypersensitivity reactions as new warning and to include rash, tongue oedema, lip oedema, pharyngeal oedema, nausea and vomiting as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should provide the number of cases excluded (patients who did not receive the study drug) providing a brief description of those cases. The MAH should provide a definition of thrombocytopenia and platelet count decreased also including the platelet count level taken into consideration to define both terms. The MAH should present a detailed description of the 7 cases from study CRPC2, where the patients who were in the enzalutamide arm developed thrombocytopenia during the first and second months of treatment. The MAH should include relevant safety information or information with a potential impact on the benefit-risk assessment retrieved from the fixed-combination therapies studies and from non-interventional studies, if available. The MAH should provide a cumulative review of peripheral oedema, and of asthenia and fatigue to assess if there is a causal relationship between enzalutamide treatment and these adverse events. Based on the outcome of these reviews, proposals for updating the product information should be provided. The MAH should provide a cumulative review of all cases which contain combined androgen antagonism (gonadotropin-releasing hormone agonists) with oral anti-androgens to evaluate if there could be a relevant association which could impact on the increased risk of acute kidney injury.

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

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

6.1.5. **Mecasermin – INCRELEX** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000704/PSUSA/01942/201408
MAH(s): Ipsen Pharma

Background

Mecasermin is a human insulin-like growth factor-1 (rhIGF-1) produced by recombinant DNA technology indicated for the long-term treatment of growth failure in children and adolescents from 2 to 18 years under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Increlex, a centrally authorised medicine containing mecasermin, 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 Increlex (mecasermin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add to the current warning on slipped capital femoral epiphysis the possible occurrence of avascular necrosis. Therefore the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAH should continue to monitor and discuss further cases of melanocytic naevus, dysplastic naevus syndrome, proliferative retinopathy, thyroid neoplasm, endocarditis, ventricular hypertrophy, loss of consciousness, autoimmune nephritis, clonus and adenoidal hypertrophy, and lack of efficacy.
- The MAH should be requested to update the relevant sections of the RMP in accordance with the revised warning on slipped capital femoral epiphysis 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.

6.1.6. **Nalmefene – SELINCRO** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002583/PSUSA/10120/201408
MAH(s): H. Lundbeck A/S

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

Background

Nalmefene is an opioid system modulator indicated for the reduction of alcohol consumption in adult patients with alcohol dependence under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Selincro, a centrally authorised medicine containing nalmefene, 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 Selincro (nalmefene) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the wording of the current contraindication in patients taking opioid analgesics and specify that this contraindication applies to patients taking opioid agonists (e.g. methadone) and opioid partial agonists (e.g. buprenorphine). Therefore the current terms of the marketing authorisation(s) should be varied[14].

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

6.1.7. **Natalizumab – TYSABRI** (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000603/PSUSA/02127/201408
MAH(s): Biogen Idec Ltd

Background

Natalizumab is a selective immunosuppressive agent indicated for the treatment of highly active relapsing remitting multiple sclerosis (MS) under certain conditions.

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

[14] Update of SmPC section 4.3. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAH should provide a cumulative overview as a summary table and Kaplan-Meier curves of safety data of important risks e.g. progressive multifocal leukoencephalopathy (PML), melanoma, leukaemia and central nervous system infections related to the available information from multiple sclerosis (MS) patients observed in post-marketing safety studies and currently available registry data. If available, the MAH is asked to share the final/interim reports from country registries with the PRAC for further review. The MAH should summarise the interim results from STRATIFY-2 (study 101-JC-402 to compare the incidence of progressive multifocal leukoencephalopathy (PML) in Tysabri treated patients who do not have detectable antibodies to John Cunningham virus (JCV) (antibody negative) with patients who have detectable antibodies to JCV (antibody positive)) in subsequent PSURs in more detail. It is in particular important to present data concerning anti-JCV seroconversion rates over time and the risk of PML development in patients who have seroconverted. This should include a thorough analysis of available data reflecting the difference between results concerning both JCV seropositivity rate and seroconversion rates depending on the use of first and second generation enzyme-linked immunosorbent assay (ELISA) tests. Literature data should also be considered in this respect. The MAH is also requested to comment upon the relevance of the anti-JCV antibody index for PML risk stratification.

  The educational material should be updated to include descriptions of the reported neonatal haematological abnormalities.

  The analysis of the data concerning PML diagnosis (magnetic resonance imaging) in MS patients before clinically suspected signs and symptoms indicates a more favourable clinical outcome relating to PML diagnosis and treatment withdrawal for asymptomatic patients. At present the number of asymptomatic PML cases with adequate follow up as well as information on MRI frequency is limited.
  The proportion of fatal events for which a causal relationship has not been assessed by the reporter of the event is high (47%). The MAH should make every effort to obtain information from the health care professionals on the causality of fatal cases in the next PSURs. For fatal events for which causality has not been assessed by the reporter, the MAH should provide a summary of his assessments in subsequent PSURs.

- A substantial body of pregnancy follow-up information is available in the natalizumab pregnancy registry and via spontaneous reports. The MAH should provide a wording for updating section 4.6 of the SmPC reflecting the available information from the literature and the results of the MS Tysabri pregnancy register analysis. In addition, the MAH should describe the risk of neonatal haematological disorders. It is deemed important to closely monitor neonates concerning transient haematological disorders e.g. thrombocytopenia. The MAH is requested to submit a type II variation.

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. **Pomalidomide – IMNOVID** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002682/PSUSA/10127/201408

MAH(s): Celgene Europe Limited

Background

Pomalidomide is an immunomodulating agent indicated in the treatment of adult patients with relapsed and refractory multiple myeloma under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Imnovid, a centrally authorised medicine containing pomalidomide, 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 Imnovid (pomalidomide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include cardiac failure, angioedema, interstitial lung disease (ILD) and hepatitis as new warnings and to include as undesirable effects hyperuricaemia, cardiac failure, atrial fibrillation, angioedema, urticaria, ILD and increased blood uric acid with a common frequency and hepatitis with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- The MAH should inform healthcare professionals of these changes via a Direct Healthcare Professional Communication (DHPC). Moreover, the conditions of the marketing authorisation should be amended regarding the healthcare professional's educational kit (additional risk minimisation measures). For the safety advice relevant to patients, description and management of dizziness and confusion, allergic reactions, hepatic disorders, cardiac failure and interstitial lung disease should also be included.
- In the next PSUR, the MAH should provide a cumulative review of cases of cerebral vascular accident (CVA) and update the product information and the RMP as appropriate. The MAH should carefully review all cases of IDL and related events to identify any cases of pulmonary fibrosis that may not have been correctly coded. The MAH should comment on enrolment issues for the non–interventional post-authorisation registry of patients with relapsed and refractory multiple myeloma treated with pomalidomide. The MAH should submit the comprehensive analysis of thromboembolic events (TEEs) requested by the FDA and discuss whether the data have any impact on the risk minimisation measures in the EU, taking note of the differences in the EU and US product information regarding the prevention of TEEs. The MAH should further analyse the reports of TEEs by region i.e. US versus EU. The MAH should also clarify why the classification of exposure by indication for each region has become less specific in the current PSUR compared to the previous one.
- The MAH should be requested to upgrade the safety concerns 'hepatic disorders' and 'cardiac failure' to important identified risks, to include the safety concerns 'angioedema' and 'interstitial lung disease' as new important identified risks, and to include the safety concern 'gastrointestinal perforation' as a new important potential risk in a revised RMP to be submitted with the next PSUR. The pharmacovigilance plan, risk minimisation measures and public summary should be updated accordingly to reflect the above changes in the safety concerns.

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

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

6.1.9. Sitagliptin – **JANUVIA** (CAP), **RISTABEN** (CAP), **TESAVEL** (CAP), **XELEVIA** (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000722/PSUSA/02711/201408, EMEA/H/C/001234/PSUSA/02711/201408, EMEA/H/C/000910/PSUSA/02711/201408, EMEA/H/C/000762/PSUSA/02711/201408
MAH(s): Merck Sharp & Dohme Limited

Background

Sitagliptin 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 Januvia, Ristaben, Tesavel and Xelevia, centrally authorised medicines containing sitagliptin, 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 Januvia, Ristaben, Tesavel and Xelevia (sitagliptin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include bullous pemphigoid and arthropathy as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[16].

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

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

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000229/PSUSA/02886/201407
MAH(s): Merck Sharp & Dohme Limited

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

Background

Temozolomide is an alkylating agent indicated for the treatment of newly-diagnosed glioblastoma multiforme under certain conditions and malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Temodal, a centrally authorised medicine containing temozolomide, 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 Temodal (temozolomide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include opportunistic infections and reactivation of infections such as cytomegalovirus and hepatitis B virus as new warnings and to include cytomegalovirus infection, infection reactivation such as cytomegalovirus, hepatitis B virus, and diabetes insipidus as new undesirable effects with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- The MAH should be requested to submit within two months a cumulative review on the concomitant use of live vaccines and temozolomide together with an update of the product information, if warranted.

