8 October 2015
EMA/PRAC/722174/2015
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 07-10 September 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 the minutes 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.

Of note, these minutes are a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 7-10 September 2015 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Kristin Thorseng Kvande, replacing Karen Pernille Harg, as the new alternate for Norway.

1.2. Adoption of agenda of the meeting on 7-10 September 2015

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

1.3. Adoption of the minutes of the previous meeting on 6-9 July 2015

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

Post-meeting note: the PRAC minutes of the meeting held on 6-9 July 2015 were published on the EMA website on 23 September 2015 (EMA/PRAC/269153/2015).

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

3.1.1. Fusafungine (NAP), nasal and oral solution - EMEA/H/A-31/1420

Applicant: Les Laboratoires Servier, various

PRAC Rapporteur: Julia Pallos; PRAC Co-rapporteur: Jana Mladá

Scope: Review of the benefit-risk balance following notification by Italy of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data
Action: For adoption of a list of questions and a timetable for the procedure

Background

Fusafungine is an antibiotic used as a nasal/oromucosal spray indicated for the treatment of sinusitis, rhinitis, rhinopharyngitis, tonsillitis, laryngitis and tracheitis.
The Italian Medicines Agency (AIFA) sent a letter of notification dated 06/08/2015 of a referral under Article 31 of Directive 2001/83/EC for the review of fusafungine-containing medicines following an increase in the reporting rate of serious allergic reactions including anaphylactic reactions associated with fusafungine. In addition, AIFA expressed concerns about the benefit risk of fusafungine as well as its potential role in promoting antibiotic resistance.

Discussion

The PRAC noted the notification letter from AIFA requesting a review of all available data on the benefits and risks of fusafungine-containing products. The PRAC discussed a list of questions to be addressed by the relevant MAHs as well as a timetable for conducting the review. The PRAC decided to consult the Paediatric Committee (PDCO) in order to obtain additional information on the clinical use of fusafungine-containing products in paediatric patients and adopted a list of questions to the PDCO. In addition, the PRAC agreed on the need to convene an ad-hoc expert group meeting in the course of the review.

The PRAC appointed Julia Pallos as Rapporteur and Jana Mladá as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions to the MAHs of fusafungine-containing medicines (EMA/PRAC/550969/2015) and a timetable for the procedure (EMA/PRAC/550970/2015).

3.2. Ongoing procedures

3.2.1. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP)
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP), SILGARD (CAP)
Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) – GARDASIL 9 (CAP) - EMEA/H/A-20/1421

MAH(s): GlaxoSmithKline Biologicals S.A. (Cervarix), Sanofi Pasteur MSD SNC (Gardasil, Gardasil 9), Merck Sharp & Dohme Limited (Silgard)

PRAC Rapporteur: Julie Williams; PRAC Co-rapporteurs: Jean-Michel Dogné, Qun-Ying Yue

Scope: Review to further clarify the safety profile of human papillomavirus (HPV) vaccines following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data
Action: For adoption of a revised timetable and discussion for the organisation of a Scientific Advisory Group (SAG)

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing to further clarify the safety profile of Cervarix, Gardasil, Gardasil 9 and Silgard (human papillomavirus vaccines) in relation to the available data regarding complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). For background information, see PRAC minutes July 2015.

Summary of recommendation(s)/conclusions

The PRAC agreed to consult the Scientific Advisory Group on Vaccines (SAG-V) and noted the provisional date for the SAG of 21 October 2015. The PRAC also agreed a revised timetable (EMA/PRAC/454661/2015 rev1) to conduct the review accordingly.

3.2.2. Natalizumab – TYSABRI (CAP) - EMEA/H/A-20/1416

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski; PRAC Co-rapporteur: Carmela Macchiarulo

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data
Action: For adoption of a recommendation or a list of outstanding issues

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for the review of Tysabri (natalizumab). For background information, see PRAC minutes May 2015.

The PRAC (Co)-Rapporteurs prepared an assessment report on the MAH's responses to the list of questions previously agreed.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusion reached by the Rapporteurs and agreed on a list of outstanding issues (LoOI), to be addressed by the MAH in accordance with a revised

timetable (EMA/PRAC/293314/2015 rev1). In addition, the PRAC agreed to consult the Scientific Advisory Group on Neurology (SAG-N) and agreed on a list of questions to the SAG provisionally scheduled early November 2015.

3.3. Procedures for finalisation

None

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

None

3.5. Others

3.5.1. Ambroxol (NAP); bromhexine (NAP) - EMEA/H/A-31/1397

MAH(s): Boehringer Ingelheim, various

PRAC Rapporteur: Margarida Guimarães; PRAC Co-rapporteurs: Jean-Michel Dogné, Jan Neuhauser

Scope: Revision of recommendation of a referral procedure under Article 31 of Directive 2001/83/EC adopted in January 2015, at the request of the European Commission
Action: For discussion and/or adoption of a revised recommendation

Background

At its last plenary meeting, the PRAC agreed the process and timelines for the revision of the PRAC recommendation adopted in January 2015 as requested by the European Commission on 23 June 2015. For background information, see PRAC minutes July 2015.

Summary of recommendation(s)/conclusions

The PRAC discussed and adopted, by majority vote, a revised PRAC recommendation addressing the European Commission's questions. The PRAC conclusions were consistent with the latest position reached in January 2015 (see PRAC minutes January 2015).

4. Signals assessment and prioritisation[1]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Daptomycin – CUBICIN (CAP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

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

Action: For adoption of PRAC recommendation
EPITT 18412 – New signal
Lead MS: UK

Background

Daptomycin is a cyclic lipopeptide that is active against Gram positive bacteria indicated only for the treatment of complicated skin and soft-tissue infections (cSSTI), right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* and *Staphylococcus aureus* bacteraemia (SAB) when associated with cSSTI or RIE.

The exposure for Cubicin, a centrally authorised medicine containing daptomycin, is estimated to have been more than 2,722,609 patients worldwide, in the period from first authorisation in 2006 until September 2014.

During routine signal detection activities, a signal of acute generalised exanthematous pustulosis (AGEP) was identified by the EMA, based on 7 cases retrieved from EudraVigilance (including 5 cases from the published literature). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account the 3 cases with skin biopsy showing subcorneal pustules, the exclusion of other drugs as a confounding factor and the clinical history of multiple pustular skin eruptions compatible with AGEP, the PRAC agreed to request the MAH to submit a cumulative review of cases of AGEP in association with daptomycin, including literature reports.

Summary of recommendation(s)

- The MAH for Cubicin (daptomycin) should submit to the EMA, with the next PSUR (DLP: 11/09/2015), a cumulative review of cases of AGEP in association with daptomycin, including literature reports. The MAH should discuss the confirmation of the diagnosis based on clinical symptomatology and skin biopsy. The MAH should highlight cases with positive dechallenge or rechallenge and/or positive skin biopsy. The MAH should also discuss the need for any potential amendment to the product information and/or the RMP as applicable.

4.1.2. Levetiracetam – KEPPRA (CAP), NAP

Applicant: UCB Pharma SA, various

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of encephalopathy
Action: For adoption of PRAC recommendation
EPITT 18423 – New signal
Lead MS: BE

Background

Levetiracetam is a pyrrolidone derivative indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy and as adjunctive therapy in the

treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy, in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy and in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

The exposure for Keppra, a centrally authorised medicine containing levetiracetam, is estimated to have been more than 8,460,190 patient-years worldwide, in the period from first authorisation in 2000 until July 2015.

A signal of encephalopathy was identified by EMA, based on information provided by the MAH of a levetiracetam generic product on a literature review of drug induced encephalopathy with levetiracetam. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from published case reports in the literature. Taking into account the 7 cases with positive dechallenge and the 7 cases assessed as possibly related to levetiracetam treatment, the PRAC agreed to request the MAH to submit a cumulative review of cases of non-infectious encephalopathy and delirium associated with levetiracetam.

Summary of recommendation(s)

- The MAH for Keppra (levetiracetam) should submit to the EMA, with the next PSUR (DLP: 30/11/2015) a cumulative review of all cases of non-infectious encephalopathy and delirium associated with levetiracetam. The cumulative review should include spontaneous reports, literature cases and any relevant studies focusing on possible mechanisms by which levetiracetam could trigger the event. The MAH should also discuss the need for any potential amendments to the product information and/or the RMP as applicable.

4.1.3. Methotrexate (NAP)

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of progressive multifocal leukoencephalopathy (PML), JC virus infection
Action: For adoption of PRAC recommendation
EPITT 18473 – New signal
Lead MS: DK

Background

Methotrexate is a folic acid antagonist classified as an antimetabolite cytotoxic agent indicated for the treatment of acute lymphocytic leukaemia, non-Hodgkin's lymphoma, osteogenic sarcoma, adjuvant treatment and in advanced breast cancer, metastatic or recurrent head and neck cancer, choriocarcinoma and similar trophoblastic diseases, advanced urinary bladder cancer, soft-tissue and osteogenic sarcomas, and solid tumours particularly breast, lung, head and neck, bladder, cervical, ovarian, and testicular carcinomas.

During routine signal detection activities, a signal of progressive multifocal leukoencephalopathy (PML) and JC virus infection was identified by the EMA, based on 8 cases retrieved from EudraVigilance (including 5 cases from the literature). Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from published case reports in the literature. Taking into account that in 8 cases a possible causal role of methotrexate in the development of PML could not be ruled out based on a temporal relationship, and considering that PML is a serious brain condition, for which early diagnosis is of paramount importance, the PRAC agreed to request the MAH to submit a cumulative review and detailed analysis of all the potential reports of PML associated with methotrexate use based on the available data from clinical trials, spontaneous reports and from the literature.

The PRAC appointed Doris Stenver as Rapporteur for the signal.

Summary of recommendation(s)

- The innovator MAH for methotrexate (Pfizer) should submit to the EMA, within 60 days, a cumulative review and detailed analysis of all the potential reports of PML associated with methotrexate use. The MAH should also discuss the need to update the product information and risk management plan for methotrexate with the risks of PML and JC virus infection.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.4. Paracetamol (NAP), phenylephrine (NAP)

Applicant: various

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of pharmacokinetic drug interaction: increased bioavailability of phenylephrine when co-administered with paracetamol
Action: For adoption of PRAC recommendation
EPITT 18474 – New signal
Lead MS: BE

Background

Paracetamol has analgesic and antipyretic activities believed to be mediated principally through its inhibition of prostaglandin synthesis in the central nervous system. Phenylephrine is a selective α1-adrenergic receptor agonist of the phenethylamine class used as a decongestant but also as an agent to dilate the pupil, and to increase blood pressure. In combination, paracetamol and phenylephrine are indicated for symptomatic relief of colds and influenza, including the relief of headaches, aches and pains, sore throat, nasal congestion and fever.

Following three recent publications by *Atkinson et al.*[234], a signal of pharmacokinetic drug interaction increasing the bioavailability of phenylephrine when co-administered with paracetamol was raised by Belgium, based on 84 cases retrieved from EudraVigilance. Belgium confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence regarding the pharmacokinetic interaction between paracetamol and phenylephrine described in the articles by *Atkinson et al. Cohen et al.*[5], *Eccles et al.*[6] and *Tark et al.*[7] as well as the cases reports in EudraVigilance.

The data from the literature highlighted the possibility of a potential pharmacokinetic interaction between paracetamol and phenylephrine. Furthermore, pharmacokinetic and pharmacodynamic simulations, clinical data and post-marketing experience do not provide sufficient information to determine the clinical impact of the interaction particularly in view of the large variability in both phenylephrine and paracetamol pharmacokinetics. Taking this into account, the PRAC agreed to request MAHs of full marketing authorisation for phenylephrine/paracetamol combination products as well as for phenylephrine and paracetamol medicinal products respectively combined with other ingredients to provide responses to a list of questions.

The PRAC appointed Veerle Verlinden as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for paracetamol and phenylephrine-containing medicines (Aspar Pharmaceuticals, Aziende Chimiche Riunite Angelini Francesco, Bayer, Beecham, Boehringer Ingelheim, GlaxoSmithKline, Kern Pharma, Novartis, Phoenix Labs and Reckitt Benckiser) should submit to the EMA, within 60 days, responses to a list of questions including a request for all available pharmacokinetic and pharmacodynamic patient level data, a cumulative review of serious cases of adverse reactions associated with paracetamol/phenylephrine combination products and of information suggesting a potential drug–drug interaction between paracetamol and phenylephrine, together with a discussion of the safety of the paracetamol/phenylephrine combination products compared with phenylephrine monotherapy.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.5. Peginterferon alfa-2a – PEGASYS (CAP)

Applicant: Roche Registration Limited

[2] Atkinson HC, Stanescu I, Anderson BJ 'Increased phenylephrine plasma levels with administration of acetaminophen', N Eng J Med, 2014; 370(12), 1171-1172.
[3] Atkinson HC, Stanescu I, Salem II, Potts AL, Anderson BJ 'Increased bioavailability of phenylephrine by co-administration of acetaminophen: results of four open-label, crossover pharmacokinetic trials in healthy volunteers', Eur J Clin Pharmacol, 2015; 71, 151-158.
[4] Atkinson HC, Potts AL, Anderson AJ 'Potential cardiovascular adverse event when phenylephrine is combined with paracetamol: simulation and narrative review' Eur J Clin Pharmacol, 2015; DOI 10.1007/s00228-015-1876-1
[5] Cohen BM 'Clinical and physiologic 'significance' of drug-induced changes in nasal flow/resistance.' Eur J Clin Pharmacol, 1972; 5(2), 81-86.
[6] Eccles R 'Substitution of phenylephrine for pseudoephedrine as nasal decongestant. An illogical way to control methamphetamine abuse' Br J Clin Pharmacol, 2006; 63(1), 10-14.
[7] Tark B, Messe S, Balucani C, Levine S 'Intracerebral hemorrhage associated with oral phenylephrine use: A case report and review of the literature' Journal of Stroke and Cerebrovascular Diseases, 2014; 23 (9), 2296-2300.

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of Guillain-Barré syndrome (GBS)
Action: For adoption of PRAC recommendation
EPITT 18402 – New signal
Lead MS: SE

Background

Peginterferon alfa-2a is a conjugate of bis-monomethoxypolyethylene glycol with interferon alfa-2a. Interferon alfa-2a is an endogenous glycoprotein with immunomodulatory, antiviral and antiproliferative properties indicated for the treatment of chronic hepatitis B under certain conditions and of hepatitis C under certain conditions.