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

6.1.11. Vemurafenib – ZELBORAF (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002409/PSUSA/09329/201408
MAH(s): Roche Registration Ltd

Background

Vemurafenib is a protein kinase inhibitor indicated for the treatment of unresectable or metastatic melanoma under certain conditions.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Zelboraf (vemurafenib) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should be requested to submit within two months a cumulative review of pancytopenia and granulocytopenia including neutropenia and agranulocytosis, from spontaneous reports, published literature, clinical trials and patient registries. Any potential mechanisms should be discussed. If applicable, the MAH should make a proposal to update the product information and 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.

6.1.12. Vernakalant – BRINAVESS (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001215/PSUSA/03109/201408
MAH(s): Cardiome UK Limited

Background

Vernakalant is an antiarrhythmic indicated for the rapid conversion of recent onset atrial fibrillation to sinus rhythm under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brinavess, a centrally authorised medicine containing vernakalant, 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 Brinavess (vernakalant) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include additional information in the current warnings and undesirable effects on atrial flutter i.e. that very rare cases of atrial flutter with 1:1 atrioventricular condition have been reported in the post-marketing setting. Therefore the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should provide the progress and results of the ongoing additional follow-up with a specific site of the SPECTRUM (prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant IV sterile concentrate) study in Germany.

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

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

6.1.13. Zaleplon – **SONATA** (CAP), NAP

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000227/PSUSA/03140/201407
MAH(s): Meda AB

Background

Zaleplon is a pyrazolopyrimidine hypnotic indicated for the treatment of patients with insomnia who have difficulty falling asleep under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sonata, a centrally authorised medicine containing zaleplon, 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 Sonata (zaleplon) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to strengthen the information on the risk of next day effects on driving and mental alertness in case of concomitant intake with alcohol and with other CNS-acting compounds. Therefore the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide further details of the temporary out-of-stock situations reported in some countries within the present PSUR and confirm that these were not associated with quality and/or safety concerns. The MAH should provide a cumulative review of all spontaneous reports which suggest next-day psychomotor impairment (providing details of patient age, concomitant medicines, dose and time of administration where known) and relevant literature articles. Next-morning effects on driving and mental alertness should be included within the category of important identified risks. The MAH should provide a cumulative review of all cardiovascular related adverse drug reactions arising during clinical trials and post-marketing experience along with any available literature relevant to cardiac effects of zaleplon, other 'z-class' agents or benzodiazepines. The MAH should continue to closely monitor emerging data on the signal of cancer and provide a comprehensive review of the literature with an overview.

The frequency of PSUR submission should be revised from three-yearly to five-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.

[19] Update of SmPC sections 4.4, 4.5 and 4.7. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.14. Zoledronic acid – ACLASTA (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000595/PSUSA/09334/201408
MAH(s): Novartis Europharm Ltd

Background

Zoledronic acid is a bisphosphonate indicated for the treatment of osteoporosis under certain conditions and of Paget's disease of the bone in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aclasta, a centrally authorised medicine containing zoledronic acid, 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 Aclasta (zoledronic acid) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include in the posology and method of administration section that patients treated with Aclasta should be given the package leaflet and the patient reminder card, to reflect the current knowledge on osteonecrosis of the jaw as set out in the warnings and undesirable effects sections. Therefore the current terms of the marketing authorisation(s) should be varied[20]. See 'PRAC recommends further measures to minimise risk of osteonecrosis of the jaw with bisphosphonate medicine' EMA/169618/2015.
- Moreover, the conditions of the marketing authorisation should be amended regarding the patient information pack (additional risk minimisation measure). The patient information pack should include the package leaflet and a patient reminder card on osteonecrosis of the jaw.
- In the next PSUR, the MAH should clarify how the reporting rate in the elderly age group >70 years (cumulatively and during this current PSUR) were calculated. The MAH also is asked to calculate the number of patients and reporting rates for patients 70-80 years, 80-90 years and >90 years in order to see if the increase is due to an increase in the 'oldest old'. The MAH is also asked to discuss the higher reporting rates during this period, compared with the cumulative rate for the elderly and to discuss possible reasons. The MAH should comment on the age pattern of reported cases of renal dysfunction and report the median patient age. The MAH should also discuss if any further risk minimisation measures would be possible.
- The MAH should be requested to submit a revised RMP within two months to reflect the addition of a new additional risk minimisation measure (introduction of the reminder card on osteonecrosis of the jaw) as well as to propose indicators to measure the effectiveness of this new measure.

[20] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

6.2. Follow-up to PSUR procedures[21]

6.2.1. **Tacrolimus – PROTOPIC** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000374/LEG 056
Procedure scope: MAH's responses to the outcome of the evaluation of PSU 055 as adopted in October 2014
MAH(s): Astellas Pharma Europe B.V.

Background

Following the most recent assessment of a PSUR for the above mentioned medicines, the PRAC requested the MAH to provide detailed reviews of cases of non-cutaneous infection and of cases of more generalised infection secondary to cutaneous infection or infected atopic dermatitis; a detailed analysis of cases of lentigo as well as a comprehensive review of cases of skin pigmentation abnormalities with a discussion of this issue in relation to topical calcineurin inhibitor (CNI) use, including potential mechanisms and relevant non-clinical data and data from the scientific literature. Finally the PRAC requested the MAH to provide detailed reviews of cases of off-label use, generalised lymphadenopathy in association with long-term use of tacrolimus ointment, increased creatinine and osteomyelitis. The MAH was also requested to provide a discussion on the use of the targeted lymphoma questionnaire including the gathering of data on such cases and to provide the questionnaire responses in its discussion of reported cases. In addition, the MAH was requested to provide further details on the prescription of tacrolimus ointment by non-specialists particularly in children under 2 years and between 2 and 16 years. Finally, the MAH was requested to provide a detailed discussion on first line use of tacrolimus ointment in relation to the European market (see PRAC Minutes October 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 the MAH should submit within two months a variation to include lentigo as an undesirable effect with an unknown frequency. In addition the PRAC agreed that the MAH should monitor and review cases of skin pigmentation abnormalities associated with the use of Protopic should further relevant data emerge, and present cases of selected infections for review in the next PSUR (DLP: 31/03/2015).

6.2.2. **Telmisartan, amlodopine – TWYNSTA** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

[21] 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/001224/LEG 012
Procedure scope: MAH's responses to the outcome of the evaluation of PSUR#6 as adopted in November 2014
MAH(s): Boehringer Ingelheim International GmbH

Background

Following the most recent assessment of a PSUR for the above mentioned medicines, the PRAC requested the MAH to submit a detailed review of case reports of interstitial lung disease (ILD), including literature, post-marketing and clinical trials data relating to all telmisartan containing products (see PRAC Minutes November 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 the MAH should monitor case reports of interstitial lung disease (ILD) via routine pharmacovigilance.

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[22]

7.1.1. **Dexamfetamine** (NAP)

- Evaluation of imposed PASS protocols

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/N/PSP/0018, EMEA/H/N/PSP/0021
Procedure scope: EMEA/H/N/PSP/0018: Protocol for a post-authorisation safety study to evaluate the long-term safety profile of dexamfetamine in children with attention deficit hyperactivity disorder (ADHD), specifically targeting key issues such as cardiovascular events, growth and psychiatric related adverse events
EMEA/H/N/PSP/0021: Protocol for a drug utilisation study of dexamfetamine to follow the use of prescribed dexamfetamine in the European Union using multiple data sources
MAH(s): Kohne Pharma GmbH

Background

According to the conclusions of a referral under Article 29(4) of Directive 2001/83/EC for dexamfetamine containing medicines, marketing authorisation holders are to conduct a post-authorisation safety study to evaluate the long-term safety profile of dexamfetamine in children with attention deficit hyperactivity disorder (ADHD), specifically targeting key issues such as cardiovascular events, growth and psychiatric related adverse events and also a drug utilisation study of dexamfetamine to follow the use of prescribed dexamfetamine in the European Union using multiple data sources. A MAH (see above) submitted a draft protocol for these two studies for assessment by the PRAC.

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

Conclusion

The PRAC appointed Julie Williams (UK) as PRAC Rapporteur for the assessment of these two protocols and agreed a timetable for the procedures.

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

See ANNEX I

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

None

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

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

- Evaluation of PASS results

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

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

Background

Rotarix, a centrally authorised medicine, is a rotavirus vaccine indicated for the active immunisation of infants aged 6 to 24 weeks for prevention of gastro-enteritis due to rotavirus infection.

As part of the RMP for Rotarix, there was a requirement for the MAH to conduct an epidemiological, observational, post marketing study of the genetic stability of GSK Biologicals' rotavirus (RV) vaccine (Rotarix) in children aged <5 years diagnosed with severe gastroenteritis, in Belgium, study EPI-ROTA-014 VS BE (category 3 study).

A first interim report with a preliminary analysis of the data from Phase I of the study was submitted in February 2012. A second interim report including a preliminary analysis of the data from Phase II of the study was submitted at the end of February 2013. The MAH submitted the final report of study EPI-ROTA-014 VS BE and thus presented the final analysis of the study data.

Summary of advice

The PRAC discussed the final results of study EPI-ROTA-014 VS BE and the extended documentation on the risk of genetic variation of the Rotarix vaccine strains provided by the MAH along with the MAH's feasibility assessment for a new study to investigate the genetic stability of Rotarix vaccine strains.

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

Although the PRAC recognised the relevance of the documentation provided by the MAH and agreed that the risk of a sustained dissemination of a variant of a vaccine strain is low, the PRAC considered that, due to the increasing exposure to Rotarix over time and geographical area, a more systematic study of shifts and drifts in vaccine derived rotavirus strains should be implemented until new evidence provides a higher level of assurance that the Rotarix strains are stable over time. The PRAC considered that a post-authorisation safety study will be necessary, with the primary objective to detect the potential occurrence of genetic drift and shift in vaccine viral strains. Core requirements for this study have been agreed by the PRAC and a new list of questions to the MAH was endorsed by the PRAC. The PRAC in addition agreed to refer the issue to the CHMP and to the Vaccine Working Party (VWP) for further evaluation.

7.5. Others

7.5.1. **Ferumoxytol – RIENSO** (CAP)

- Evaluation of a PASS feasibility study

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002215/MEA 017
Procedure scope: Evaluation of European databases for studies evaluating the risk of hypersensitivity reactions in users of intravenous iron compounds (database feasibility evaluation report)
MAH(s): Takeda Pharma A/S

See also under 11.3.

Background

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

As part of the RMP for Rienso, following the assessment of PSUV/014 (see PRAC Minutes July 2014) and in line with the outcome of the Article 31 referral procedure on intravenous iron-containing medicinal products (EMEA/H/A-31/1322), there was a request to conduct a post-authorisation safety study (PASS) to further characterise the safety concerns relating to serious hypersensitivity reactions (category 1 study).

The MAH submitted a database feasibility evaluation report (evaluation of European databases for studies evaluating the risk of hypersensitivity reactions in users of intravenous iron compounds) for this PASS.

Summary of advice

The PRAC discussed the database feasibility evaluation report submitted by the MAH and agreed that whilst the MAH is correct that there are limitations when evaluating the risk of anaphylaxis in the databases identified, other databases need to be considered as does the possibility to complement data from healthcare databases with information to be obtained through other methods. The PRAC supported the Rapporteur's comments regarding the anticipated sample size and ways to enhance it, the frequency of anaphylaxis / hypersensitivity reactions, as well as the need for case verification in this particular study.

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

See ANNEX I

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. On-going or concluded pharmacovigilance inspection

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

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

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

10.1.1. **Epoetin beta – NEORECORMON** (CAP)

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

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

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

Background

For background, see PRAC Minutes June 2014 and PRAC Minutes December 2014.

Summary of advice and conclusion(s)

Based on the review of the available evidence and considering that premature infants are routinely monitored for retinopathy associated with hypoxia and small gestational weight as part of clinical practice in neonatal intensive care units, the PRAC considered that a DHPC to advise careful monitoring was not necessary. With regard to the proposed updates to the product information, the PRAC suggested some further amendments to clarify the wording of the package leaflet.

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

None

10.3. Other requests

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

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

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

Administrative details:
Procedure number(s): EMEA/H/C/000252/LEG 089; EMEA/H/C/000581/LEG 045; EMEA/H/C/000338/LEG 090; EMEA/H/C/000494/LEG 080; EMEA/H/C/000707/LEG 070; EMEA/H/C/000250/LEG 071; EMEA/H/C/000249/LEG 080; EMEA/H/C/000797/LEG 040; EMEA/H/C/002574/LEG 014; EMEA/H/C/000533/LEG 049; EMEA/H/C/000594/LEG 043; EMEA/H/C/002312/LEG 031; EMEA/H/C/000900/LEG 048; EMEA/H/C/000534/LEG 076; EMEA/H/C/000128/LEG 039; EMEA/H/C/000107/LEG 052; EMEA/H/C/000673/LEG 007; EMEA/H/C/000190/LEG 038; EMEA/H/C/000764/LEG 031; EMEA/H/C/000368/LEG 118; EMEA/H/C/000183/LEG 061; EMEA/H/C/002264/LEG 026; EMEA/H/C/000127/LEG 039; EMEA/H/C/000113/LEG 065; EMEA/H/C/000110/LEG 060; EMEA/H/C/000419/LEG 270; EMEA/H/C/000631/LEG 068
Procedure scope: Review of class labelling on mitochondrial dysfunction, lactic acidosis and lipodystrophy
MAH(s): AbbVie Ltd (Kaletra, Norvir), Boehringer Ingelheim International GmbH (Aptivus, Viramune), Bristol-Myers Squibb Pharma EEIG (Reyataz, Sustiva, Zerit), Bristol-Myers Squibb and Gilead Sciences Ltd.(Atripla), Gilead Sciences International Ltd.(Emtriva, Eviplera, Stribild, Truvada, Tybost, Viread), Janssen-Cilag International N.V.(Edurant, Intelence, Prezista), Merck Sharp & Dohme Ltd (Crixivan, Isentress, Stocrin), Roche Registration Ltd. (Invirase), ViiV Healthcare UK Limited (Celsentri, Combivir, Epivir, Lamivudine Viiv, Kivexa, Telzir, Trizivir, Ziagen)

Background

For background, see PRAC Minutes June 2014 and PRAC Minutes July 2014.

Summary of advice and conclusion(s)

Based on the review of the available information and assessment of the risk of lipodystrophy, the PRAC advised consultation of the Scientific Advisory Group (SAG) HIV/viral diseases to provide input on the evidence for a causal relationship between certain nucleotide reverse transcriptase inhibitors (NRTIs) displaying mitochondrial toxicity and lipoatrophy as well as on the absence of convincing evidence of a causal relationship between exposure to any particular antiretroviral drug or drug classes, and intra-abdominal fat accumulation. The PRAC advised requesting MAHs to provide evidence in case the agent is lipid neutral.

With regard to the review of lactic acidosis, the PRAC advised requesting the MAHs of zidovudine containing-products, lamivudine, and abacavir to submit additional data to be further assessed by the PRAC and the SAG HIV/viral diseases before advising on any potential labelling changes. The PRAC

also advised requesting the input from the SAG HIV/viral diseases on whether current evidence on lactic acidosis with NRTIs supports a differential risk within the class.

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

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

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

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

Administrative details:
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 February 2015.

Summary of advice and conclusion(s)

Based on the review of all available information, the PRAC advised requesting MAHs to revise their product information, in order to ensure that the lowest approved effective dose is used to provide adequate control of the symptoms of anaemia whilst maintaining a haemoglobin concentration below or at 12 g/dl (7.45 mmol/l), together with adequate warnings.

In terms of communication, the PRAC did not support the distribution of a DHPC as the issue of non-responders is well known and clinical practice guidelines in the field (Kidney Disease Improving Global Outcomes (KDIGO)) have since 2012 already addressed the non-responders problem. The PRAC recommended alternative ways of communication including communication to HCPs through the Healthcare Professionals Working Party (HCPWP) as well as the possibility of dialogue with the European Renal Best Practice (ERBP) under the aegis of the European Renal Association-European Dialysis Transplantation Association (ERA-EDTA).

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Azithromycin oral and intravenous formulations (NAP)

- PRAC consultation on a safety-related variations upon Finland's request

Regulatory details:
Lead member: Terhi Lehtinen (FI)

Administrative details:
Procedure number: FI/H/XXXX/WS/23
Procedure scope: PRAC consultation on a variation procedure evaluating the draft PASS protocol (A0661209) for a non-imposed non-interventional study in the Kaiser Permanente databases to examine the effects of azithromycin use on cardiovascular outcome
MAH(s): Pfizer (Zithromax)

Background

Azithromycin is a macrolide antibiotic indicated for the treatment of infections caused by susceptible organisms (respiratory, skin and subcutaneous tissue, sexually transmitted disease (STD)). Azithromycin is also indicated in long term use in patients with advanced HIV infection for prophylaxis and treatment against Mycobacterium avium intracellular complex (MAC/DMAC).
For background information, see PRAC Minutes January 2015. Following previous advice, the PRAC was further consulted on the evaluation of the MAH's responses to a list of questions.