The exposure for Pegasys, a centrally authorised medicine containing peginterferon alfa-2a, is estimated to have been around 2,750,000 patients worldwide, in the period from first authorisation in 2002 until July 2014.

During routine signal detection activities, a signal of Guillain-Barré syndrome (GBS) was identified by the EMA, based on 22 cases retrieved from EudraVigilance, including 4 well documented cases. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account that the 4 well documented cases were considered at least possibly related to peginterferon alfa-2a and that under-reporting for serious adverse events (such as GBS) may be high, even if the number of cases is within the expected background rates for GBS, the PRAC agreed to request the MAH to submit a cumulative review of cases of GBS and related terms including data from the literature.

Summary of recommendation(s)

- The MAH for Pegasys (peginterferon alfa-2a) should submit to the EMA, within 60 days, a cumulative review of cases of Guillain-Barre syndrome and related terms including data from the literature. The MAH should also discuss the need for any potential amendment to the product information and/or the RMP as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.6. Pemetrexed – ALIMTA (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Corinne Fechant

Scope: Signal of scleroderma
Action: For adoption of PRAC recommendation
EPITT 18383 – New signal
Lead MS: FR

Background

Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication, indicated for the treatment of malignant pleural mesothelioma under certain conditions and of non-small cell lung cancer under certain conditions.

The exposure for Alimta, a centrally authorised medicine containing pemetrexed, is estimated to have been more than 1,350,000 patients worldwide, in the period from first authorisation in 2004 until February 2015.

During routine signal detection activities, a signal of scleroderma was identified by the EMA, based on 8 cases retrieved from EudraVigilance (including 5 cases from the literature). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account that in 5 cases a possible causal role of pemetrexed cannot be excluded in the development of localised scleroderma in the lower limbs based on the chronology, the compatible time to onset and the possible biological plausibility, the PRAC agreed to request the MAH for Alimta to provide a cumulative review and detailed analysis of all cases of local and systemic scleroderma and related terms, including data from studies, spontaneous reports and from the literature.

Summary of recommendation(s)

- The MAH for Alimta (pemetrexed) should submit to the EMA, by 31 October 2015 as a PSUR follow-up to the ongoing PSUR procedure (DLP: 04/02/2015) (PSUSA/00002330/201502), a cumulative review and detailed analysis of all cases of local and systemic scleroderma and related terms, including data from studies, spontaneous reports and from the literature, and to consider the need to amend the product information and RMP as applicable.
  See also under 6.1.17.

4.1.7. Tyrosine kinase inhibitors (TKI): bosutinib – BOSULIF (CAP); dasatinib - SPRYCEL (CAP); imatinib – GLIVEC (CAP); nilotinib – TASIGNA (CAP); ponatinib – ICLUSIG (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG (Sprycel), Novartis Europharm Ltd (Glivec, Tasigna), Pfizer Limited (Bosulif), Ariad Pharma Ltd (Iclusig)

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of hepatitis B virus (HBV) reactivation
Action: For adoption of PRAC recommendation
EPITT 18405 – New signal
Lead MS: UK, ES, DK, DE

Background

Tyrosine kinase inhibitors (TKI) are enzymes responsible for the activation of many proteins by signal transduction cascades and are typically used as anticancer drugs. Bcr-abl is a fusion gene that juxtaposes the Abelson murine leukemia viral oncogene homolog 1 (Abl1) gene on chromosome 9 to a part of the BCR ('breakpoint cluster region') on chromosome 22. Bcr-Abl tyrosine-kinase inhibitors are indicated for the treatment of Philadelphia

chromosome positive chronic myelogenous leukaemia (Ph+ CML) and in Philadelphia chromosome positive chronic acute lymphoblastic leukemia (Ph+ LAL).

The exposure for Bosulif, a centrally authorised medicine containing bosutinib, is estimated to have been more than 2,735 patient-years worldwide, in the period from first authorisation in 2013 until September 2014. The exposure for Sprycel, a centrally authorised medicine containing dasatinib, is estimated to have been more than 91,119 patient-years worldwide, in the period from first authorisation in 2006 until June 2014. The exposure for Glivec, a centrally authorised medicine containing imatinib, is estimated to have been more than 918,000 patient-years worldwide, in the period from first authorisation in 2001 until May 2012. The exposure for Tasigna, a centrally authorised medicine containing nilotinib, is estimated to have been more than 61,009 patient-years worldwide, in the period from first authorisation in 2007 until January 2014. The exposure for Iclusig, a centrally authorised medicine containing ponatinib, is estimated to have been more than 542 patient-years worldwide, in the period from first authorisation in 2013 until June 2014.

Following two cases reports retrieved from the French Pharmacovigilance database, a signal of hepatitis B virus (HBV) reactivation was identified by France, based on 30 cases retrieved in EudraVigilance (26 cases for imatinib and 4 cases with nilotinib) and a review of the literature (12 cases including 10 cases already reported in EudraVigilance). France confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account the compatible temporal relationship and the possible biological plausibility, the PRAC agreed to request the MAHs for Glivec (imatinib), Sprycel (dasatinib), Tasigna (nilotinib), Bosulif (bosunitib) and Iclusig (ponatinib) to provide a cumulative review of spontaneous cases and adverse events from clinical trials related to reactivation of HBV in patients treated with imatinib, dasatinib, bosutinib, nilotinib and ponatinib along with a literature search.

The PRAC appointed Dolores Montero Corominas as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Glivec (imatinib), Sprycel (dasatinib), Tasigna (nilotinib), Bosulif (bosunitib) and Iclusig (ponatinib) should submit to the EMA, within 60 days, a cumulative review of spontaneous cases and adverse events from clinical trials related to reactivation of HBV in patients treated with imatinib, dasatinib, bosutinib, nilotinib and ponatinib. A literature search on this issue should also be provided. The MAHs should discuss possible mechanism(s) by which bcr-abl tyrosine kinase inhibitors (TKI) could cause HBV reactivation, as well as any factors that might suggest variation in the effect across the class, taking into account any differences in pharmacological mechanisms. Based on the assessment of this signal, the MAHs should propose an update of the product information to include HBV reactivation in SmPC section 4.8 and to include a general statement on HBV reactivation in patients treated with bcr-abl TKIs in section 4.4, including screening before initiating treatment with bcr-abl TKIs and further recommendations. The implications of screening and the proposed actions relating to those patients who are screened positive should be fully discussed by the MAHs. The Package Leaflet should be updated accordingly.

- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.8. Regorafenib – STIVARGA (CAP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Signal of haemolysis
Action: For adoption of PRAC recommendation
EPITT 18437 – New signal
Lead MS: NL

Background

Regorafenib is a protein kinase inhibitor indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) under certain conditions and for the treatment of unresectable or metastatic gastrointestinal stromal tumours (GIST) under certain conditions.

Stivarga, a centrally authorised medicine containing regorafenib, is estimated to have been used by more than 45,000 patients worldwide, in the period from 2013 until March 2015.

During routine signal detection activities, a signal of haemolysis was identified by the EMA, based on 5 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance. Taking into account the well documented cases reporting events associated with increased breakdown of haemoglobin and suggesting a possible role of regorafenib, the PRAC agreed to request the MAH for Stivarga to provide a cumulative review of cases of haemolytic disorders in association with regorafenib, taking into account all sources of information (studies, literature, spontaneous reports).

Summary of recommendation(s)

- The MAH for Stivarga (regorafenib) should submit to the EMA, by 9 September 2015 in the framework of the ongoing PSUR procedure (DLP: 26/03/2015) (EMEA/H/C/PSUSA/00010133/201503), a cumulative review of cases of haemolytic disorders in association with regorafenib, taking into account all sources of information. The MAH should also discuss the aetiology of the cases of haemolytic anaemia.

4.1.9. Regorafenib – STIVARGA (CAP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Signal of acute pancreatitis
Action: For adoption of PRAC recommendation
EPITT 18440 – New signal
Lead MS: NL

Background

Regorafenib is a protein kinase inhibitor indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) under certain conditions and for the treatment of unresectable or metastatic gastrointestinal stromal tumours (GIST) under certain conditions.

Stivarga, a centrally authorised medicine containing regorafenib, is estimated to have been used by more than 45,000 patients worldwide, in the period from 2013 until March 2015.

During routine signal detection activities, a signal of acute pancreatitis was identified by the EMA, based on 4 cases retrieved from EudraVigilance and a trial-level meta-analysis of >10,000 patients in clinical trials with and without tyrosine kinase inhibitors (TKIs)[8] which showed a relative risk of 1.95 (p=0.042, 95% CI: 1.02 to 3.70) of pancreatitis, without difference among TKIs. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account the known risk of pancreatic enzyme increase with regorafenib, the possibility of a class effect and the seriousness of acute pancreatitis, the PRAC agreed to request the MAH for Stivarga to provide a cumulative review of (acute) pancreatitis, taking into account all sources of information (studies, literature, and spontaneous reports), and discuss the need for an update of the product information.

Summary of recommendation(s)

- The MAH for Stivarga (regorafenib) should submit to the EMA, by 9 September 2015, in the framework of the ongoing PSUR procedure (DLP: 26/03/2015) (EMEA/H/C/PSUSA/00010133/201503), a cumulative review of (acute) pancreatitis, taking into account all sources of information, and discuss the need for an update of the product information as applicable.

4.1.10. Sunitinib – SUTENT (CAP)

Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Signal of pneumatosis intestinalis
Action: For adoption of PRAC recommendation
EPITT 18396 – New signal
Lead MS: IT

Background

Sunitinib is a protein kinase inhibitor indicated for the treatment of gastrointestinal stromal tumours (GIST) under certain conditions, metastatic renal cell carcinoma (MRCC) under certain conditions and pancreatic neuroendocrine tumours (pNET) under certain conditions.

[8] Ghatalia P. et al. 'Pancreatitis with vascular endothelial growth factor receptor tyrosine kinase inhibitors' Critical Reviews in Oncology/Hematology 94 (2015); 136–145

The exposure for Sutent, a centrally authorised medicine containing sunitinib, is estimated to have been more than 285,889 patients worldwide, in the period from first authorisation in 2006 until April 2014.

During routine signal detection activities, a signal of pneumatosis intestinalis was identified by the EMA, based on 11 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account the biological plausibility and that positive dechallenge occurred in all 9 patients without intestinal perforation (including 1 positive dechallenge after dose reduction), the PRAC agreed to request the MAH for Sutent to provide a cumulative review of all cases of pneumatosis intestinalis associated with sunitib.

Summary of recommendation(s)

- The MAH for Sutent (sunitinib) should submit to the EMA, by 8 October 2015 in the framework of the ongoing PSUR procedure (DLP: 30/04/2015) (EMEA/H/C/PSUSA/00002833/201504) a cumulative review of all cases of pneumatosis intestinalis. The biological plausibility should be also discussed by the MAH. Based on the cumulative review, the MAH should propose amendments to the product information and/or to the RMP as applicable.

4.2. New signals detected from other sources

4.2.1. Clozapine (NAP)

Applicant: various

PRAC Rapporteur: Julie Williams

Scope: Signal of myocarditis
Action: For adoption of PRAC recommendation
EPITT 18414 – New signal
Lead MS: UK

Background

Clozapine is an atypical antipsychotic indicated for the treatment of schizophrenia. Due to the risk of agranulocytosis, the therapeutic indication has been restricted to treatment-resistant schizophrenic patients or patients intolerant to other antipsychotics. Clozapine is also indicated for the treatment of psychotic disorders occurring during the course of Parkinson's disease, where standard treatment has failed.

Following the publication in Acta Psychiatrica Scandinavia by *Ronaldson et al.*[9], a signal of myocarditis was identified by Denmark, suggesting that the incidence of myocarditis is around 3%. Currently myocarditis is labelled as a rare adverse drug reaction in the SmPC (frequency ≥ 1/10,000, < 1/1,000). Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

[9] Ronaldson KJ, Fitzgerald PB, McNeil JJ (2015). Clozapine-induced myocarditis, a widely overlooked adverse reaction. Acta Psychiatrica Scandinavia: 1-10

Discussion

The PRAC noted the published review by *Ronaldson et al.*, in which the authors suggested that the incidence of clozapine-induced myocarditis may be higher than that currently stated in the product information. The PRAC considered that although this study had a number of limitations it would nevertheless be important to explore the available information from clinical trials to obtain the most up-to-date information regarding the incidence of myocarditis and cardiomyopathy. Taking this into account, the PRAC agreed to request the originator MAH for clozapine in the EU (Novartis/Sandoz) to provide estimates from its clinical trials database for the frequency of occurrence of cases of myocarditis and cardiomyopathy (and related terms) and to consider the implications for the current product information and risk minimisation measures.

The PRAC appointed Julie Williams as Rapporteur for the signal.

Summary of recommendation(s)

- The originator MAH for clozapine in the EU (Novartis/Sandoz) should submit to the EMA, within 60 days, estimates from its clinical trials database for the frequency of occurrence of cases of myocarditis and cardiomyopathy and to propose amendments to the product information and risk minimisation measures as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: following a request from the MAH which was considered justified, the PRAC agreed for a modification of the timetable for submission of responses by 30 days.

4.2.2. Thioctic acid (NAP)

Applicant: various

PRAC Rapporteur: Marina Dimov Di Giusti

Scope: Signal of insulin autoimmune syndrome (IAS)
Action: For adoption of PRAC recommendation
EPITT 18406 – New signal
Lead MS: HR

Background

Thioctic acid, also known as α-lipoic acid, is an organosulfur compound derived from octanoic acid indicated mainly for the treatment of diabetic polyneuropathy. A signal of insulin autoimmune syndrome (IAS) was identified by Germany, following information provided by a MAH of thioctic acid-containing medicinal products and based on published case reports of IAS possibly related to treatment with thioctic acid. Croatia confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from published case reports and from case reports in EudraVigilance. A plausible cause-effect relationship between the intake of thioctic acid and the occurrence of IAS is suggested considering the number of well-documented published case reports, some with positive rechallenge, the association with a genetic predisposition that identifies a specific patient subpopulation in which IAS might occur, and

the identified pathway describing how thioctic acid (and other sulfhydryl-containing drugs) can trigger IAS in that patient subpopulation. Based on the analysis of the available data, the PRAC considered that there is evidence of a causal relationship between intake of thioctic acid and development of IAS in susceptible patients with the human leukocyte antigen (HLA) HLA-DRB1*04:06 and HLA-DRB1*04:03 alleles. Taking this into account, the PRAC agreed that the product information should be updated to include IAS as a new warning and as a new undesirable effect.