Summary of advice and conclusion(s)

Based on the review of the available information, the PRAC acknowledged the limitations in the proposed Veterans Affairs (VA) database study, and supported Finland's view on potential confounding by indication and severity. The PRAC also supported that the population in the proposed study might not be representative of the population of interest. Therefore, the PRAC agreed with Finland's conclusions that did not support the proposal to perform the VA database study, while PRAC agreed with pursuing studies using the Kaiser Permanente databases (North and South California; KPNC and KPSC).

11.2. Renewals of the Marketing Authorisation

None

11.3. Other requests

11.3.1. Iron for intravenous (IV) use (NAP)

- PRAC consultation on the evaluation of a PASS feasibility study upon Member State's request

Regulatory details:
Lead member: Arnaud Batz (FR)

Administrative details:
Procedure number: *Not applicable*

Procedure scope: Evaluation of European databases for studies evaluating the risk of hypersensitivity reactions in users of intravenous iron compounds (database feasibility evaluation report), literature review of ferumoxytol and other IV iron containing medicinal products and hypersensitivity reactions, annual cumulative reviews of hypersensitivity reactions for IV iron-containing medicinal products
MAH(s): various

Background

Intravenous (IV) iron containing products, nationally authorised medicinal products, are indicated in the treatment of iron deficiency when the oral route is insufficient or poorly tolerated especially in CKD patients (hemodialysis), but also in pre- or post-operative situations, or in case of intestinal absorption disorders.

As part of the outcome of the Article 31 referral procedure on intravenous iron-containing medicinal products (EMEA/H/A-31/1322), the MAHs were requested to conduct a post-authorisation safety study (PASS) to further characterise the safety concerns relating to serious hypersensitivity reactions.

To address this request, a consortium of MAHs of IV iron compounds has been established with the objective of assessing the feasibility of conducting a European multinational PASS on the utilisation of IV iron compounds and the risk of serious hypersensitivity reactions among users of IV iron compounds, to be conducted in several existing population-based automated health care data sources. A common protocol synopsis for the PASS feasibility assessment was submitted to the National Competent Authorities (NCAs) by each concerned MAH of each IV iron medicinal product within their RMP submission.

France, who was Rapporteur for the Article 31 referral procedure on intravenous iron-containing medicinal products (EMEA/H/A-31/1322), requested the advice of the PRAC on this feasibility study report.

Summary of advice and conclusion(s)

Based on the review of the available information the PRAC agreed that whilst the MAHs are correct that there are limitations when evaluating the risk of anaphylaxis in the databases identified, other databases need to be considered as does the possibility to complement data from healthcare databases with information to be obtained through other methods. The PRAC supported the Rapporteur's view on the feasibility of the study and supported the Rapporteur's comments regarding the anticipated sample size and ways to enhance it, the frequency of anaphylaxis / hypersensitivity reactions, as well as the need for case verification in this particular study.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

- Implementation of new Committee's agenda template

The EMA Secretariat presented the new Committee's agenda template. This initiative is to harmonise the agenda templates for all the EMA committees. The new template will be used as of April 2015.

12.2. Pharmacovigilance audits and inspections

12.2.1. Pharmacovigilance Systems and their Quality Systems

None

12.2.2. Pharmacovigilance Inspections

None

12.2.3. Pharmacovigilance Audits

None

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

12.3.1. Periodic Safety Update Reports

None

12.3.2. PSURs Repository

12.3.2.1. Audit report and PRAC recommendation: timelines

The EMA Secretariat presented the timelines for the independent audit report to become available and for the adoption of the PRAC recommendation. As per the legislation, the EMA management board is to confirm and announce that the PSUR repository has achieved full functionality based on the functional specifications (i.e. auditable requirements). This announcement should be based on an independent audit report and a PRAC recommendation and is currently planned for the next EMA management board meeting. The use of the PSUR repository will then become mandatory 12 months after the EMA management board announcement. The draft audit report together with the EMA mitigation action plan will be circulated by 20/03/2015 and an interactive questions and answers session on the PSUR repository audit outcome, including a presentation by the independent auditors, will be held by the Project and Maintenance Group 2 on 26/03/2015. The audit outcome along with the feedback on the Q&A session will be presented at the April 2015 PRAC followed by the adoption of a PRAC recommendation.

12.3.2.2. Pilot and phased implementation: Update

The EMA Secretariat provided an update on the pilot phase. Nine PSUR procedures were included in the pilot phase with a February 2015 start and another 10 PSUR procedures with a March 2015 start will also be included in the pilot. An explanatory note on the integration of the PSUR Repository into Member States' business processes was circulated to the PRAC on 26/02/2015. An interactive questions and answers session with the national competent authorities is scheduled on 17/03/2015 to cover uploading of the updated PRAC Rapporteur assessment report and member states' comments into the repository. In advance of this interactive Q&A session, feedback from the PRAC Rapporteur teams to assess their initial experience using the repository will be collected.

12.3.2.3. Post-audit functionalities: action plan

The EMA Secretariat presented the planning for the delivery of post-audit functionalities for the PSUR repository with a view of consulting the PRAC on the proposed planning. In addition to the auditable functionalities, additional key functionalities were requested to be included in the PSUR Repository as part of the consultation with Member States. Subject to approval of the audit report by the EMA management board at their next meeting, development of the post-audit functionalities as well as additional functionalities prioritised by EMA and Project and Maintenance Group 2 will start in July 2015

with the aim of having user acceptance testing in October 2015 and these new functionalities available by December 2015.

12.3.3. Periodic Safety Update Single Assessment (PSUSA)

- PRAC assessment report publication

The topic was deferred to a later PRAC meeting.

12.3.4. Union Reference Date List

- Consultation on the draft list, version March 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 and welcomed the progress being made.
The PRAC endorsed the draft revised EURD list version March 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 March 2015, the updated EURD list was adopted by the CHMP and CMDh at their March 2015 meeting and published on the EMA website on 01/04/2015, 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)

12.4. Signal Management

12.4.1. Signal Management

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

At the organisational matters teleconference held on 26 March 2015, the PRAC was updated on the outcome of the March 2015 SMART Working Group meeting, where the results of the EudraVigilance analysis on interstitial lung disease (ILD) were discussed. This topic will be further discussed in future SMART Working Group meetings. A review and a proposal for an update to designated medical events were presented and will be further discussed at the next SMART Working Group meeting. Finally, the publication of PRAC recommendations on signals for updates to the product information in all EU languages which started for the January 2015 relevant signals, was further discussed in particular the timing of implementation of labelling changes. The standard for MAHs to submit a variation is 60-days from publication of the English text. It was discussed whether the 60-days should count from the publication of the translations and publish them earlier i.e. at the same time as English text.

Post-meeting note: following consultation of the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) it was agreed to publish the English text and the translations at the same time.

- Statistical guideline update

At the organisational matters teleconference held on 26 March 2015, the EMA secretariat presented a proposal to review the current guideline on the use of statistical signal detection methods in the

EudraVigilance data analysis system. The focus of the review will be on the selection of a disproportionality method, the thresholds for defining signals of disproportionate reporting (SDR) and stratification and subgroup analysis. The draft revised guideline will be circulated to the PRAC in April 2015. It was agreed to run a pilot on the electronic Reaction Monitoring Reports (eRMRs) in the next five months to collect information on the proposed changes. The draft revised guideline will be then circulated to the PRAC for comments prior to release for public consultation.

12.5. Adverse Drug Reactions reporting and additional reporting

12.5.1. Management and Reporting of Adverse Reactions to Medicinal Products

None

12.5.2. Additional Monitoring

None

12.5.3. List of Products under Additional Monitoring

- Consultation on the draft list, version March 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 25/03/2015 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.6. EudraVigilance Database

12.6.1. Activities related to the confirmation of full functionality

12.6.1.1. EudraVigilance: revised business requirements

The EMA Secretariat presented the revised EudraVigilance business requirements. A set of detailed business requirements related to EudraVigilance functionalities, more specifically in relation to the EudraVigilance Data Analysis System (EVDAS), electronic Reaction Monitoring Reports (eRMRs) and the public ADR website were prepared and reviewed by the Project and Maintenance Group 1 in consultation with the EudraVigilance Expert Working Group (EV-EWG). The detailed requirements were circulated to the Signal Management Review Technical (SMART) Working Group – Work Stream 1 - in advance of their March 2015 meeting and also to the PRAC for consultation. Members were invited to provide comments in writing until 31/03/2015.

12.6.1.2. Individual Case Safety Report (ICSR): revised form

The EMA Secretariat presented the revised individual case safety report (ICSR) form. The current Council for International Organizations of Medical Sciences (CIOMS) I form had to be updated to incorporate the new structure and data fields for ICH-E2B(R3) ICSRs. EMA drafted a new form based on the R3 fields at the end of 2014. The objective of the form is to support the review of individual cases for the purpose of signal detection, validation, confirmation and evaluation. This draft form was discussed at the joint EudraVigilance Expert Working Group and Project and Maintenance Group 1 workshop in December 2014, followed by a consultation with EV-EWG, Project and Maintenance Group 1 and the EMA Signal Management Group. Following the consultation a revised report was presented to

the EudraVigilance Expert Working Group and Project and Maintenance Group 1 in February 2015. The PRAC was invited to provide comments in writing by 31/03/2015.

12.6.2. EudraVigilance annual report

- 2014 EudraVigilance (human) annual report

The EMA Secretariat presented some highlights of the 2014 EudraVigilance annual report. The report was presented to the EMA Management Board in March 2015 and will be published on the EMA website.

12.7. Risk Management Plans and Effectiveness of risk Minimisations

12.7.1. Risk Management Systems

12.7.2. RMP assessment process

- Implementation of the revised process

The EMA Secretariat presented an update on the implementation of the revised RMP review process. The revised templates, process and schedule will be presented in detail at the April 2015 PRAC for endorsement. Some training for the national competent authorities on the revised RMP review process is planned and the roll-out is planned for initial Marketing Authorisation applications starting as of May 2015.

12.7.3. Tools, Educational Materials and Effectiveness Measurement for Risk Minimisation

None

12.8. Post-authorisation Safety Studies

12.8.1. Post-Authorisation Safety Studies

None

12.9. Community Procedures

12.9.1. Referral Procedures for Safety Reasons

None

12.9.2. Referral procedures: revised assessment process

At the organisational matters teleconference held on 26 March 2015, the EMA presented the updated process for referrals which reflects the experience of the first three years of PRAC. The updated process would benefit from earlier dialogue between NCAs and EMA on defining clear scope and establishing guidance on the best use of regulatory tools for handling an issue/procedure. Best use of network resources and support to (co-)rapporteurs and assessors will be provided together with involvement of a multidisciplinary team at EMA. The implementation phase is being prioritised for pharmacovigilance referrals which are now completed. The proposals for implementation include revised templates and process improvements such as strengthening the (pre-) draft notification phase with early notification of the MAHs concerned, earlier Rapporteurship appointment for

pharmacovigilance referrals, preparation of the start of procedure, timelines, and a strengthening assessment phase. Training via a webinar will be provided in April 2015.

12.10. Renewals, conditional renewals, annual reassessments

None

12.11. Risk communication and Transparency

12.11.1. Public Participation in Pharmacovigilance

None

12.11.2. Safety Communication

None

12.12. Continuous pharmacovigilance

None

12.12.1. Incident Management

None

12.13. Interaction with EMA Committees and Working Parties

12.13.1. Committees

None

12.13.2. Working Parties

None

12.13.3. Others

12.13.3.1. Geriatric Expert Group (GEG)

- Points to Consider on frailty evaluation instruments for baseline characterisation of clinical trial populations

At the organisational matters teleconference held on 26 March 2015, the EMA Secretariat presented to the PRAC the draft Points to Consider on Frailty Evaluation Instruments for Baseline Characterisation of Clinical trial populations agreed by the Geriatric Expert Group. The PRAC was invited to send comments in writing by 24 April 2015.

12.13.3.2. 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

In follow-up to its discussion at the February 2015 meeting, the PRAC finalised the action plan for the implementation of 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 for a patient reminder card. These are currently being implemented for Aclasta (see 6.1.14.) and will be considered during the upcoming periodic reviews for all other bisphosphonates for intravenous use as well as for denosumab.

12.14. Interaction within the EU regulatory network

None

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

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

None

12.15.2. Others

12.15.2.1. International Society for Pharmacoepidemiology (ISPE)

- Analysis of patient and healthcare professional input into EMA communications relating to the oral contraceptives referral, following the symposium, October 2014

At the organisational matters teleconference held on 26 March 2015, the EMA Secretariat presented feedback on the analysis of patient and healthcare professional input into the EMA communications relating to the oral contraceptive referral presented at the International Society for Pharmacoepidemiology at its conference in October 2014.

12.16. Others

- Interaction with patients, consumers and organisations: revised framework

At the organisational matters teleconference held on 26 March 2015, the EMA Secretariat presented the revised framework for interaction between the European Medicines Agency and patients and consumers and their organisations, which was adopted by the EMA management board in December 2014. The aim of this revised framework was to clarify the objectives and consolidate the methodology for such interactions. The PRAC welcomed this important progress and anticipated strengthening its interactions with patients and consumers using the new framework.

13. Any other business

13.1. Medication errors

- Risk minimisation strategy for medication errors with high strength/fixed combination insulins

As a follow-up to the discussion at the February 2015 PRAC, the EMA Secretariat presented revised draft guidance and a revised draft EMA safety communication for patients and HCPs on the risk minimisation strategy for medication errors with high strength/fixed combination insulins taking into

account the comments raised. The PRAC was invited to submit further comments by 20/03/2015 and a revised proposal from the drafting group will be presented at the April 2015 PRAC.

13.2. Pharmacovigilance programme and revised implementation governance

At the organisational matters teleconference held on 26 March 2015, the EMA Secretariat presented the Pharmacovigilance Programme Update (third edition from March 2015).

13.3. Product Information: revision of the review process for initial marketing authorisation

At the organisational matters teleconference held on 26 March 2015, the EMA Secretariat presented the revision of the product information review process for initial marketing authorisation applications. Earlier identification of issues, greater consistency and a simplified process were the aim of this review. These process changes will be reflected in the relevant SOP/WIN[26] and guidance documents. Training for the network is planned in March 2015 to present these changes and the implementation plan. The revised process has been presented to all the relevant committees (CHMP, PRAC and CAT) in March 2015 and it will start being implemented for initial marketing authorisation applications in April 2015.

13.4. Type II variations: revised procedural timetables

The EMA Secretariat presented some changes to the monthly-start type II variations timetables. As some clarifications were requested by the PRAC, this proposal was further discussed at the organisational matters teleconference held on 26 March 2015. It was agreed to further discuss this proposal at the April 2015 PRAC.

[26] Standard operating procedure(s)/work Instructions

14. ANNEX I - Risk Management Plans

Medicines in the pre-authorisation phase

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

14.1.1. Allogenic human heterologous liver cells

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

Administrative details:
Product number(s): EMEA/H/C/003750, *Orphan*
Intended indication(s): Treatment of urea cycle disorders (UCD)
Applicant: Cytonet GmbH&Co KG

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/004008, *Generic, Hybrid*
Intended indication(s): Treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder

14.1.3. Atazanavir, cobicistat

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

Administrative details:
Product number(s): EMEA/H/C/003904
Intended indication(s): Treatment of HIV-1 infected patients

14.1.4. Dasiprotimut

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

Administrative details:
Product number(s): EMEA/H/C/002772, *Orphan*
Intended indication(s): Treatment of non-Hodgkin's lymphoma (FL)
Applicant: Biovest Europe Ltd
For adoption: PRAC RMP AR, PRAC RMP assessment overview and advice

14.1.5. Docetaxel

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

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

14.1.6. Ferric citrate coordination complex

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

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

14.1.7. Guanfacine

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

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

14.1.8. Human alfa1-proteinase inhibitor

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

Administrative details:
Product number(s): EMEA/H/C/002739
Intended indication(s): Maintenance treatment to slow the underlying destruction of lung tissue leading to emphysema in adults with alpha1-proteinase inhibitor deficiency with clinically evident lung disease

14.1.9. Lumacaftor, ivacaftor

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

Administrative details:
Product number(s): EMEA/H/C/003954, *Orphan*
Intended indication(s): Treatment of cystic fibrosis (CF)
Applicant: Vertex Pharmaceuticals (U.K.) Ltd.