The PRAC appointed Marina Dimov Di Giusti as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for thioctic acid-containing medicinal products should submit to the relevant EU national competent authorities (NCAs), within 60 days, a variation to include IAS as a new warning and as a new undesirable effect.

For the full PRAC recommendations, see EMA/PRAC/590240/2015 published on the EMA website.

4.3. Signals follow-up and prioritisation

4.3.1. Amikacin (NAP)

Applicant: Bristol-Myers Squib, B. Braun Melsungen AG

PRAC Rapporteur: Maia Uusküla

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)
Action: For adoption of PRAC recommendation
EPITT 18304 – Follow-up to May 2015

Background

For background information, see PRAC minutes May 2015. The MAH replied to the request for information on the signal of drug reaction with eosinophilia and systemic symptoms (DRESS) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. Having considered the available evidence, the PRAC agreed that the number of possible cases of drug reaction with eosinophilia and systemic symptoms (DRESS) with a temporal relationship to amikacin is very small and that the likelihood of a causal relationship between treatment with amikacin and DRESS is not sufficiently robust at this stage to recommend a change to the product information.

Summary of recommendation(s)

- The innovator MAH (Bristol-Myers Squibb) should continue to monitor severe cutaneous adverse reactions (SCAR) reports and review this topic in the next PSUR (DLP: 05/06/2017). Considering the seriousness of DRESS syndrome, the MAH should assure that sufficient information (dechallenge, rechallenge, results of the patch tests) has been obtained in such cases in order to allow a thorough assessment.

4.3.2. Bisphosphonates: alendronic acid (NAP); alendronic acid, clodronic acid (NAP); colecalciferol - ADROVANCE (CAP), FOSAVANCE (CAP), VANTAVO (CAP); etidronic

Applicant: Amgen Europe B.V. (Prolia, Xgeva), Merck Sharp & Dohme Limited (Adrovance, Fosavance, Vantavo), Novartis Europharm Ltd (Aclasta, Zometa), Roche Registration Ltd (Bondronat, Bonviva), various

PRAC Rapporteur: Julie Williams

Scope: Signal of osteonecrosis of the external auditory canal
Action: For adoption of PRAC recommendation
EPITT 18256 – Follow-up to March 2015

Background

For background information, see PRAC minutes March 2015. The MAHs replied to the request for information on the signal of osteonecrosis of the external auditory canal and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. The PRAC noted that the MAHs' responses had identified some further case reports of osteonecrosis of the external auditory canal in association with a number of different bisphosphonates and also discussed how the known pathophysiological mechanisms with osteonecrosis of the jaw may also be applicable in this case. Taking into account the evidence from clinical trials, published literature and spontaneous reporting, the PRAC agreed that the product information of bisphosphonates-containing medicinal products should be updated to include osteonecrosis of the external auditory canal as a new warning and as a new undesirable effect, and also agreed some key messages for communication at a national level.

Taking into account the available evidence from clinical trials, the published literature and spontaneous case reports of osteonecrosis of the external auditory canal in association with denosumab, the PRAC agreed that no changes are necessary to the product information of denosumab-containing products at present. Nevertheless, the PRAC recommended that osteonecrosis of the external auditory canal should be added to the RMP of Prolia and Xgeva as an important potential risk.

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 EMA or to the relevant EU national competent authorities (NCAs), within 60 days, a variation to include osteonecrosis of the external auditory canal as a new warning and as a new undesirable effect.
- In addition to the proposed updates to the product information for all-bisphosphonate-containing products, the PRAC considered important to raise awareness of the

possibility of osteonecrosis of the auditory canal in association with bisphosphonates among prescribers and also Ear Nose and Throat (ENT) specialists.

- The MAH of Prolia and Xgeva (denosumab) should submit to EMA, within 60 days, a variation to amend the RMP and include osteonecrosis of the external auditory canal as a new important potential risk.

For the full PRAC recommendations, see EMA/PRAC/590240/2015 published on the EMA website.

4.3.3. Digoxin (NAP)

Applicant: various

PRAC Rapporteur: Carmela Macchiarulo

Scope: Signal of mortality in patients with atrial fibrillation
Action: For adoption of PRAC recommendation
EPITT 18259 – Follow-up to May 2015

Background

For background information, see PRAC minutes May 2015. The PRAC Rapporteur presented their further review of the cohort study by *Freeman et al.*[10] and in addition their review of the available literature on mortality related to the use of digoxin in patients with atrial fibrillation, with or without heart failure.

Discussion

The PRAC discussed this signal, and the further review of the retrospective, propensity-score matched cohort study by *Freeman et al,* the three recently published meta-analysis by *Vamos M et al.*[11], *Ouyang A-J et al.*[12] and *Ziff O et al.*[13] 2015 as well as the systematic review of scientific literature, conducted by the Rapporteur. The systematic review, including non-interventional studies as well as post-hoc analyses of clinical trials, investigated on the risk of mortality related to the use of digoxin in patients with atrial fibrillation with or without heart failure and took into account risk factors such as elevated digoxin plasma levels, age and impaired renal function.The PRAC also noted a non-urgent information (NUI) circulated by the Rapporteur to collect information regarding the indication for use for digoxin in the Member States. Taking into account the available evidence with their limitations, the PRAC agreed that the available evidence from non-interventional studies is likely to be subject to confounding and that the clinical trials, from which the post-hoc analyses of safety were performed, were not specifically developed to address the safety of digoxin. Furthermore, the PRAC was informed that European clinical guidelines on the use of digoxin, including risk minimisation recommendations regarding

[10] Digoxin and Risk of Death in Adults with Atrial Fibrillation (AF), Freeman JV et al., Circ Arrhythm Electrophysiol. 2015 Feb;8(1):49-58
[11] Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. European Heart Journal 2015; doi:10.1093/eurheartj/ehv143
[12] Ouyang A-J, Lv Y-N, Zhong H-L, Wen J-H, Wei X-H, Peng H-W, et al. Meta-analysis of digoxin use and risk of mortality in patients with atrial fibrillation. Am J Cardiol [Internet]. 2015 Apr 1 [cited 2015 Apr 14];115(7):901–6.
[13] Ziff Oliver J, Lane Deirdre A, Samra Monica, Griffith Michael, Kirchhof Paulus, Lip Gregory Y H, Steeds Richard P, Townend Jonathan, Kotecha Dipak 'Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data', BMJ 2105;351:h4451 | doi: 10 .113 6/bmj.h4451

dose, are being developed and near completion. Considering both aspects, the PRAC agreed that at present, no changes are warranted in the product information.

Summary of recommendation(s)

- No regulatory action was considered necessary based on the evaluation of this signal.

4.3.4. Hormone replacement therapy medicinal products containing oestrogens or oestrogens and progestogens in combination (NAP); bazedoxifene, oestrogens conjugated – DUAVIVE (CAP)

Applicant: Pfizer Limited (Duavive), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of increased risk of ovarian cancer
Action: For adoption of PRAC recommendation
EPITT 18258 – Follow-up to June 2015

Background

For background information, see PRAC minutes April 2015 and PRAC minutes June 2015. The PRAC Rapporteur assessed the additional information provided by the principal investigator of the published meta-analysis[14].

Discussion

The Collaborative Group on Epidemiological Studies of Ovarian Cancer submitted detailed answers in response to a list of questions adopted by the PRAC in June 2015 on the meta-analysis of epidemiological studies published in the Lancet. In addition to providing written responses, the principal investigator[15] of the meta-analysis was invited to present at the plenary meeting. The PRAC considered that the results from the large meta-analysis and the responses to questions provided robust evidence to justify a revision of the current product information of hormone replacement therapy products containing oestrogens and combined oestrogen-progestagen regarding the risk of ovarian cancer.

Summary of recommendation(s)

- The MAHs for hormone replacement therapy medicinal products containing oestrogens (including tibolone) or oestrogens and progestogens in combination, except for pharmaceutical forms for vaginal use, should submit to the EMA, within 30 days, comments on the proposed wording by the PRAC to revise the existing wording on the risk of ovarian cancer in the current CMDh core SmPC and Package Leaflet for post-menopausal hormone replacement therapy products (CMDh/131/2003 Rev 4).
- The MAH for Duavive (bazedoxifene, oestrogens conjugated) should submit to the EMA, within 30 days, comments on the PRAC proposed wording to reflect the risk of ovarian cancer in the product information.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[14] Collaborative group on epidemiological studies of ovarian cancer. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies; Collaborative Group on Epidemiological Studies of Ovarian Cancer; The Lancet, February, 13, 2015
[15] Professor Valerie Beral

4.3.5. Leflunomide – ARAVA (CAP) – EMEA/H/C/000235/SDA/055, LEFLUNOMIDE WINTHROP (CAP) – EMEA/H/C/001129/SDA/024

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Sabine Straus

Scope: Signal of pulmonary hypertension
Action: For adoption of PRAC recommendation
EPITT 18221 – Follow-up to April 2015

Background

For background information, see PRAC minutes April 2015. The MAH replied to the request for information on the signal of pulmonary hypertension and the responses were assessed by the Rapporteur.

Discussion

Taking into account the available evidence in EudraVigilance, the literature, and the additional data submitted by the MAH, and the known association of leflunomide with interstitial lung disease, the PRAC agreed that the product information of leflunomide-containing medicinal products should be updated to include pulmonary hypertension as a new warning and as a new undesirable effect.

Summary of recommendation(s)

- The MAH for leflunomide-containing medicinal products should submit to EMA or to the relevant EU national competent authorities (NCAs) as applicable, within 60 days, a variation to include pulmonary hypertension in the current warnings on respiratory reactions and interstitial lung disease and to include pulmonary hypertension as a new undesirable effect.

For the full PRAC recommendations, see EMA/PRAC/590240/2015 published on the EMA website.

4.3.6. Lenalidomide – REVLIMID (CAP) – EMEA/H/C/000717/SDA/045

Applicant: Celgene Europe Limited

PRAC Rapporteur: Corinne Fechant

Scope: Signal of pulmonary alveolar haemorrhage
Action: For adoption of PRAC recommendation
EPITT 18300 – Follow-up to May 2015

Background

For background information, see PRAC minutes May 2015. The MAH for Revlimid (lenalidomide), Thalidomide Celgene (thalidomide) and Imnovid (pomalidomide) replied to the request for information on the signal of pulmonary alveolar haemorrhage and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's cumulative review of reported cases of pulmonary alveolar haemorrhage as well as pulmonary haemorrhage and hemoptysis. Taking into account the

cumulative review of cases from clinical trials, post-marketing experience and literature provided by the MAH, the PRAC considered that a causal relationship with lenalidomide, thalidomide or pomalidomide could not be excluded based on a suggestive temporal association and biological plausibility.

Summary of recommendation(s)

- The MAH Revlimid (lenalidomide), Thalidomide Celgene (thalidomide) and Imnovid (pomalidomide) should keep the signal of pulmonary alveolar haemorrhage under ongoing review and provide a detailed review of pulmonary alveolar haemorrhage and pulmonary haemorrhage with lenalidomide, thalidomide and pomalidomide in the next PSURs.
  When the MAH reviews future cases of pulmonary haemorrhage/pulmonary alveolar haemorrhage, the use of confounding factors to exclude a contributory role for lenalidomide, thalidomide, pomalidomide should be carefully considered.
  The MAH should suggest an update of the product information if more evidence becomes available and should take into account the potential benefit of prompt treatment interruption if a casual association is suspected.

4.3.7. Liraglutide – SAXENDA (CAP) – EMEA/H/C/003780/SDA/012, VICTOZA (CAP) – EMEA/H/C/001026/SDA/034; liraglutide, insulin degludec - XULTOPHY (CAP) – EMEA/H/C/002647/SDA/002

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Signal of medullary thyroid cancer (MTC)
Action: For adoption of PRAC recommendation
EPITT 18292 – Follow-up to May 2015

Background

For background information, see PRAC minutes May 2015. The MAH for Victoza (liraglutide) and Xultophy (liraglitude, insulin degludec) replied to the request for information on the signal of medullary thyroid cancer and the responses were assessed by the Rapporteur.

Discussion

Taking into account all the available evidence from post-marketing case reports, clinical trials, non-clinical data and the literature, the PRAC agreed that currently there is insufficient evidence to confirm a causal relationship between medullary thyroid cancer (MTC) and liraglutide. Although non-clinical data suggests a mechanism for an increased risk of MTC after liraglutide exposure, the available data in human use provides insufficient evidence to designate this as an identified risk. Because at present a causal relationship cannot be established, the PRAC considered that the current warning on thyroid cancers and the non-clinical information with regard to observations in animals sufficiently reflect the currently available data regarding MTC. Therefore, no changes to this wording are warranted at the moment. MTC is already a potential risk in the RMP and should be continuously monitored and new relevant cases of MTC should be presented and assessed in future PSURs for liraglutide.

Summary of recommendation(s)

- The MAH Victoza (liraglutide) and Xultophy (liraglitude, insulin degludec) should continue to monitor case reports of medullary thyroid cancer as part of routine safety surveillance and provide a comprehensive discussion in future PSURs.

4.3.8. Tamsulosin (NAP)

Applicant: Astellas Pharma Europe B.V., various

PRAC Rapporteur: Sabine Straus

Scope: Signal of urinary incontinence
Action: For adoption of PRAC recommendation
EPITT 18317 – Follow-up to May 2015

Background

For background information, see PRAC minutes May 2015. The MAH for Omnic (tamsulosin) replied to the request for information on the signal of urinary incontinence and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the cumulative review provided by the MAH. Taking into account all the available evidence, the PRAC agreed that concomitant medications, comorbidities and the underlying disease in patients with benign prostatic hyperplasia provide a more plausible explanation and a causal relationship between the treatment with tamsulosin and the development of urinary incontinence cannot be confirmed. Therefore changes in the product information are not considered warranted at the moment.

Summary of recommendation(s)

- The MAH for Omnic (Astellas Phama) should continue to monitor case reports of urinary incontinence as part of routine safety surveillance and discuss the new relevant cases in future PSURs. If new relevant information arises from the evaluation of the cases, the MAH should inform the national competent authorities accordingly.

4.3.9. Trabectedin – YONDELIS (CAP) - EMEA/H/C/000773/SDA/028

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Torbjörn Callreus

Scope: Signal of capillary leak syndrome
Action: For adoption of PRAC recommendation
EPITT 18115 – Follow-up to April 2015

Background

For background information, see PRAC Minutes December 2014 and PRAC minutes April 2015. Following the PRAC discussion in April 2015, the MAH submitted additional data and a justification for not submitting the variation as requested by the PRAC which were assessed by the Rapporteur.