14.1.10. Mercaptamine

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

Administrative details:
Product number(s): EMEA/H/C/004038, *Orphan*
Intended indication(s): Treatment of corneal cystine deposits
Applicant: Lucane Pharma

14.1.11. Netupitant, palonosetron

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

Administrative details:
Product number(s): EMEA/H/C/003728
Intended indication(s): Prevention of chemotherapy-induced nausea and vomiting (CINV)

14.1.12. Parathyroid hormone

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

Administrative details:
Product number(s): EMEA/H/C/003861, *Orphan*
Intended indication(s): Treatment of hypoparathyroidism

Applicant: NPS Pharma Holdings Limited

14.1.13. Pemetrexed

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

Administrative details:
Product number(s): EMEA/H/C/004072, *Generic*
Intended indication(s): Treatment of unresectable malignant pleural mesothelioma metastatic non-small cell lung cancer

14.1.14. Pregabalin

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

Administrative details:
Product number(s): EMEA/H/C/004010, EMEA/H/C/004070, *Generics*
Intended indication(s): Treatment of epilepsy and generalised anxiety disorder (GAD)

14.1.15. Pregabalin

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

Administrative details:
Product number(s): EMEA/H/C/003900, *Generic*
Intended indication(s): Treatment of epilepsy and generalised anxiety disorder (GAD)

14.1.16. Voriconazole

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

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

Medicines already authorised

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

RMP in the context of a variation[27] – PRAC-led procedure

14.1.17. Desloratadine – AERIUS (CAP), AZOMYR (CAP), NEOCLARITYN (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/000313/WS0641/0077, EMEA/H/C/000310/WS0641/0080, EMEA/H/C/000314/WS0641/0075

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

Procedure scope: Updated RMP (version 1.0) in line with the request of the EMA as a result of the assessment of the follow-up measure FUM PSU 048 of the ninth PSUR for Aerius, Azomyr and Neoclarityn
MAH(s): Merck Sharp & Dohme Limited

14.1.18. Ibritumomab tiuxetan – ZEVALIN (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Torbjörn Callreus (DK)

Administrative details:

Procedure number(s): EMEA/H/C/000547/II/0043
Procedure scope: Updated RMP (version 4.0) to reflect the completion and analysis of study SAG 307722. A type II variation (EMEA/H/C/000547/II/0039) to update the product information following analysis of the data from study SAG 307722 was approved in April 2014
MAH(s): Spectrum Pharmaceuticals B.V.

14.1.19. Pioglitazone – ACTOS (CAP), GLUSTIN (CAP)
pioglitazone, metformin – COMPETACT (CAP), GLUBRAVA (CAP)
pioglitazone, glimepiride – TANDEMACT (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Almath Spooner (IE)

Administrative details:

Procedure number(s): EMEA/H/C/000285/WS0705/0067, EMEA/H/C/000286/WS0705/0065, EMEA/H/C/000655/WS0705/0052, EMEA/H/C/000893/WS0705/0038, EMEA/H/C/000680/WS0705/0042
Procedure scope: Change of the due date for reporting of the pan-European multiple database bladder cancer risk characterisation study ER12-9433 from 30 December 2014 to 31 July 2015. In addition, an administrative change has been introduced to include mention of a drug utilisation study using the medical registries in Denmark (Pioglitazone 5019) and associated timelines
MAH(s): Takeda Pharma A/S

14.1.20. Pregabalin – LYRICA (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/000546/II/0073/G
Procedure scope: Revised RMP (version 11.2) to update targeted report form/follow-up questionnaire for abuse, misuse, dependence and change risk of misuse, abuse and dependence from potential to identified as requested by the PRAC during the EMEA/H/C/000546/PSUV/0069 procedure - change the due date of PASS A0081096
MAH(s): Pfizer Limited

14.1.21. Teduglutide – REVESTIVE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:

PRAC Rapporteur: Torbjörn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002345/II/0009
Procedure scope: Updated RMP (version 6.0) proposing the use of nursing services as a risk minimisation measure to decrease the adverse events of fluid overload
MAH(s): NPS Pharma Holdings Limited

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

14.1.22. Abatacept – ORENCIA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000701/II/0087/G
Procedure scope: Introduction of a prefilled pen presentation for Orencia 125 mg solution for injection (pack size of 4 pre-filled pens) and addition of a pack size of 12 pre-filled pens for Orencia 125 mg solution for injection
MAH(s): Bristol-Myers Squibb Pharma EEIG

14.1.23. Aflibercept – EYLEA (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/002392/II/0018
Procedure scope: Update of SmPC sections 4.8, 5.1 and 5.2 to reflect full 2 year efficacy and safety data from the ongoing studies VIVID-DME and VISTA-DME, post-authorisation measures (RECs) agreed as part of variation II/09. The package leaflet has been revised accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in SmPC section 5.1
MAH(s): Bayer Pharma AG

14.1.24. 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/0041
Procedure scope: Update of SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 to include an expanded therapeutic indication for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1). In addition, the MAH took the opportunity to update Annex II to reflect a change in the PSUR frequency. The package leaflet is updated accordingly
MAH(s): Glaxo Group Ltd

14.1.25. Capsaicin – QUTENZA (CAP)

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

Regulatory details:
PRAC Rapporteur: Magda Pedro (PT)

Administrative details:
Procedure number(s): EMEA/H/C/000909/II/0039
Procedure scope: Extension of indication to include treatment of diabetic patients with peripheral neuropathic pain based on the results of studies E05-CL-3004 (STEP) and E05-CL-3002 (PACE). As a consequence, SmPC sections 4.1, 4.4 and 4.8 have been updated, and Annex II (additional risk minimisation measures) and the package leaflet have been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II, labelling and package leaflet
MAH(s): Astellas Pharma Europe B.V.

14.1.26. Dolutegravir, abacavir, lamivudine – TRIUMEQ (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/002754/II/0005 (with RMP)
Procedure scope: In compliance with the agreed RMP (MEA 02, category 3 study), submission of in vitro study report to assess the affinity of dolutegravir for melanocortin receptors
MAH(s): ViiV Healthcare UK Limited

14.1.27. Dolutegravir, abacavir, lamivudine – TRIUMEQ (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/002754/II/0006 (with RMP)
Procedure scope: In compliance with the agreed RMP (MEA 03, category 3 study), submission of in vitro study report to assess the affinity of dolutegravir
MAH(s): ViiV Healthcare UK Limited

14.1.28. Dolutegravir, abacavir, lamivudine – TRIUMEQ (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/002754/II/0004/G
Procedure scope: Grouped variations to update: 1) SmPC section 5.2 following the results of an in vitro study to investigate whether dolutegravir might be a substrate for the hepatic uptake transporters OATP1B1 and OATP1B3; 2) SmPC section 4.5 on the basis of pharmacokinetic analyses from the dolutegravir-boceprevir interaction study ING115697; 3) SmPC section 4.5 and 5.2 on the potential for interaction with midazolam/CYP3A4
MAH(s): ViiV Healthcare UK Limited

14.1.29. 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/0019
Procedure scope: Update of SmPC section 4.8 to include 'thrombotic microangiopathy (TMA) with acute renal failure'. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to make a minor change to SmPC section 4.8 clarifying that the safety data included are derived both from studies and from post-marketing reports
MAH(s): GlaxoSmithKline Trading Services

14.1.30. Epoetin beta – NEORECORMON (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/000116/II/0083
Procedure scope: Update of the product information to implement the outcome of the PSUR (covering the period 2007-2010) concerning the increased risk of retinopathy of prematurity (RoP)
MAH(s): Roche Registration Ltd

See under 10.1.1.

14.1.31. 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/0063
Procedure scope: Update of SmPC sections 4.2 and 5.1 to reflect the data from a multicentre, placebo-controlled, double-blind, randomised-withdrawal, parallel group study (GO KIDS) in children (2 to 17 years of age) with active polyarticular juvenile idiopathic arthritis (pJIA). The package leaflet is updated accordingly
MAH(s): Janssen Biologics B.V.

14.1.32. Insulin degludec, liraglutide – XULTOPHY (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002647/II/0001/G
MAH(s): Novo Nordisk A/S

14.1.33. Insulin degludec, liraglutide – XULTOPHY (CAP)

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

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

Administrative details:
Procedure number(s): EMEA/H/C/002647/II/0002

Procedure scope: Extension of indication to include the transfer of patients from glucagon-like peptide-1 (GLP1) receptor agonist (RA) treatment to Xultophy. Consequently, SmPC sections 4.1, 4.2, 4.4, and 5.1 as well as the package leaflet are updated accordingly
MAH(s): Novo Nordisk A/S

14.1.34. Maraviroc – CELSENTRI (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/000811/II/0041
Procedure scope: Update of SmPC sections 4.4 and 5.1 further to the 48-week time-point results of study A4001098 conducted to evaluate the safety of Maraviroc in combination with other antiretroviral agents in HIV-1-infected subjects co-infected with hepatitis C and/or hepatitis B virus (MEA 010.3)
MAH(s): ViiV Healthcare UK Limited

14.1.35. Methylnaltrexone bromide – RELISTOR (CAP)

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

Regulatory details:

PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:

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

14.1.36. Perampanel – FYCOMPA (CAP)

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

Regulatory details:

PRAC Rapporteur: Julie Williams (UK)

Administrative details:

Procedure number(s): EMEA/H/C/002434/II/0016
Procedure scope: Extension of indication as adjunctive treatment of primary generalised tonic-clonic seizures in patients with epilepsy aged 12 years and older. SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 and the package leaflet are updated accordingly
MAH(s): Eisai Europe Ltd

14.1.37. 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 takes 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

14.1.38. Regorafenib – STIVARGA (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/002573/II/0008
Procedure scope: Update of SmPC section 5.1 to reflect final results from study 15808 (randomized, double blind, placebo controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy). The MAH took also the opportunity to introduce minor corrections and editorial changes throughout the product information
MAH(s): Bayer Pharma AG