Discussion

Taking into account the available evidence from case reports in EudraVigilance and from data submitted by the MAH, the PRAC agreed that there is a reasonable possibility of a causal relationship between capillary leak syndrome and the use of trabectedin. The PRAC did not consider that additional data from two randomised clinical trials (ET743-OVA-301 and ET743-SAR-3007) submitted by the MAH refuted the signal. Considering the seriousness of the condition, the PRAC agreed that an update of the product information is warranted.

Summary of recommendation(s)

- The MAH for Yondelis (trabectedin) should submit to the EMA, within 60 days, a variation to update the product information to include 'capillary leak syndrome' as an undesirable effect with an uncommon frequency.

For the full PRAC recommendations, see EMA/PRAC/590240/2015 published on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

Please refer to the CHMP pages for upcoming information (http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights).

See also Annex I. 14.1.

5.1.1. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence - EMEA/H/C/003854, Orphan

Applicant: GlaxoSmithKline Trading Services, ATMP[16]

Scope: Treatment of severe combined immunodeficiency
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.2. Betulae cortex dry extract - EMEA/H/C/003938

Scope: Treatment of partial thickness wounds
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.3. Cobimetinib - EMEA/H/C/003960

Scope: Treatment of metastatic melanoma
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

[16] Advanced-therapy medicinal product

5.1.4. Idarucizumab – EMEA/H/C/003986

Scope: Prevention and treatment of dabigatran-associated haemorrhage
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.5. Necitumumab - EMEA/H/C/003886

Scope: Treatment of squamous non-small cell lung cancer
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.6. Opicapone - EMEA/H/C/002790

Scope: Treatment of Parkinson's disease and motor fluctuations
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.1.7. Selexipag - EMEA/H/C/003774, Orphan

Applicant: Actelion Registration Ltd

Scope: Treatment of pulmonary arterial hypertension (PAH)
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

5.2. Medicines in the post-authorisation phase – PRAC-led procedures

See also Annex I. 14.2.

5.2.1. Denosumab – PROLIA (CAP) - EMEA/H/C/001120/II/0051

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP version 12 to reflect the introduction of the patient reminder card on risk of osteonecrosis of the jaw and changes to the SmPC
Action: For adoption of PRAC AR

Background

Denosumab is a human monoclonal antibody (IgG2) indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In addition, it is indicated for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

The PRAC is evaluating a type II variation procedure for Prolia, a centrally authorised medicine containing denosumab, to update the RMP to reflect the introduction of the patient reminder card on the risk of osteonecrosis of the jaw (ONJ) and changes to the product information previously endorsed. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP version 12 for Prolia (denosumab) in the context of the variation under evaluation by the PRAC and CHMP is considered acceptable as detailed in the adopted assessment report.

- The PRAC considered that the MAH's proposed strategy to measure the effectiveness of the risk minimisation measure for ONJ, consisting of routine monitoring and evaluation of post-marketing and clinical study safety data through PSURs as well as comparisons of post marketing rates of ONJ in EU before and after the introduction of the patient card and to the rest of the world, is acceptable. The distribution of the patient reminder card should be appropriately tracked to ensure that it is distributed in accordance with the plan agreed with NCAs. Additional requests for patient reminder cards and web downloads should also be recorded as an indicator of ongoing use of the patient reminder card.

5.2.2. Denosumab – XGEVA (CAP) - EMEA/H/C/002173/II/0039

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP version 14 to reflect the introduction of the patient reminder card on risk of osteonecrosis of the jaw and changes to the SmPC and DHPC to remind practitioners that unhealed lesions from dental or oral surgery is a contraindication
Action: For adoption of PRAC AR

Background

Denosumab is a human monoclonal antibody (IgG2) indicated for the prevention of skeletal related events in adults with bone metastases from solid tumours as well as for the treatment of adults and skeletally mature adolescents with a giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The PRAC is evaluating a type II variation procedure for Xgeva, a centrally authorised medicine containing denosumab, to update the RMP to reflect the introduction of the patient reminder card on the risk of osteonecrosis of the jaw (ONJ), the distribution of a DHPC to remind HCPs that unhealed lesions from dental or oral surgery is now a contraindication and changes to the product information previously endorsed. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP version 14 for Xgeva (denosumab) in the context of the variation under evaluation by the PRAC and CHMP is considered acceptable as detailed in the adopted assessment report.
- The PRAC considered that the MAH's proposed strategy to measure the effectiveness of the risk minimisation measure for ONJ, consisting of routine monitoring and evaluation of post-marketing and clinical study safety data through PSURs as well as comparisons of post marketing rates of ONJ in EU before and after the introduction of the patient card and to the rest of the world, is acceptable. The distribution of the patient reminder card should be appropriately tracked to ensure that it is distributed in accordance with the plan agreed with NCAs. Additional requests for patient reminder cards and web downloads should also be recorded as an indicator of ongoing use of the patient reminder card. In addition, the survey (study 20110102) already in place in EU countries to assess the knowledge of oncologists of the risk minimisation

recommendations for ONJ in the prescribing information should provide further information.

5.2.3. Zoledronic acid – ACLASTA (CAP) - EMEA/H/C/000595/II/0056

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 11.0) in order to introduce a patient reminder card as an additional risk minimisation measure for the existing identified risk of osteonecrosis of the jaw and to propose indicators to measure the effectiveness of this new measure. Furthermore, the clinical trial exposure data from the Aclasta study ZOL446H2301E2 has been updated
Action: For adoption of PRAC AR

Background

Zoledronic acid is a bisphosphonate indicated for the treatment of osteoporosis in post-menopausal women and in adult men at increased risk of fracture, including those with a recent low-trauma hip fracture. It is also indicated for the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in adult men at increased risk of fracture as well as for the treatment of Paget's disease of the bone in adults.

The PRAC is evaluating a type II variation procedure for Aclasta, a centrally authorised medicine containing zoledronic acid, to update the RMP to reflect, in particular, the introduction of the patient reminder card on the risk of osteonecrosis of the jaw (ONJ). The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP version 11.0 for Aclasta (zoledronic acid) in the context of the variation under evaluation by the PRAC and CHMP could be considered acceptable provided that satisfactory responses to the list of questions detailed in the adopted assessment report are submitted.
- The PRAC considered that the MAH's proposal to measure the effectiveness of the risk minimisation measure for ONJ, consisting of routine monitoring and evaluation of post-marketing and clinical study safety data through PSURs, is acceptable. Nevertheless, the MAH should provide within the next PSUR post marketing rates of ONJ in EU before and after the introduction of the patient card and compared to the rest of the world. The RMP should be updated accordingly. In addition, as a process indicator for the distribution of the patient reminder card, the MAH should also monitor the extent of its delivery through existing tools and processes at EU and local levels.

5.2.4. Zoledronic acid – ZOMETA (CAP) - EMEA/H/C/000336/II/0069

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Submission of an updated RMP to include an additional new minimisation measure (introduction of the patient reminder card) as well as to propose indicators to measure its

effectiveness. The MAH has also taken the opportunity to add the targeted follow-up checklist for the identified risk hypocalcaemia in Annex 7 of the RMP
Action: For adoption of PRAC AR

Background

Zoledronic acid is a bisphosphonate indicated for the prevention of skeletal related events in adult patients with advanced malignancies involving bone and for the treatment of adult patients with tumour-induced hypercalcaemia (TIH).

The PRAC is evaluating a type II variation procedure for Zometa, a centrally authorised medicine containing zoledronic acid, to update the RMP to reflect, in particular, the introduction of the patient reminder card on the risk of osteonecrosis of the jaw and changes to the product information. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP version 10 for Zometa (zoledronic acid) in the context of the variation under evaluation by the PRAC and CHMP could be considered acceptable provided that satisfactory responses to the list of questions detailed in the adopted assessment report are submitted.
- The PRAC considered that the MAH's proposal to measure the effectiveness of the risk minimisation measure for ONJ, consisting of routine monitoring and evaluation of post-marketing and clinical study safety data through PSURs, is acceptable. The RMP should be updated to reflect the changes previously included in the product information on the routine risk minimisation measure for ONJ.

5.3. Medicines in the post-authorisation phase – CHMP-led procedures

See also Annex I. 14.3.

5.3.1. Infliximab – REMICADE (CAP) - EMEA/H/C/000240/II/0188

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4, 4.5, 4.6 and 4.8 of the SmPC in order to include updated pregnancy information following submission of the final report of the Pregnancy and Infant Outcomes Registry and additional reports on infections and agranulocytosis in neonates and infants in utero exposure to Remicade. The Package Leaflet is updated accordingly. Furthermore, the Patient Alert Card which is part of Annex III A is updated accordingly. In addition, the MAH took the opportunity to revise Annex II D to bring it in line with Annex 10 of the RMP. An updated RMP (version 11.0) has been submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

Background

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

The CHMP is evaluating a type II variation procedure for Remicade, a centrally authorised product containing infliximab, to include updated pregnancy information in the product information following the submission of the final report of the Pregnancy and Infant Outcomes registry (PRIORITY) and additional reports on infections and agranulocytosis in neonates and infants who have been exposed to Remicade in utero. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation, following previous advice (see PRAC minutes May 2015).

Summary of advice

- The RMP version 11.1 for Remicade (infliximab) in the context of the variation under evaluation by the CHMP was considered acceptable by the PRAC.
- The PRAC noted the Vaccine Working Party (VWP) report on the recommendations related to the administration of a live vaccine to an infant previously exposed in utero to a TNF inhibitor. The VWP concluded that the existing recommendations are sufficient in the light of the available evidence. Taking this into consideration together with the assessment of the MAH's responses to the list of questions, the PRAC considered that 'BCG[17] breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab' should be added to the safety specifications as an important identified risk. The physician educational programme and the patient alert card will be updated to reflect the risk for BCG breakthrough infection after BCG vaccination in infants who have been exposed to infliximab in utero, for up to six months of age.

5.3.2. Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0024/G

Applicant: Roche Registration Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4, 4.5 and 4.8 of the SmPC in order to update information on the risk of potentiation of radiation toxicity and updating the risk of progression of cancers with RAS mutations with information on progression of pre-existing pancreatic adenocarcinoma with KRAS mutation. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

Background

Vemurafenib is a protein kinase inhibitor indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

The CHMP is evaluating a type II grouped variation procedure for Zelboraf, a centrally authorised product containing vemurafenib, to update the product information on the risk of potentiation of radiation toxicity and on the risk of progression of cancers with RAS mutations with information on progression of pre-existing pancreatic adenocarcinoma with KRAS mutation. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation, following previous advice (see PRAC minutes July 2015).

Summary of advice

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

- The RMP version 8.3 for Zelboraf (vemurafenib) in the context of the variation under evaluation by the CHMP was considered acceptable provided that an updated RMP and satisfactory responses to the PRAC list of questions are submitted.
- The PRAC considered that it was acceptable to add 'potentiation of radiation toxicity' as an important identified risk. In addition, the PRAC considered appropriate to disseminate a DHPC to HCPs to raise awareness of a risk of radiotoxicity in patients, where radiation therapy is indicated. Therefore, the MAH should be requested to submit a draft DHPC with a draft communication plan.

6. Periodic safety update reports (PSURs)

6.1. PSUR procedures including centrally authorised products (CAPs) only

See also Annex I. 15.1.

6.1.1. Agomelatine – THYMANAX (CAP), VALDOXAN (CAP) - PSUSA/00071/201502

Applicant: Servier (Ireland) Industries Ltd, Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and serotonin receptor antagonist (5-HT_{2C} receptor) indicated in adult patients for the treatment of major depressive episodes.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Thymanax and Valdoxan, centrally authorised medicines containing agomelatine, 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 Thymanax and Valdoxan (agomelatine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add 'confusional state' as a new undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should provide a detailed review of the publications by *Bastiampillai et al.*[19] and by *Imboden et al.*[20] and discuss whether akathisia is a safety

[18] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[19] Bastiampillai T, Tibrewal P, Banham KL, Dhillon R. Agomelatine-induced akathisia in a 38-year-old woman with depression. Prim Care Companion CNS Disord. 2014;16(3):PCC.14 l01631

concern associated with agomelatine. The MAH should also provide a detailed review of the publication by *Tan et al.*[21] and discuss whether gynaecomastia is a safety concern associated with agomelatine. In addition, the MAH should perform a detailed review of possible cardiovascular effects of agomelatine and discuss the possible mechanisms by which agomelatine could influence heart rate and blood pressure.

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

6.1.2. Betaine anhydrous – CYSTADANE (CAP) - PSUSA/00390/201502 (with RMP)

Applicant: Orphan Europe S.A.R.L.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Betaine anhydrous belongs to the pharmacotherapeutic group of 'other' alimentary tract and metabolism products and is indicated as an adjunctive treatment of homocystinuria, involving deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylene-tetrahydrofolate reductase (MTHFR) and cobalamin cofactor metabolism (cbl).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cystadane, a centrally authorised medicine containing betaine anhydrous, 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 Cystadane (betaine anhydrous) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to clarify that cases of cerebral oedema were reported only in patients with the CBS subtype. Therefore the current terms of the marketing authorisation(s) should be varied[22].

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. Bosutinib – BOSULIF (CAP) - PSUSA/10073/201503

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

[20] Imboden C, Hatzinger M. Agomelatine-induced akathisia with concomitant duloxetine medication: a case report. Pharmacopsychiatry. 2012;45(4):162-163
[21] Tan HL: Agomelatine-induced gynaecomastia. Aust N Z J Psychiatry 2013; 47(12):1211-2
[22] 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

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Bosutinib is a protein kinase inhibitor indicated for the treatment in adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bosulif, a centrally authorised medicine containing bosutinib, 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 Bosulif (bosutinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add hypertension as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide a detailed analysis of the observed medication errors when the product is cut or crushed, in particular whether this represents a risk to patients. Measures to address the risk of medication error should be proposed as appropriate. In addition, the MAH should provide a detailed discussion of all cases of second primary malignancies. In particular, the MAH should compare frequencies of second primary malignancies in clinical trials between patients treated with bosutinib and those treated with placebo.

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

6.1.4. Brentuximab vedotin – ADCETRIS (CAP) - PSUSA/10039/201502

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Brentuximab vedotin is an antibody drug conjugate (ADC) indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) under certain conditions.