14.1.39. Rituximab – MABTHERA (CAP)

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

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000165/X/0101/G
Procedure scope: Grouped variation: 1) line extension to add a new strength 1,600 mg solution for subcutaneous injection as well as a new indication for this strength; 2) update the product information of the existing strengths as a consequence of the line extension application; 3) update of the RMP (version 13.0)
MAH(s): Roche Registration Ltd

14.1.40. Vemurafenib – ZELBORAF (CAP)

- Evaluation of an RMP in the context of a variation

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

Administrative details:
Procedure number(s): EMEA/H/C/002409/II/0018
Procedure scope: Update of SmPC section 4.8 to add pancreatitis with an uncommon frequency further to a cumulative review conducted by the MAH. The package leaflet is updated accordingly
MAH(s): Roche Registration Ltd

14.1.41. Vismodegib – ERIVEDGE (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/002602/II/0015/G

Procedure scope: Grouped variation to update: 1) SmPC section 4.3 following the review of the GP28465 study report to delete the contraindication with St John's wort, section 4.4 to delete the warning regarding concomitant treatment with strong CYP inducers and section 4.5 to update the effects of concomitant medicinal products on vismodegib. The package leaflet is updated accordingly, the RMP has been updated to reflect the newly generated clinical pharmacology data; 2) SmPC section 4.2 following the review of the GP27839 study report as well as new clinical pharmacokinetic (PK) and PK modelling data generated since the initial marketing authorisation to change the posology information for patients with hepatic and renal impairment and section 5.2 to reflect the new PK data generated in patients with hepatic and renal impairment. In addition the RMP has been updated to reflect the newly generated data in patients with hepatic and renal impairment; 3) Submission of a summary document outlining new non-clinical, clinical PK data generated since the initial marketing authorisation to complement the existing oral contraceptive drug-drug interaction data
MAH(s): Roche Registration Ltd

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

14.1.42. Filgrastim – NIVESTIM (CAP)

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

Regulatory details:
PRAC Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/001142/R/0025
MAH(s): Hospira UK 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).

Evaluation of PSUR procedures

15.1.1. Azilsartan medoxomil – EDARBI (CAP), **IPREZIV** (CAP)

- Evaluation of a PSUSA[28] procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002293/PSUSA/00280/201408, EMEA/H/C/002517/PSUSA/00280/201408
MAH(s): Takeda Pharma A/S

[28] PSUR single assessment

15.1.2. **Bosutinib – BOSULIF** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002373/PSUSA/10073/201409
MAH(s): Pfizer Limited

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

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002455/PSUSA/10039/201408
MAH(s): Takeda Pharma A/S

15.1.4. **Cobicistat – TYBOST** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002572/PSUSA/10081/201408
MAH(s): Gilead Sciences International Ltd

15.1.5. **Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil – STRIBILD** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002574/PSUSA/10082/201408
MAH(s): Gilead Sciences International Ltd

15.1.6. **Crizotinib – XALKORI** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002489/PSUSA/10042/201408
MAH(s): Pfizer Limited

15.1.7. Dabrafenib – TAFINLAR (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002604/PSUSA/10084/201408
MAH(s): GlaxoSmithKline Trading Services

15.1.8. Deferiprone – FERRIPROX (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000236/PSUSA/00940/201408
MAH(s): Apotex Europe BV

15.1.9. Dexmedetomidine – DEXDOR (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002268/PSUSA/00998/201409
MAH(s): Orion Corporation

15.1.10. Elosulfase alfa – VIMIZIM (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002779/PSUSA/10218/201408
MAH(s): BioMarin Europe Ltd

15.1.11. Elvitegravir – VITEKTA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002577/PSUSA/02577/201408
MAH(s): Gilead Sciences International Ltd

15.1.12. **Fenofibrate, simvastatin – CHOLIB** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002559/PSUSA/10096/201408
MAH(s): Abbott Healthcare Products Ltd.

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

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002553/PSUSA/10094/201408
MAH(s): Piramal Imaging Limited

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

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000285/PSUSA/02417/201407, EMEA/H/C/000655/PSUSA/02417/201407, EMEA/H/C/000893/PSUSA/02417/201407, EMEA/H/C/000286/PSUSA/02417/201407, EMEA/H/C/000680/PSUSA/02417/201407
MAH(s): Takeda Pharma A/S

15.1.15. **Human coagulation factor VIII, human von willebrand factor – VONCENTO** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002493/PSUSA/10102/201408
MAH(s): CSL Behring GmbH

15.1.16. **Ibuprofen – PEDEA** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000549/PSUSA/01712/201407
MAH(s): Orphan Europe S.A.R.L.

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

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000966/PSUSA/01743/201408, EMEA/H/C/000957/PSUSA/01743/201408
MAH(s): Sanofi Pasteur

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

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000758/PSUSA/01745/201408
MAH(s): Novartis Vaccines and Diagnostics GmbH

15.1.19. Linaclotide – CONSTELLA (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002490/PSUSA/10025/201408
MAH(s): Almirall S.A

15.1.20. Loxapine – ADASUVE (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002400/PSUSA/10113/201408
MAH(s): Alexza UK Ltd.

15.1.21. Midazolam – BUCCOLAM (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002267/PSUSA/10118/201409
MAH(s): ViroPharma SPRL

15.1.22. Moroctocog alfa – REFACTO AF (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000232/PSUSA/02089/201408
MAH(s): Pfizer Limited

15.1.23. Nonacog alfa – BENEFIX (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000139/PSUSA/02183/201408
MAH(s): Pfizer Limited

15.1.24. Pirfenidone – ESBRIET (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002154/PSUSA/02435/201408
MAH(s): InterMune UK Ltd.

15.1.25. Pandemic influenza vaccine (H5N1, whole virion, vero cell derived, inactivated) – PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP)
Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture) - VEPACEL (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/001200/PSUSA/02282/201408,
EMEA/H/C/002089/PSUSA/02282/201408
MAH(s): Baxter AG

15.1.26. Protein C – CEPROTIN (CAP), NAP

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/000334/PSUSA/02563/201407
MAH(s): Baxter AG

15.1.27. Pyronaridine, artesunate – PYRAMAX (Art 58)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/W/002319/PSUV/0009
Scientific Opinion Holder(s) (SOH): Shin Poong Pharmaceutical Co., Ltd.

15.1.28. Ruxolitinib – JAKAVI (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002464/PSUSA/10015/201408
MAH(s): Novartis Europharm Ltd

15.1.29. Tasonermin – BEROMUN (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000206/PSUSA/02850/201408
MAH(s): Boehringer Ingelheim International GmbH

15.1.30. Teduglutide – REVESTIVE (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Torbjörn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002345//PSUSA/09305/201408
MAH(s): NPS Pharma Holdings Limited

15.1.31. Teriparatide – FORSTEO (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000425/PSUSA/02903/201409
MAH(s): Eli Lilly Nederland B.V.

15.1.32. **Trastuzumab emtansine – KADCYLA** (CAP)

- Evaluation of a PSUSA procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/002389/PSUSA/10136/201408
MAH(s): Roche Registration Limited

15.1.33. **Ulipristal – ESMYA** (CAP)

- Evaluation of a PSUSA procedure

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

Administrative details:
Procedure number(s): EMEA/H/C/002041/PSUSA/09325/201408
MAH(s): Gedeon Richter Plc.

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. **Aprotinin** (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Veerle Verlinden (BE)

Administrative details:
Procedure number(s): EMEA/H/N/PSP/0004.1
Procedure scope: Evaluation of a revised protocol for a non-interventional post-authorisation safety study of pattern of use of Nordic aprotinin
MAH(s): Disphar International B.V (Nordic Group)

16.1.2. **Flupirtine** (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number: EMEA/H/N/PSP/0005.3
Procedure scope: Evaluation of a revised protocol for a non-interventional post-authorisation safety study to evaluate the effectiveness of the risk minimisation measures for the use of flupirtine 100 mg immediate-release capsules in daily practice
MAH(s): Meda Pharma (Flupigil, Metanor)

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

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number: EMEA/H/N/PSP/0007.2
Procedure scope: Evaluation of a revised protocol for a multi-centre European observational drug utilisation study (DUS) of post-commitment BLI800 to assess drug utilisation in the real life setting in a representative sample of the European target population
MAH(s): Ipsen Pharma (Eziclen, Izinova)

16.1.4. Umeclidinium bromide – INCRUSE (CAP)
Umeclidinium bromide, vilanterol – ANORO (CAP), **LAVENTAIR** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number: EMEA/H/C/PSP/J/003.1
Procedure scope: Revised PASS protocol for a non-interventional observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with UMEC/VI compared with tiotropium (study 201038) as a condition of the licence
MAH(s): Glaxo Group Ltd

16.1.5. Dulaglutide – TRULICITY (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/002825/MEA 001
Procedure scope: PASS protocol for a drug utilisation study to provide information on the use of dulaglutide after approval in the EU
MAH(s): Eli Lilly Nederland B.V.