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Adcetris, a centrally authorised medicine containing brentuximab vedotin, 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 Adcetris (brentuximab vedotin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to the EMA, within 90 days, further information regarding the occurrence of hepatotoxicity and should update the product information accordingly as appropriate.
- In the next PSUR, the MAH should provide a detailed discussion on pulmonary toxicity in the monotherapy setting together with any relevant information from PASS study MA25101[24] and AETHERA study (SGN35-005)[25]. In addition, the MAH should provide detailed discussions of cases of weight decrease/weight loss and cases of abdominal pain.

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

6.1.5. Brimonidine – MIRVASO (CAP) - PSUSA/10093/201502 (with RMP)

Applicant: Galderma International

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Brimonidine is a selective alpha$_2$-adrenergic receptor agonist 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.

[24] Observational cohort study of the safety of brentuximab vedotin in the treatment of relapsed or refractory CD30+ Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma
[25] Randomized, double-blind, placebo-controlled phase 3 study of SGN-35 (brentuximab vedotin) and best supportive care (BSC) versus placebo and BSC in the treatment of patients at high risk of residual Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT)

- Nevertheless, the product information should be updated to include hypotension and angioedema as undesirable effects with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[26].
- The MAH should submit to the EMA, within 90 days, a variation to evaluate the proposal for an initial test period for the application of brimonidine. The MAH should include a detailed discussion of the evidence for the effectiveness of a test period and should propose an update of the product information as appropriate. Any other possible measures to minimise the risk of symptom aggravation should be discussed. Finally, the MAH should discuss the potential role of excipients in causing symptom aggravation.
- In the next PSUR, the MAH should further discuss the average duration of treatment and should also provide a discussion on the method for calculation of estimated exposure. In addition, the MAH should provide a detailed analysis of the trends in reporting of events of 'condition aggravated' and to consider whether the product information should be further updated. Moreover, the MAH should provide the final study report for the Phase 4 MIRACLE[27] study and provide a discussion on symptom worsening, including an estimate of the number of patients who experienced 'condition aggravated'.

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. Carglumic acid – CARBAGLU (CAP) - PSUSA/00564/201501 (with RMP)

Applicant: Orphan Europe S.A.R.L.

PRAC Rapporteur: Magda Pedro

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Carglumic acid is an analogue of N-acetylglutamate indicated for the treatment of hyperammonaemia under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Carbaglu, a centrally authorised medicine containing carglumic 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 Carbaglu (carglumic acid) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to underline in the section on 'method of administration' that the medicine is for oral use only (ingestion or via a

[26] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[27] Mirvaso in use study: managing rosacea through assessment and control of its erythema

nasogastric tube using a syringe, if necessary). In addition, rash should be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[28].

- The MAH should submit a cumulative review and analysis of cases of off-label use, lack of efficacy and medication errors, within a year of the finalisation of the current procedure.
- In the next PSUR, the MAH should provide a detailed review of cases of exposure during pregnancy and their outcomes.
- The MAH should amend the RMP as part of the conclusions of this procedure at 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. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC is not required and the EURD list should be updated accordingly.

6.1.7. Collagenase clostridium histolyticum – XIAPEX (CAP) - PSUSA/00871/201502

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Collagenase clostridium histolyticum belongs to the pharmacotherapeutic group of 'other drugs for disorders of the musculo-skeletal system–enzymes' and is indicated for the treatment of Dupuytren's contracture in adult patients with a palpable cord and for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Xiapex (collagenase clostridium histolyticum) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to update the warning on 'corporal rupture (fracture of penis) or other serious injury to the penis in the treatment of Peyronie's disease' to add that surgical intervention may be required in case of signs and symptoms consequential to corporal rupture or severe penile

[28] Update of SmPC sections 4.2 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

haematoma. Therefore the current terms of the marketing authorisation(s) should be varied[29].

- In the next PSUR, the MAH should provide a review on the trigger and outcome of penile rupture on cases with fracture of penis and cases where a fracture can be assumed. The long term outcome with regard to erectile dysfunction, urinary dysfunction or remaining pain is of special interest. In addition, the MAH should provide a definition on severe cases with penile hematoma and explanation on the handling of future cases. Moreover, the MAH should provide a detailed review of cases with peripheral vascular disorders and the possible underlying mechanism of cold intolerance and remaining peripheral vascular disorders. Finally, the MAH should provide further information on the number of cases with serious adverse reactions related to medication errors.

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. Crizotinib – XALKORI (CAP) - PSUSA/10042/201502

Applicant: Pfizer Limited

PRAC Rapporteur: Corinne Fechant

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

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).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xalkori, a centrally authorised medicine containing crizotinib, 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 Xalkori (crizotinib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on cardiac failure to ensure that patients with or without pre-existing cardiac disorders receiving crizotinib, should be monitored for signs and symptoms of heart failure. In addition, cardiac failure should be added as an undesirable effect with a common frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[30].

[29] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[30] 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

- In the next PSUR, the MAH should provide detailed reviews of cases of fracture, pneumothorax, pancreatitis and cases of off-label use. In addition, the MAH should provide a revised review of cases of oesophageal disorders including appropriate causality assessment. Moreover, the MAH should provide a detailed discussion on cases of optic neuropathy, blindness, tumour lysis syndrome, rhabdomyolysis, posterior reversible encephalopathy syndrome (PRES) and venous thromboembolic events. Finally, the MAH should review the publication by *Shaw et al.*[31] as well as cumulative events of decreased blood testosterone from clinical trials and post-marketing sources.

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.

6.1.9. Enzalutamide – XTANDI (CAP) - PSUSA/10095/201502

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Enzalutamide is an androgen receptor signalling inhibitor indicated for the treatment of adult men with metastatic castration-resistant 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 add thrombocytopenia and diarrhoea as undesirable effects with unknown frequencies. Therefore the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH should provide a detailed review of cases of overdose and a proposal to update the product information accordingly, as appropriate. In addition, the MAH should provide a cumulative review of cases of 'ischaemic coronary artery disorders' and cases of 'depression/depression suicidal and completed suicide' and should consider updating the RMP accordingly adding these events as important potential risks. Finally, the MAH should provide a review of any new cases of severe cutaneous adverse reactions (SCARs).

[31] Crizotinib in ROS1-rearranged non-small-cell lung cancer, The New England journal of medicine.,2014;371(21):1963-71
[32] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The 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.

6.1.10. Fingolimod – GILENYA (CAP) - PSUSA/01393/201502

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Gilenya, a centrally authorised medicine containing fingolimod, 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 Gilenya (fingolimod) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to amend the current contraindication in known active malignancies by deleting the exception for patients with cutaneous basal cell carcinoma. In addition, the product information should be updated to amend the current warnings on bradyarrhythmia in order to include T-wave inversion, to include a new warning on basal cell carcinoma, and to amend the current warning on infections to include opportunistic infections. Finally, the product information should be updated to include as new undesirable effects nausea with an uncommon frequency, basal cell carcinoma with a common frequency, lymphoma with a rare frequency, T-wave inversion with a very rare frequency, peripheral oedema with an unknown frequency, and to amend the description of the undesirable effect hypersensitivity reactions, and to update the paragraph relating to infections in the description of selected adverse reactions. Therefore the current terms of the marketing authorisation(s) should be varied[33].
- The MAH should submit in an appropriate regulatory procedure all available data regarding pregnancy after in-utero exposure.
- In the next PSUR, the MAH should address some safety issues and continue to closely monitor some undesirable effects. The MAH should also re-discuss the way to prevent fingolimod dose reduction because of a low lymphocyte count despite the fact that it is

[33] Update of SmPC sections 4.3, 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

not recommended. The study report in primary progressive multiple sclerosis (PPMS) should be provided as soon as finalised. The MAH should also reclassify cases as minor or major malformations according to the EUROCAT[34] classification.

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. Florbetaben (^{18}F) – NEURACEQ (CAP) - PSUSA/10094/201502

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Florbetaben (^{18}F) is a diagnostic radiopharmaceutical indicated for positron emission tomography (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Neuraceq, a centrally authorised medicine containing florbetaben (^{18}F), 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 Neuraceq (florbetaben (^{18}F)) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to the EMA, within 60 days, a variation to update the product information to reflect the data from clinical study 14595[35]. The MAH should also provide a rationale to support each of the proposed additions including separate listing of 'hypertension' and 'procedural hypertension'.

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. Gadoversetamide – OPTIMARK (CAP) - PSUSA/01508/201501

Applicant: Mallinckrodt Deutschland GmbH

PRAC Rapporteur: Almath Spooner

[35] Open-label, non-randomized study to evaluate the efficacy and safety of BAY94-9172 (ZK 6013443) positron emission tomography (PET) imaging for detection/exclusion of cerebral beta-amyloid when compared to post-mortem histopathology

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Gadoversetamide is a chelate containing gadolinium indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver, providing contrast enhancement and facilitating visualisation and helping with the characterisation of focal lesions and abnormal structures in the CNS and liver in adult patients and in children of two years and older with known or highly suspected pathology.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Optimark, a centrally authorised medicine containing gadoversetamide, 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 Optimark (gadoversetamide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include in the undesirable effects section that cases of gadolinium-associated skin plaques with demonstrated sclerotic bodies on histology have been reported with some gadolinium-containing contrast agents in patients who do not otherwise have symptoms or signs of nephrogenic systemic fibrosis. Therefore the current terms of the marketing authorisation(s) should be varied[36].
- The MAH should submit a detailed review of all relevant information on brain accumulation that has become available since the finalisation of the referral procedure along with a discussion of the possible safety implications as previously agreed by the PRAC (see PRAC minutes May 2015).
- In the next PSUR, the MAH should provide some analysis for patterns or trends in post-authorisation patient exposure. Drug Utilisation data, if available, should also be discussed.

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. Gimeracil, oteracil potassium, tegafur – TEYSUNO (CAP) - PSUSA/02875/201501

Applicant: Nordic Group B.V.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

[36] 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

Gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor, oteracil potassium, an orotate phosphoribosyltransferase (OPRT) inhibitor and tegafur, a 5-fluorouracil (5-FU) prodrug are indicated in combination in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Teysuno, a centrally authorised medicine containing gimeracil/oteracil potassium/tegafur, 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 Teysuno (gimeracil/oteracil potassium/tegafur) in the approved indication(s) remains favourable,
- Nevertheless, the product information should be updated to refine the section on 'pregnancy' to state that foetal abnormalities have been reported. Therefore the current terms of the marketing authorisation(s) should be varied[37].

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.

6.1.14. Nalmefene – SELINCRO (CAP) - PSUSA/10120/201502

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Nalmefene is an opioid system modulator indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (DRL), without physical withdrawal symptoms and who do not require immediate detoxification.

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.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to the EMA, within 60 days, a variation to amend the RMP to add 'suicidality' as an important potential risk.

[37] Update of SmPC section 4.6. 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 detailed review of the risk of 'off-label use' and 'drug withdrawal' and propose RMP changes accordingly as appropriate.

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.

6.1.15. Peginterferon beta-1a – PLEGRIDY (CAP) - PSUSA/10275/201501 (with RMP)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Peginterferon beta-1a is an immunomodulating agent indicated in adult patients for the treatment of relapsing remitting multiple sclerosis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Plegridy, a centrally authorised medicine containing peginterferon beta-1a, 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 Plegridy (peginterferon beta-1a) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to the EMA, within 60 days, a detailed review of cases of medication errors. The review should include further details on the proposed corrective and preventative measures including precise action dates for key milestones and a synopsis of the planned usability study relating to the updates to patient information leaflet. In addition, the MAH should provide a detailed review on reported error rates by country and the impact of specific training programmes and materials. Moreover, the MAH should provide a detailed discussion on the impact of medication errors on the effectiveness of the medicinal product, particularly the potential consequences of repeated premature locking of the needle shield (PLNS) in an individual patient. Finally, the MAH should provide long-term injection error rates and discuss whether their increase is related to the worsening of multiple sclerosis-related disability. The MAH should consider updating the RMP accordingly, as appropriate.

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.

6.1.16. Pegloticase – KRYSTEXXA (CAP) - PSUSA/10046/201501

Applicant: Crealta Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Pegloticase is an uricase enzyme conjugated with monomethoxypolyethylene glycol (mPEG) indicated for the treatment of severe debilitating chronic tophaceous gout in adult patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Krystexxa, a centrally authorised medicine containing pegloticase, 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 Krystexxa (pegloticase) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be amended to reflect that close monitoring is required for at least 2 hours instead of 1 hour after the end of infusion to minimise the risk of anaphylaxis, and that delayed-type hypersensitivity reactions have also been reported. In addition, the product information should be refined to emphasize the importance of not taking oral urate-lowering medication before monitoring the serum acid levels, in order to avoid masking the rise of serum uric acid associated with loss of therapeutic efficacy, and placing patients at greater risk of infusion reactions and anaphylaxis.
- In the next PSUR, the MAH should closely monitor all cases consequential to failure to test for glucose-6-phosphate dehydrogenase (G6PD) deficiency such as anaemia and haemolytic anaemia. In addition, the MAH should provide information on the current methods for testing for G6PD deficiency, their sensitivity and specificity and provide proposals for reliable testing. In addition, the MAH should closely monitor cases of worsening/exacerbation of pre-existing congestive heart failure (CHF), cardiac arrhythmias and ischemic events, as well as cases of infections, and further investigate on possible pre-medication before infusion. Moreover, the MAH should closely monitor cases of uric acid level increase and assess the possible relationship with concomitant use of ethambutol. Furthermore, the MAH should provide an explanation for the drug interaction mechanism with ribavirin with regard to antibody development and the effect on patients. Finally, the MAH should provide a detailed review of the publication by *Gentry et al.*[38] on the investigation of pegloticase-associated adverse events.

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

6.1.17. Pemetrexed – ALIMTA (CAP) - PSUSA/02330/201502 (with RMP)

Applicant: Eli Lilly Nederland B.V.

[38] Gentry et al, Investigation of pegloticase-associated adverse events from a nationwide reporting system database. Am J Health Syst Pharm. 2014 May 1;71(9):722-7.

PRAC Rapporteur: Corinne Fechant

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Pemetrexed is a folic acid analogue indicated in combination for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma. It is also indicated in combination for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLCL) other than predominantly squamous cell histology, and as monotherapy for the first line treatment of patients with locally advanced or metastatic NSCLCL other than predominantly squamous cell histology. Finally, it is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic NSCLCL other than predominantly squamous cell histology.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Alimta, a centrally authorised medicine containing pemetrexed, 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 Alimta (pemetrexed) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to specify that haemolytic anaemia reported in patients treated with pemetrexed is immune-mediated. Therefore the current terms of the marketing authorisation(s) should be varied[39].
- The MAH should submit to the EMA, by 31 October 2015, a detailed analysis of cases pertaining to local and systemic scleroderma with a review of pertinent published literature. The MAH should consider updating the product information and RMP accordingly as appropriate.
- The MAH should submit to the EMA, by 31 January 2016, detailed reviews of cases of acute myeloid leukaemia, rhabdomyolysis, posterior reversible encephalopathy syndrome (PRES), leukoencephalopathy, palmar-plantar erythrodysaesthesia as well as cases of atrial fibrillation with a thorough analysis on a possible causal association between cardiac disorders and pemetrexed.
- In the next PSUR, the MAH should provide details in the management of associated hydration together with the review of cases of renal failure. In addition, the MAH should provide a cumulative review of all the fatal cases.
- The MAH should amend the RMP as part of the conclusions of this procedure at 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.

[39] 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

6.1.18. Pomalidomide – IMNOVID (CAP) - PSUSA/10127/201502 (with RMP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Pomalidomide is an immunomodulating agent indicated in combination for 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 refine the warning on arterial thromboembolic to specifically mention that, myocardial infarction and cerebrovascular accident, can occur with pomalidomide in combination with dexamethasone. In addition, myocardial infarction and intracranial haemorrhage should be added as undesirable effects with common frequencies under 'all adverse reactions' and uncommon frequencies under 'grade 3-4 adverse reactions'. Cerebrovascular accident should be also added with an uncommon frequency under 'all adverse reactions' and 'grade 3-4 adverse reactions'. Therefore the current terms of the marketing authorisation(s) should be varied[40].
- The MAH should amend the RMP as part of the conclusions of this procedure at the next regulatory procedure affecting the RMP.
- In the next PSUR, the MAH should discuss the feasibility of meeting the study milestones for the PASS[41] reflected in Annex II of the product information. In addition, the MAH should provide a detailed review of cases of non-melanoma skin cancer and propose an update of the product information and the RMP accordingly, as appropriate. Moreover, the MAH should provide reviews of all cases of viral reactivation.

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.

[40] 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
[41] To conduct a non interventional post authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma to monitor incidence of adverse reactions and to monitor the implementation and compliance of Celgene pregnancy prevention programme and off label use and controlled distribution system on a country basis in agreement with relevant National Competent Authorities

6.1.19. Ranolazine – RANEXA (CAP) - PSUSA/02611/201501

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Ranolazine is a piperazine derivative indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant of first-line antianginal therapies.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ranexa, a centrally authorised medicine containing ranolazine, 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 Ranexa (ranolazine) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add hyponatremia as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[42].

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

6.1.20. Velaglucerase alfa – VPRIV (CAP) - PSUSA/03103/201502 (with RMP)

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Velaglucerase alfa is a glycoprotein indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.

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

Summary of recommendation(s) and conclusions

[42] 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

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Vpriv (velaglucerase alfa) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, an updated RMP to include key elements for educational material as an additional risk minimisation measure, the revised laboratory test requisition form for data on infusion-related reactions (IRR) and lack of efficacy from patients tested for antibodies in line with the MAH's antibody test guideline[43].
- In the next PSUR, the MAH should present additional data and detailed reviews of cases of IRR and antibody testing, the Gaucher Outcome Survey (GOS) and data for all patients enrolled in study VELA-CS-03[44].

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. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

See also Annex I. 15.2.

6.2.1. Orlistat – ALLI (CAP), XENICAL (CAP), NAP - PSUSA/02220/201502

Applicant: Glaxo Group Ltd, Roche Registration Ltd, various

PRAC Rapporteur: Corinne Fechant

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Orlistat is a long-acting inhibitor of gastrointestinal lipases indicated for weight loss in adults with a body mass index (BMI) greater or equal to 30 kg/m² or overweight (body mass index, BMI, ≥28 kg/m2) with associated risk factors and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Alli and Xenical, centrally authorised medicines containing orlistat, and nationally authorised medicines containing orlistat, 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 orlistat-containing medicinal products in the approved indications remains favourable.

[43] Guidelines for Collection, Preparation, and Shipment of Lab Specimens
[44] Open, non-controlled, non-interventional study on home infusion therapy with velaglucerase in Germany and Austria

- Nevertheless, the product information should be updated to include reported cases of reduced efficacy of benzodiazepines, antidepressants, antipsychotics and lithium when associated with orlistat 60 mg, and reduced efficacy of benzodiazepines when associated with orlistat 120 mg in the interaction with other medicinal products and other forms of interactions section. Therefore the current terms of the marketing authorisations should be varied[45].
- In the next PSUR, the MAHs should provide detailed reviews of cases of hepatotoxicity and nephrotoxicity. The MAHs should also discuss all available mechanistic evidence assessing the potential relationship between orlistat and hepatotoxicity, and in particular, provide the available literature in the public domain on the mechanism of action regarding hepatotoxicity as well as proposals for future research to better understand this risk.

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.

6.2.2. Pregabalin – LYRICA (CAP), PREGABALIN PFIZER (CAP), NAP - PSUSA/02511/201501

Applicant: Pfizer Limited, various

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Pregabalin is a gamma-aminobutyric acid analogue indicated for the treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy in adults with partial seizures with or without secondary generalisation and for the treatment of generalised anxiety disorder (GAD) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lyrica and Pregabalin Pfizer, centrally authorised medicines containing pregabalin, and nationally authorised medicines containing pregabalin, 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 pregabalin-containing medicinal products in the approved indications remains favourable.
- The current terms of the marketing authorisations should be maintained.
- The MAH for Lyrica and Pregabalin Pfizer should submit to the EMA, within 60 days, a discussion of positive de-challenge or re-challenge of post-marketing cases reporting a

[45] 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

temporal association between pregabalin use and the occurrence of hyponatraemia/syndrome of inappropriate antidiuretic hormone secretion (SIADH).

- In the next PSUR, the MAHs should provide a detailed review of misuse, abuse and drug dependence, an update on the measures put in place at national level and discuss their impact on reporting rates of abuse, misuse and drug dependence. The MAHs should also provide a detailed review on seizures as a possible consequence of overdose, and should propose an update of the product information accordingly, as appropriate. In addition, the MAHs should present further detailed results from the collaborative study of ENTIS[46] with Motherisk, in which the risks for major birth defects and other pregnancy outcomes were investigated in women exposed to pregabalin during pregnancy, and discuss whether an update of the product information is warranted based on the final results. Moreover, the MAHs should provide a detailed analysis of cases of agranulocytosis, evaluate whether it should be included in the safety specification as an important potential risk and should consider updating the product information accordingly, as appropriate.

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.

6.2.3. Repaglinide – NOVONORM (CAP), PRANDIN (CAP), NAP - PSUSA/02618/201412

Applicant: Novo Nordisk A/S, various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Repaglinide is a short-acting oral secretagogue indicated in adults with type 2 diabetes mellitus under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of NovoNorm, Prandin, centrally authorised medicines containing repaglinide, and nationally authorised medicines containing repaglinide, 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 repaglinide-containing medicinal products in the approved indications remains favourable.
- Nevertheless, the product information should be updated to include a drug-drug interaction with clopidogrel in the section on 'interaction with other medicinal products

[46] European Network of Teratology Information Services

and other forms of interactions'. Therefore the current terms of the marketing authorisations should be varied[47].

- The MAH for NovoNorm and Prandin should submit to the EMA, within 60 days, further data regarding concomitant use with clopidogrel and discuss whether advice that concomitant use of clopidogrel and repaglinide should be avoided needs to be included in the product information. Also, the MAH should comment on the usefulness of performing additional clinical and blood monitoring during concomitant use, both after the administration of a loading dose of clopidogrel and with the use of clopidogrel daily dose of 75 mg. Depending on the outcome of the analysis of these data, the MAH should provide an appropriate variation.
- In the next PSUR, the MAH for NovoNorm and Prandin should present the safety outcomes from studies PR-1111 and SURH1 once finalised.

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.

6.2.4. Rivastigmine – EXELON (CAP), PROMETAX (CAP), RIVASTIGMINE 1A PHARMA (CAP), RIVASTIGMINE HEXAL (CAP), RIVASTIGMINE SANDOZ (CAP), NAP - PSUSA/02654/201501

Applicant: Novartis Europharm Ltd, 1 A Pharma GmbH, Hexal AG, Sandoz GmbH, various

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

Background

Rivastigmine is an acetyl-and butyrylcholinesterase inhibitor of the carbamate type indicated for symptomatic treatment of mild to moderately severe Alzheimer's dementia and for the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Exelon, Prometax, Rivastigmine 1a Pharma, Rivastigmine Hexal and Rivastigmine Sandoz, centrally authorised medicines containing Rivastigmine, and nationally authorised medicines containing rivastigmine, 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 repaglinide-containing medicinal products in the approved indications remains favourable.
- Nevertheless, the product information should be updated to add a warning on bradycardia, a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. In addition, nightmares should be added as an undesirable

[47] 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

effect with an unknown frequency for patch formulations and common frequency for oral formulations. Therefore the current terms of the marketing authorisation(s) should be varied[48].

- In the next PSUR, the MAHs should provide a detailed review of cases of neuroleptic malignant syndrome (NMS), and rhabdomyolysis and cases of overdose. In addition, the MAHs should discuss the causal role of rivastigmine and confounding factors for relevant cases of sudden deaths, torsade de pointes and QT interval prolongation. Moreover, the MAHs should provide a detailed review of cases describing confusion between rivastigmine patches.

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 and published on the European medicines web-portal.

6.3. PSUR procedures including nationally authorised products (NAPs) only

See also Annex I. 15.3.

6.3.1. Altizide, spironolactone (NAP) – PSUSA/02781/201501

Applicant: various

PRAC Lead: Viola Macolić Šarinić

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Altizide is a thiazide diuretic and spironolactone a steroidal antimineralocorticoid. In combination, altizide/spironolactone is indicated for the treatment of congestive heart failure, essential hypertension, hepatic cirrhosis accompanied by oedema and/or ascites, nephrotic syndrome, other oedematous conditions, and in patients taking digitalis when other diuretics are inadequate or inappropriate to maintain electrolyte balance.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing altizide/spironolactone, 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 altizide/spironolactone-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on the concomitant use of medicinal products known to cause hyperkalaemia and on the concomitant use of 'trimethoprim/sulfamethoxazole' with 'altizide/spironolactone' as it may result in severe hyperkalaemia. Moreover, the product information should be

[49] Update of SmPC sections 4.4, 4.5 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

updated to add pemphigoid as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[49].

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.

6.3.2. Androstanolone (NAP) - PSUSA/00212/201412

Applicant: various

PRAC Lead: Corinne Fechant

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Androstanolone is a testosterone metabolite indicated for the treatment of male hypogonadism and gynecomastia as well as for the treatment of lichen sclerosus in both men and women.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing androstanolone, 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 androstanolone-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a detailed analysis of the sales trend by EU member states and the possible relationship with misuse in body-builders and sportsmen. In addition, the MAHs should closely monitor cases of pulmonary embolism. Finally, the MAHs should put in place a survey on misuse in body-builders and sportsmen and provide results in line with the conclusions of this procedure.

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.

6.3.3. Cyproheptadine (NAP) - PSUSA/00000902/201412

Applicant: various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

[49] Update of SmPC sections 4.4, 4.5 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

Cyproheptadine is an antihistaminic drug with antiserotonergic and anticholinergic properties, indicated for allergic and pruritic conditions, for the symptomatic treatment of carcinoid syndrome, by reducing serotonin-induced diarrhoea and flushing, and also as an appetite stimulant.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing cyproheptadine, 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 cyproheptadine-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning to minimise the risk of medication errors with the powder and solvent for oral solution pharmaceutical form and to give instructions on the correct reconstitution of the solution prior to use. Therefore the current terms of the marketing authorisations should be varied[50].
- In the next PSUR, the MAHs should provide detailed reviews on cases of febrile convulsion, abrupt withdrawal of cyproheptadine resulting in serotonin toxicity, apnoea or apnoeic attack, fatal cases as well as on cases in patients suffering from epilepsy.

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.

6.3.4. Delapril (NAP) - PSUSA/00000946/201501

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Delapril is an angiotensin-converting-enzyme (ACE) inhibitor indicated for the treatment of hypertension under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing delapril, 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 delapril-containing products in the approved indication(s) remains favourable.

[50] Update of SmPC sections 4.2 and 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Nevertheless, the product information should be updated to add angioedema, acute renal impairment and hyperkalaemia with unknown frequencies. Therefore the current terms of the marketing authorisation(s) should be varied[51].

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.

6.3.5. Domperidone (NAP) - PSUSA/00001158/20150

Applicant: various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Domperidone is a dopamine-receptor antagonist indicated for the prevention of nausea and vomiting under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing domperidone, 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 domperidone-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should closely monitor cases of cardiac disorders and fatalities, electrocardiogram QT prolonged, extrapyramidal symptoms, neuroleptic malignant syndrome, erythema multiforme, insomnia, eye movement disorders, oculogyric crisis, paradoxical action of domperidone, infants exposed via breastfeeding with a focus on extrapyramidal symptoms as well as patients with Parkinson's disease. In addition, the MAHs should provide a cumulative review and analysis of cases of pregnancy or lactation in accordance with the 'Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data' (EMEA/CHMP/313666/2005). Finally, the MAHs should provide a detailed review of off-label use in gastro-oesophageal reflux in children and lactation stimulation.

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

[51] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.6. 5-Fluorouracil (topical application) (NAP) - PSUSA/00010000/201412

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

5-fluorouracil is a pyrimidine analog indicated for the topical treatment of superficial pre-malignant and malignant skin lesions; keratoses including senile, actinic and arsenical forms; keratoacanthoma; Bowen's disease; erythroplasia of Queyrat; superficial basal-cell carcinoma as well as condyloma acuminata.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing 5-fluorouracil (topical application), 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 5-fluorouracil-containing products (topical application) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add warnings on the need to avoid exposure to ultraviolet (UV)-radiation and use under occlusive dressing. In addition, headache, dizziness and nausea should be also added as undesirable effects with unknown frequencies. Moreover, the product information should be further updated to clarify that it is unlikely that treatment will have any effect on the ability to drive and use machines when used according to the dosage instructions. Therefore, the current terms of the marketing authorisation(s) should be varied[52].
- In the next PSUR, the MAHs should ensure that teratogenicity, photosensitivity, severe application site reactions as well as increased systemic drug exposure and toxicity are listed as important identified risks and herpes zoster as an important potential risk. In addition, the MAHs should provide a review of all cases of herpes zoster. The MAHs should also evaluate whether the interaction with methotrexate is in accordance with medical knowledge and propose to update the product information accordingly as appropriate.
- The MAHs should submit to NCAs a variation including all supportive evidence on 5-fluorouracil topical use in pregnancy, breastfeeding and fertility including pharmacokinetic (PK) data and update the product information accordingly, as appropriate.