16.1.6. Dulaglutide – TRULICITY (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/002825/MEA/002
Procedure scope: PASS protocol for a prospective study to monitor the occurrence of events of interest and ensure that the profile and rate remains consistent with what has been seen in clinical trials
MAH(s): Eli Lilly Nederland B.V.

16.1.7. Flutemetamol (^{18}F) – VIZAMYL (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002557/MEA 003
Procedure scope: PASS protocol for a drug utilisation study as an additional pharmacovigilance activity to further characterise the safety concern (GE067-028)
MAH(s): GE Healthcare Ltd

16.1.8. Linaclotide – CONSTELLA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002490/MEA 009
Procedure scope: Revised PASS protocol for the linaclotide safety study for the assessment of diarrhoea—complications and associated risk factors in selected European populations with irritable bowel syndrome with constipation (IBS-C)
MAH(s): Almirall S.A

16.1.9. Linaclotide – CONSTELLA (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002490/MEA 010
Procedure scope: Revised PASS protocol for the linaclotide utilisation study in selected European populations
MAH(s): Almirall S.A

16.1.10. Ramucirumab – CYRAMZA (CAP)

- Evaluation of a PASS protocol

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

Administrative details:
Procedure number(s): EMEA/H/C/002829/MEA 001
Procedure scope: PASS protocol for a prospective observational registry of safety and effectiveness of ramucirumab in patients with advanced gastric cancer in the European Union and North America (I4T-MC-JVDD)
MAH(s): Eli Lilly Nederland B.V.

16.1.11. Boceprevir – VICTRELIS (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002332/II/0033 (without RMP)
Procedure scope: Final report of healthcare professionals (HCP) educational material impact study for Victrelis compiling the results of all the EU countries where the product is marketed (France, Germany, Spain, United Kingdom and Italy)
MAH(s): Merck Sharp & Dohme Limited

16.1.12. Dabigatran – PRADAXA (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Torbjörn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/II/0066 (with RMP)
Procedure scope: Final clinical study report (CSR) for study 1160.86 (open label, non-comparative pharmacokinetic and pharmacodynamic study to evaluate the effect of Pradaxa on coagulation parameters including a calibrated thrombin time test in patients with moderate renal impairment undergoing primary unilateral elective total knee or hip replacement surgery). The RMP has been updated accordingly
MAH(s): Boehringer Ingelheim International GmbH

16.1.13. Dolutegravir – TIVICAY (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002753/II/0010 (with RMP)
Procedure scope: Results of a study investigating the in vitro potential for dolutegravir to inhibit a series of melanocortin receptors
MAH(s): ViiV Healthcare

16.1.14. Dolutegravir – TIVICAY (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002753/II/0011 (with RMP)
Procedure scope: Results of a phototoxicity study (category 3) to assess phototoxicity in dolutegravir
MAH(s): ViiV Healthcare

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/0179 (without RMP)
Procedure scope: Final report from the organisation of teratology information specialists (OTIS) registry

MAH(s): Pfizer Limited

16.1.16. Etanercept – ENBREL (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000262/II/0180 (without RMP)
Procedure scope: Clinical study report for study British Society for Rheumatology Biologics register (BSRBR)
MAH(s): Pfizer Limited

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

- Evaluation of PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000703/WS0698/0056/G, EMEA/H/C/000732/WS0698/0052/G (with RMP)
Procedure scope: Final report for vaccine impact population study in 4 Nordic countries for P033 and the extension of the due date to December 2015 (instead of June 2015) for submission of final study report MEA 20.6 for Protocol 018 (long-term follow up study in adolescents)
MAH(s): Sanofi Pasteur MSD SNC

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

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000832/II/0077 (without RMP)
Procedure scope: Report on a retrospective pharmacoepidemiological study in Canada (Quebec) and follow-up cases. This submission fulfils condition ANX-115 of the marketing authorisation. Annex II is updated accordingly
MAH(s): GlaxoSmithKline Biologicals

16.1.19. Imatinib – GLIVEC (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000406/ANX 191.1
Procedure scope: First progress report on the European observational registry collecting efficacy and safety data in newly diagnosed paediatric Philadelphia positive (Ph+) acute lymphoblastic leukemia (ALL) patients treated with chemotherapy + imatinib ± hematopoietic stem cell treatment (±HSCT) (study STI571I2201)

MAH(s): Novartis Europharm Ltd

16.1.20. Azilsartan medoxomil – EDARBI (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/002293/MEA 001.2
Procedure scope: First annual study report on a drug utilisation study one and five years post-launch in the EU
MAH(s): Takeda Pharma A/S

16.1.21. Bazedoxifene – CONBRIZA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000913/MEA 012.6
Procedure scope: Third progress report on PASS study B1781044: cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe
MAH(s): Pfizer Limited

16.1.22. Boceprevir – VICTRELIS (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002332/MEA 017.6
Procedure scope: Third interim status report on observational PASS of Victrelis (boceprevir) amongst chronic hepatitis C patients (P08518)
MAH(s): Merck Sharp & Dohme Limited

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

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Torbjörn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001211/MEA 015, EMEA/H/C/001114/MEA 017, EMEA/H/C/001210/MEA 015
Procedure scope: Fourth interim report for a PASS study QAB149B2432 of indacaterol prescribing and safety (using HealthCore database in the US)
MAH(s): Novartis Europharm Ltd

16.1.24. Infliximab – REMICADE (CAP)

- Evaluation of interim PASS results

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

Administrative details:
Procedure number(s): EMEA/H/C/000240/MEA 133.9
Procedure scope: Seventh annual paediatric inflammatory bowel disease (IBD) registry (DEVELOP) report
MAH(s): Janssen Biologics B.V.

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/MEA 102
Procedure scope: Annual review of the safety and efficacy of oseltamivir in immunocompromised patients up to final submission of the clinical trial NV20234 study report (treatment) as flu and season permits
MAH(s): Roche Registration Ltd

16.1.26. Perampanel – FYCOMPA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002434/MEA 004.2
Procedure scope: Annual progress report for a post-marketing observational safety study to evaluate the long-term safety and tolerability of Fycompa as add-on therapy in epilepsy patients (PASS Study E2007-G000-402)
MAH(s): Eisai Europe Ltd.

16.1.27. Voriconazole – VFEND (CAP)

- Evaluation of interim PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000387/MEA 090
Procedure scope: Final feasibility assessment for a potential non-interventional study to evaluate the association between voriconazole use and squamous cell carcinoma (SCC) of the skin in children aged less than 18 years
MAH(s): Pfizer Limited

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

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

17.1.1. Antithrombin alfa – ATRYN (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/000587/S/0021 (without RMP)
MAH(s): GTC Biotherapeutics UK Limited

17.1.2. Fampridine – FAMPYRA (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002097/R/0021 (without RMP)
MAH(s): Biogen Idec Ltd.

17.1.3. Vismodegib – ERIVEDGE (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

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

Administrative details:
Procedure number(s): EMEA/H/C/002602/R/0016 (without RMP)
MAH(s): Roche Registration Ltd

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 March 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
Harald Herkner	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement
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
Jana Mladá	Member	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
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Terhi Lehtinen	Alternate via telephone	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 via telephone	Germany	No interests declared	Full involvement
Leonidas Klironomos	Member	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Artūras Kažemekaitis	Alternate	Lithuania	No interests declared	Full involvement
Nadine Petitpain	Alternate	Luxembourg	No restrictions applicable to this meeting	Full involvement
Amy Tanti	Member	Malta	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
Adam Przybylkowski	Member	Poland	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
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Alternate	Romania	No interests declared	Full involvement
Jana Novakova	Alternate	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to meetings	Full involvement
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 this meeting	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Hervé 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
Marco Greco	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Corinne Fechant	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Jens Rotthauwe	Expert -	Germany	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
	via telephone*			
Peter Volkers	Expert - via telephone*	Germany	No interests declared	Full involvement
Dörte Schwabe	Expert - via telephone*	Germany	No interests declared	Full involvement
Eleanor Carey	Expert - in person*	Ireland	No interests declared	Full involvement
Anna Marie Coleman	Expert - in person*	Ireland	No interests declared	Full involvement
Liana Gross-Martirosyan	Expert - in person*	Netherlands	No interests declared	Full involvement
Miroslava Matíková	Expert - in person*	Slovakia	No restrictions applicable to this meeting	Full involvement
Helena Möllby	Expert - in person*	Sweden	No interests declared	Full involvement
Olle Karlström	Expert - via telephone*	Sweden	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Juliana Min	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Angelika Siapkara	Expert - in person*	United Kingdom	No interests declared	Full involvement
Claire Davies	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Claire Doe	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Max Lagnado	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Andrew Ruddick	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	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 talk about.