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.

[52] Update of SmPC sections 4.4, 4.7, 4.8 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.7. Furosemide (NAP) - PSUSA/00001491/201501

Applicant: various

PRAC Lead: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Furosemide is a loop diuretic indicated for the treatment of congestive heart failure and oedema under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing furosemide, 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 furosemide-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to refine the warning on caution and/or dose reduction requirement regarding symptomatic hypotension leading to dizziness, fainting or loss of consciousness. In addition, dizziness, fainting and loss of consciousness (caused by symptomatic hypotension), acute generalised exanthematous pustulosis (AGEP) and deafness (sometimes irreversible) should be added as undesirable effects with unknown frequencies. Therefore the current terms of the marketing authorisation(s) should be varied[53].

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. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC is not required and the EURD list should be updated accordingly.

6.3.8. Hydrochlorothiazide, ramipiril (NAP) - PSUSA/00001660/201501

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Hydrochlorothiazide is a thiazide diuretic and ramipiril is an angiotensin-converting enzyme (ACE), kinase II inhibitor. In combination, hydrochlorothiazide/ramipiril is indicated for treatment of hypertension in patients whose blood pressure is not adequately controlled with ramipril alone or hydrochlorothiazide alone.

[53] 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 CMDh for adoption of a position

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing hydrochlorothiazide/ramipiril, 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 hydrochlorothiazide/ramipiril-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide detailed reviews of cases of lip malignancies associated with hydrochlorothiazide, drug reaction with eosinophilia and systemic symptoms (DRESS) as well as cases of throat irritation and malaise and propose to update the product information accordingly as appropriate.
- In the next PSUR, the MAH Sanofi-Aventis should closely monitor cases of medication errors and discuss any trend in increasing the potential for medication error.

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.

6.3.9. Hydrochlorothiazide, spironolactone (NAP) - PSUSA/00001662/201501

Applicant: various

PRAC Lead: Viola Macolić Šarinić

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Hydrochlorothiazide is a thiazide diuretic and spironolactone a steroidal antimineralocorticoid. In combination, hydrochlorothiazide/spironolactone is indicated for the treatment of hypertension and oedematous states involved with congestive heart failure, ascitic phase of hepatic cirrhosis and nephrotic syndrome.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing hydrochlorothiazide/spironolactone, 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 hydrochlorothiazide/spironolactone-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add a warning on the concomitant use of medicinal products known to cause hyperkalaemia and on the concomitant use of 'trimethoprim/sulfamethoxazole' with 'hydrochlorothiazide/spironolactone' as it may result in severe hyperkalaemia. Moreover, the product information should be updated to add pemphigoid as an

undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[54].

- In the next PSUR, the MAHs for Aldactazide, Ondolen Forte, Spiridazide, Spironolactone HCTZ Mylan, Spironothiazid should closely monitor cases of mycosis fungoides.

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.

6.3.10. Levonorgestrel (NAP) - PSUSA/00001856/201412

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Levonorgestrel is a second generation progestin (synthetic progesterone) indicated as hormonal contraceptive, alone or in combination. Furthermore, levonorgestrel is indicated for emergency contraception, for the treatment of heavy menstrual bleeding and protection from endometrial hyperplasia during oestrogen replacement therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing levonorgestrel, 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 levonorgestrel-containing products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- The MAHs for levonorgestrel-containing progestin only pills should submit to NCAs, within 90 days, the nationally appropriate procedure to amend the package leaflet with clear and concise information on the Pearl Index.
- The MAH for Mirena and Jaydess should closely monitor cases of arthralgia, breast discharge as well as the possible interaction with lamotrigine and submit to relevant NCAs cumulative reviews within a year of finalisation of this PSUSA procedure.

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.

6.3.11. Lormetazepam (NAP) - PSUSA/00001910/201412

Applicant: various

[54] Update of SmPC sections 4.4, 4.5 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

PRAC Lead: Marianne Lunzer

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Lormetazepam is a benzodiazepine receptor agonist indicated for short term use in moderate to severe insomnia under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing lormetazepam, 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 lormetazepam-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information for oral formulations should be updated to state that a dose reduction should be considered for patients with mild to moderate chronic respiratory insufficiency or hepatic insufficiency. In addition, the product information for intravenous formulations should be updated to add a warning to exercise caution when treating patients with severe hepatic insufficiency as benzodiazepines may precipitate encephalopathy, as well as a warning when lormetazepam is used in patients with mild to moderate hepatic insufficiency, due to the limited pharmacokinetic data available. Therefore the current terms of the marketing authorisation(s) should be varied[55].
- In the next PSUR, the MAHs should discuss the article by *Obiora et al.*[56] and propose an update of the product information accordingly as appropriate. The MAHs should also closely monitor Alzheimer's disease in the context of lormetazepam use. In order to analyse the adverse outcomes in the elderly population, the MAHs are requested to stratify case reports by age. In addition, the MAHs should ensure that 'abuse, dependence and withdrawal reactions', 'psychiatric and paradoxical reactions', 'risk of falling in elderly patients' and 'respiratory depression and coma following overdose' are monitored as important identified risks. Moreover, the MAHs should further evaluate the scientific literature with respect to the consequences of concomitant administration of benzodiazepines with other drug classes (beta-blockers, cardiac glycosides, methylxantines, oral contraceptives and several antibiotics) and update the product information accordingly with further guidance as appropriate. Finally, the MAHs should provide detailed reviews of cases of hypersensitivity reactions.
- In the next PSUR, the MAH Bayer should also provide a review of intentional self-injury/self-injurious behaviour and propose to update the product information accordingly as appropriate. In addition, the MAH should provide further information on parkinsonism and related terms (hypokinesia, tremor) as well as reviews of severe skin reactions, haematologic reactions, hepatobiliary disorders and inappropriate antidiuretic

[55] Update of SmPC section XX. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[56] The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. Eneanya Obiora, Richard Hubbard, Robert D Sanders, Puja R Myles Thorax Online, December 5, 2012, 10.1136/thoraxjnl-2012-202374

hormone secretion. Finally, further information on any non-overdose cases concerning apnoea, bradypnoea, respiratory failure and respiratory arrest should be provided.

- In the next PSUR, the MAH Meda should also provide reviews of cases of severe skin reactions.

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

6.3.12. Methylprednisolone (NAP) - PSUSA/00002026/201411

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure
Action: For adoption of an updated recommendation to CMDh

Background

Methylprednisolone is a glucocorticoid with potent anti-inflammatory and immunosuppressive effects. It is indicated in the treatment of patients with endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, oedematous states, trichinosis, tuberculous meningitis, and cerebral oedema.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing methylprednisolone, and issued a revised recommendation on their marketing authorisations. See PRAC minutes July 2015.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of methylprednisolone-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information of methylprednisolone-containing medicinal products for systemic use should be updated to include a warning on the need for appropriate monitoring of hepatobiliary disorders as well as a warning on caution to apply when using corticosteroids in patients who have or may be predisposed to thromboembolic disorders. In addition, leukocytosis, thrombotic events, epidural lipomatosis, chorioretinopathy and increase of liver enzymes should be added to the product information of medicinal products for systematic use as undesirable effects with unknown frequencies. Moreover, the product information of parenteral formulations should be updated to include hepatitis as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[57].

[57] 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 CMDh for adoption of a position

- In the next PSUR, all MAHs should closely monitor cases of posterior reversible encephalopathy syndrome (PRES). For oral and parenteral formulations, relevant MAHs should provide detail reviews of concomitant administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of corticosteroids, effects of glucocorticoids on hypothyroid patients or patients with hepatic cirrhosis, steroid 'withdrawal syndrome' following abrupt discontinuation of glucocorticoids, interaction with CYP3A4 inhibitors and diltiazem and of tendon ruptures. In addition, the MAHs for parenteral formulations should provide detailed reviews of immunosuppressant effects/increased susceptibility to infections, endocrine effects, ocular effects, influence on blood glucose levels, pre-existing diabetes, and predisposition to diabetes mellitus, psychiatric adverse reactions, use in in patients with seizure disorders and myasthenia gravis, acute myopathy as well as cases of acute pancreatitis.

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.

6.3.13. Phenylephrine (NAP) - PSUSA/00002378/201501

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Phenylephrine is a selective agonist of the α1-adrenergic receptors indicated for increasing blood pressure, inducing mydriasis by contracting the dilating muscle of the pupil, and as a decongestant under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing phenylephrine, 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 phenylephrine-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information for medicinal products containing 50 mg/ml (5%) and 100 mg/ml (10%) phenylephrine for ophthalmic use should be updated to add pulmonary oedema as an undesirable effect in the paediatric population with an unknown frequency. The product information for medicinal products containing 25 mg/ml (2.5%) phenylephrine should be updated to add periorbital pallor in preterm patients as an undesirable effect in the paediatric population with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[58].

[58] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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.

6.3.14. Potassium para aminobenzoate (NAP) - PSUSA/00010130/201502

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For discussion: Preliminary PRAC Rapporteur AR

Background

Potassium para aminobenzoate belongs to the pharmacotherapeutic group of antifibrosis agents and is indicated for the reduction of progression of penile curvature in active induratio penis plastica (IPP/Peyronie's disease) and scleroderma.

The PRAC is currently reviewing the benefit-risk balance of potassium para aminobenzoate–containing products, in the framework of a PSUSA procedure due for PRAC recommendation in October 2015.

Summary of conclusions

The PRAC member of the lead Member State presented the preliminary assessment of the currently ongoing PSUSA procedure. In line with GVP module VII on PSURs, the Committee discussed the different options in preparation for the adoption of the PRAC recommendation in October 2015.

6.3.15. Pseudoephedrine, triprolidine (NAP) - PSUSA/00003047/201412

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Pseudoephedrine is a natural stereoisomer of ephedrine and triprolidine is a competitive histamine H1 antagonist. In combination, pseudoephedrine/triprolidine is indicated for symptomatic treatment of acute, allergic or vasomotor rhinitis if accompanied by nasal congestion under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing pseudoephedrine/triprolidine, 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 pseudoephedrine/triprolidine-containing products in the approved indication(s) remains favourable.

- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide detailed reviews of cases of Kounis syndrome and chorioretinopathy. In addition, cases of off-label use should be closely monitored with a particular focus on use in children.

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.

6.3.16. Roxithromycin (NAP) - PSUSA/00002669/201412

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Roxithromycin is a macrolide indicated for the treatment of upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), skin and soft tissue infections (SSTI) and genital infections under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing roxithromycin, 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 roxithromycin-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide detailed reviews of cases of cardiac arrest, eye disorders, multiorgan failure, septic shock, renal and urinary disorders, skin and subcutaneous tissue disorder, particularly, cases of drug reaction with eosinophilia and systemic symptoms (DRESS) and dermatitis exfoliative. In addition, the MAHs should provide a cumulative review and analysis of cases of pregnancy or lactation in accordance with the 'Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data' (EMEA/CHMP/313666/2005).

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

6.3.17. Tizanidine (NAP) - PSUSA/00002977/201412

Applicant: various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

Background

Tizanidine is a centrally acting skeletal muscle relaxant indicated for painful muscle spasms associated with static and functional disorders of the spine (cervical and lumbar syndromes) and following surgery. Tizanidine is also indicated for spasticity due to neurological disorders.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing tizanidine, 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 tizanidine-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add abdominal pain, vomiting, pruritus, rash, dysarthria and hypersensitivity reactions as undesirable effects with unknown frequencies. Therefore the current terms of the marketing authorisations should be varied[59].
- In the next PSUR, the MAHs should provide reviews of cases of convulsion (seizures), hypoaesthesia and paraesthesia, and propose an update to the product information accordingly as appropriate.

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.

6.3.18. Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium (NAP) – PSUSA/03090/201501

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

Background

Valproic acid is an acidic organic compound, and valproate and related salts and esters are indicated for the treatment of generalised, partial or other epilepsy, and for the treatment of manic episodes under certain conditions. Valproate is also indicated to prevent migraine headaches.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing valproic acid, sodium valproate, valproate

[59] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate and valproate magnesium, 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 valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate and valproate magnesium -containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add obesity as an undesirable effect with a rare frequency. Nail and nail bed disorders should be also added with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[60].
- In the next PSUR, the MAHs should closely monitor cases of dyslipidaemia and metabolic syndrome.

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.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I. 15.4.

6.4.1. Alogliptin – VIPIDIA (CAP) - EMEA/H/C/002182/LEG 009 alogliptin, metformin - VIPDOMET (CAP) - EMEA/H/C/002654/LEG 008 alogliptin, pioglitazone – INCRESYNC (CAP) - EMEA/H/C/002178/LEG 008

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to PSUSA/00010061/201410 following PRAC adoption in April 2015
Action: For adoption of advice to CHMP

Background

Alogliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated, alone or in combination with metformin, a biguanide, or pioglitazone, a thiazolidinedione, in adult patients aged 18 years and older for the treatment of type 2 diabetes mellitus under certain conditions.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicines, the PRAC requested the MAH to submit further data (see PRAC minutes April 2015). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should continue to monitor the feasibility to extend the ongoing drug utilisation study (DUS)[61] for pioglitazone-containing medicinal products to Incresync

[60] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[61] Drug utilisation study on the utilisation of pioglitazone-alogliptin containing medicinal products in clinical practice with regard to diabetic treatment regimen and comorbidities. The objective of this drug utilisation study is to verify the success

(alogliptin/pioglitazone), to measure the effectiveness of its risk minimisation measures. The MAH should provide a status update in each PSUR, including on overview of the patient exposure of Incresync per EU member state.

- The MAH should submit to EMA, within 60 days, an updated RMP including 'heart failure' as an important potential risk for all alogliptin-containing products with close monitoring as a proportionate pharmacovigilance activity.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[62]

See also Annex I 16.1.

7.1.1. Afamelanotide – SCENESSE (CAP) – EMEA/H/C/PSP/0022.1

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Revised PASS protocol for study CUV-PA001: disease registry to assess long-term safety and generate data on the clinical benefits of afamelanotide 16 mg implant in patients with erythropoietic protoporphyria (EPP)
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

Background

Scenesse is a centrally authorised medicine containing afamelanotide, a melanocortin receptor agonist, indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

A revised protocol for a disease registry to assess long term safety data and outcome endpoints and generate data on the clinical benefits of afamelanotide 16 mg implant in patients with EPP, was submitted to the PRAC by the MAH in accordance with the conditions to the marketing authorisation(s).

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 5 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for the above listed medicinal product.

In addition, the MAH should perform pre-testing in several users for the inventory of activity questionnaire prior to the start of the study. Furthermore, the MAH should address the following issues within 90 days:

- An updated study protocol together with the statistical analysis plan (SAP) where the section on data analysis is amended by providing adequate information on the analyses that will be performed.

of the risk minimisation measures for alogliptin/ pioglitazone. Safety concerns addressed: bladder cancer, heart failure, off-label use as first line therapy
[62] In accordance with Article 107n of Directive 2001/83/EC

- A discussion on risk factors and confounders and to describe their handling and incorporation in analyses upon submission of an updated study protocol and SAP.
- The scoring algorithm for the EPP-quality of life (QoL) version 2 questionnaire and inventory of activity questionnaire together with the SAP and the updated study protocol.

7.1.2. Thiocolchicoside (NAP) - EMEA/H/N/PSP/j/0030

Applicant: Sanofi-Aventis Recherche & Développement, various

PRAC Rapporteur: Amelia Cupelli

Scope: Drug utilisation study to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription
Action: For adoption of procedure timetable

Background

Thiocolchicoside is a semi-synthetic sulfurated colchicoside derivative indicated for the treatment of painful muscular contractures in different settings in rheumatological and/or orthopaedic conditions.

In line with the conclusions of a referral under Article 31 of Directive 2001/83/EC conducted by the CHMP in 2013 for thiocolchicoside-containing medicines (EMA/H/A-31/1361), MAHs were required to conduct a post-authorisation safety study (drug utilisation study) to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess the main reasons for prescription of thiocolchicoside. A consortium of MAHs submitted a draft protocol for this study for assessment by the PRAC.

Conclusion

- The PRAC appointed Amelia Cupelli as PRAC Rapporteur for the assessment of the protocol and agreed a timetable for this procedure.

7.1.3. Valproate (NAP) - EMEA/H/N/ PSP/j/0029

Applicant: Sanofi Aventis R&D, various

PRAC Rapporteur: Sabine Straus

Scope: PASS protocol for a drug utilisation study (DUS) to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

Background

Valproic acid is an acidic organic compound, and valproate and related salts and esters are indicated for the treatment of generalised, partial or other epilepsy, and for the treatment of manic episodes under certain conditions. Valproate is also indicated to prevent migraine headaches.

A protocol for a post-authorisation safety study (drug utilisation study) to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate was submitted to the PRAC by a consortium of MAHs in accordance with conditions to the marketing authorisation included in the EC decision Annex IV for the referral under Article 31 of Directive 2001/83/EC (EMA/612389/2014) for valproate-containing medicines.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol, as the Committee considered that that the design of the study did not fulfil the study objectives. The study objectives as proposed by the MAHs do not match with the aims and objectives of the key elements of the risk minimisation measures which were imposed as part of the referral procedure under Article 31 of Directive 2001/83/EC. The MAH should reformulate the aims and objectives to ensure that the study will be able to assess the effectiveness of the imposed risk minimisation measures. To achieve this, the key elements of the approved risk minimisation measures should be taken into account. Furthermore, not all the key elements are likely to be measurable or can be assessed in databases. The MAHs should recognize that the databases are insufficient to collect relevant information for the analyses of the requested outcomes prompted by the circumstances and a healthcare professional survey will be required in addition to the database study, which should be conducted in the same countries as the database study, to better address the measurement of effectiveness of the risk minimisation measures. A number of concerns as described above should be resolved before the final approval of the protocol. The PRAC therefore recommended that:

- The MAH should submit to EMA, within 60 days, a revised PASS protocol. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[63]

See also Annex I. 16.2.

7.2.1. Rituximab – MABTHERA (CAP) - EMEA/H/C/000165/MEA 093

Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope: PASS protocol on long-term surveillance study of rituximab-treated patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)
Action: For adoption of advice to CHMP

Background

Mabthera is a centrally authorised medicine containing rituximab, a genetically engineered chimeric mouse/human monoclonal antibody, indicated for non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), rheumatoid arthritis as well as for granulomatosis with polyangiitis and microscopic polyangiitis under certain conditions.

[63] 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

As part of the RMP for Mabthera, the MAH was required to conduct a PASS to determine the long-term safety of rituximab for the treatment of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). The aim was to better characterize the risk profile of rituximab by collecting safety-focused data in patients with GPA/MPA who have been treated with rituximab or other available therapies. The MAH therefore submitted a draft protocol for such PASS, using data submitted to the UKIVAS as the data source for the RItuximab surveillance study in VASculitis (RIVAS), which has been assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The given milestones are relevant, but 6-monthly data collection and yearly cumulative reporting from the principal investigator to the MAH and yearly inclusion of findings in the PSUR to EMA should be added to those listed.
- Regarding the research objectives the MAH should specify what 'characterize the long term safety' profile implies and add a specific objective: compare the risk of each safety event over time between the rituximab group and the group treated with other agents.
- The proposed RIVAS study design is appropriate for the overall purpose of the study, but the MAH should clarify how exposure will be estimated, explain how to handle switchers and patients only treated for a short period in the analysis, provide details with regard to selection of the control group, clarify whether a stratification of patients is envisaged, and provide a statistical analysis plan. The PRAC considered that the UKIVAS database appears to be an appropriate data source for the study, but the MAH is requested to clarify a number of points.
- The study protocol for this PASS could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA within 60 days.

7.2.2. Vernakalant – BRINAVESS (CAP) - EMEA/H/C/001215/MEA 026

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to PASS protocol for vernakalant intravenous (IV) sterile concentrate prospective safety registry study: a prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant IV sterile concentrate (study 6621 049-00)
Action: For adoption of advice to CHMP

Background

Brinavess is a centrally authorised medicine containing vernakalant, an antiarrhythmic, indicated for the rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults under certain conditions.

As part of the RMP for Brinavess, the MAH was required to conduct a PASS to characterise normal conditions of use, dosing and safety following administration of vernakalant. The aim was to estimate the incidence of the following medically significant health outcomes of

interest (HOIs) reported during treatment: significant hypotension, sustained ventricular tachycardia (VT), torsade de pointes (TdP), ventricular fibrillation of any duration, significant atrial flutter and significant bradycardia, to investigate the potential risk of overdose and medication error and to evaluate the effectiveness of the risk minimisation activities. The MAH submitted an updated protocol for a prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant intravenous (IV) sterile concentrate (SPECTRUM registry) which has been assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for this PASS could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA within 60 days.
- The MAH should provide more details on the enrolment rate regarding the proposal to extend the study duration by one year. The actual enrolment number should be compared with the expected number, and strategies to ensure the sufficient enrolment in the proposed extension should be discussed. Alternative solutions (such as adding extra study sites and/or more countries) should be considered and discussed as well. In addition, the MAH should justify the choice to exclude two countries from the study.
- With the newly proposed amendments, some difficulties were noted regarding the study conduct in Germany and compliance with German national legislation that would impair further study conduct in Germany. Therefore, a national German amendment of the protocol needs to be introduced to allow further conduct of the study in Germany.

7.3. Results of PASS imposed in the marketing authorisation(s)[64]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[65]

See Annex I.16.4.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[66]

See also Annex I. 16.5.

7.5.1. Data collection on adverse events of anti-HIV[67] drugs (D:A:D) study - PRAC evaluation of D:A:D data merger results

Applicant: various

PRAC Representatives: Filip Josephson, Deborah Ashby

[64] In accordance with Article 107p-q of Directive 2001/83/EC
[65] 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
[66] In line with the revised variations regulation for any submission before 4 August 2013
[67] Human immunodeficiency virus

Scope: Evaluation of the fifteen data merger
Action: For adoption of advice to CHMP

Background

The PRAC discussed the assessment of the D:A:D[68] study's 15th data merger - relating mainly to the relative safety of antiretroviral therapy – performed by the EMA representatives on the Highly Active Antiretroviral Therapy (HAART) Oversight Committee. The ongoing regulatory areas of special interest with the D:A:D study include the association of antiretroviral drug exposure with cardiovascular, renal, end stage liver disease (ESLD) and cancer endpoints.

Summary of advice

- The PRAC discussed various findings relating to the risks under investigation in the cohort and concluded that the 15th data merger does not contain any data that would require further questions to be put to the D:A:D study investigators, or any other regulatory action.

7.6. Other

See also Annex I. 16.6.

7.6.1. Ketoconazole – KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/ANX 002.1

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Viola Macolic Sarinic

Scope: MAH's responses to ANX 002 [results of ercusyn feasibility study] as adopted in May 2015
Action: For adoption of advice to CHMP

Background

Ketoconazole HRA is a centrally authorised medicine containing ketoconazole, a steroidogenesis inhibitor, indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

As part of the RMP for Ketoconazole HRA, a post-authorisation study (PASS) is requested to collect clinical information on patients with Cushing's syndrome exposed to ketoconazole (preferably utilising the existing *European Registry on Cushing's syndrome (ERCUSYN) registry where feasible*), to assess drug utilisation patterns and to document the safety and effectiveness of ketoconazole (category 1 study).

As requested by the PRAC, the MAH submitted their responses to the list of questions adopted in May 2015 along with a revised study report of the feasibility of adding safety items to the existing ERCUSYN[69] database. For further background, see PRAC minutes May 2015.

[68] D:A:D is a large prospective 'meta-cohort' studying outcomes in patients with HIV infection, most of whom receive antiretroviral therapy
[69] European register on Cushing's syndrome

Summary of advice

- Taking into account all available data submitted by the MAH on the ERCUSYN feasibility study, including the positive feedback from the last investigators' meeting with physicians participating in the ERCUSYN registry held in May 2015, the proposed study to collect clinical information in patients with Cushing's syndrome exposed to ketoconazole using ERCUSYN registry was considered feasible by the PRAC.
- There are several outstanding issues which the MAH should address in the study protocol. In particular, the MAH should clarify whether information describing 'liver function tests' and 'ECG/blood pressure' concerns all visits, regardless of whether results were normal or not. In addition, the MAH should ensure that any data relating to additional countries where Ketoconazole HRA is placed on the market during the course of the study, can be entered in the registry.

8. Renewals of the marketing authorisation, conditional renewal and annual reassessments

8.1. Annual reassessments of the marketing authorisation

See Annex I.17.1.

8.2. Conditional renewals of the marketing authorisation

None

8.3. Renewals of the marketing authorisation

8.3.1. Cabazitaxel – JEVTANA (CAP) - EMEA/H/C/002018/R/0030 (with RMP)

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Corinne Fechant

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of advice to CHMP

Background

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

Jevtana, a centrally authorised medicine containing cabazitaxel, was authorised in 2011.

The MAH submitted an application for the renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this five year-renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Jevtana and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal

of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds relating to the risk of neutropenia and its complications, and to the risk of bleeding and respiratory disorders, that should continue to be closely monitored. In addition, the post-marketing phase III study EFC11785[70] is still ongoing and the results are expected to yield important new safety and efficacy data to optimize cabazitaxel dosage. With regard to the RMP, the MAH should reclassify study EFC11785 as a category 3 study.

8.3.2. Fingolimod – GILENYA (CAP) - EMEA/H/C/002202/R/0036 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of advice to CHMP

Background

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

Gilenya, a centrally authorised medicine containing fingolimod, was authorised in 2011.

The MAH submitted an application for the renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this five year-renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Gilenya and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds. Uncertainties remain in the knowledge of some unfavourable effects, in particular regarding the immunosuppressive effects that need to be closely monitored. Moreover, several safety issues including acute disseminated encephalomyelitis (ADEM)-like events, malignant neoplasms, sudden unexplained death, thromboembolic events, atypical multiple sclerosis relapse and long-term exposure should continue to be closely monitored. The RMP is acceptable.

See also under 6.1.10.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

[70] Randomized, open label multicentre study comparing cabazitaxel at 20 mg/m² and at 25 mg/m² every 3 weeks in combination with prednisone for the treatment of metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen (PROSELICA)

9.2. Ongoing or concluded pharmacovigilance inspections

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

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Mycophenolate mofetil – CELLCEPT (CAP) – EMEA/H/C/000082/II/0121

Applicant: Roche Registration Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.4 and 4.6 of the SmPC in order to add a warning for pregnant women and update the safety information related to pregnancy
Action: For adoption of advice to CHMP

Background

Mycophenolate mofetil is an immunosuppressive agent indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

A type II variation proposing to update the product information of Cellcept on safety information related to pregnancy is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC noted the latest information on the risk of congenital malformations and spontaneous abortions, while also considering the maintenance of access to this widely used and important medicine with appropriate safeguards.
- The PRAC advised updating the product information to reflect that mycophenolate mofetil should not be used during pregnancy unless no suitable alternative is available and that repeat pregnancy tests should be performed as clinically required. The other proposed changes by the CHMP to document product information in the pregnancy section are supported by the PRAC. The PRAC also supported disseminating communication to a broader HCP community than just to transplantologists as off label use exist in diverse auto-immune diseases. The PRAC also advised to update the EURD list to align the requirements in terms of PSUR submission for mycophenolate mofetil and all mycophenolic acid-containing products and supported requesting yearly PSURs, including detailed reviews of pregnancy cases. In addition, pregnancy cases should be followed up with a specific questionnaire in order to gain more understanding of the circumstances and details of exposure during pregnancy and outcome. Finally, the PRAC

advised requesting the MAH to develop educational material dedicated for HCPs and to patients to support the update advice.

10.2. Timing and message content in relation to Member States' safety announcements

None

10.3. Other requests

10.3.1. Antiretroviral medicinal products: Abacavir –ZIAGEN (CAP) - EMEA/H/C/000252/LEG 089.1; abacavir, lamivudine – KIVEXA (CAP) - EMEA/H/C/000581/LEG 045.1; abacavir, lamivudine, zidovudine – TRIZIVIR (CAP) - EMEA/H/C/000338/LEG 090.1; atazanavir– REYATAZ (CAP) - EMEA/H/C/000494/LEG 080.1; darunavir – PREZISTA (CAP) - EMEA/H/C/000707/LEG 070.1; efavirenz – STOCRIN (CAP) - EMEA/H/C/000250/LEG 071.1, SUSTIVA (CAP) - EMEA/H/C/000249/LEG 080.1; efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/LEG 040.1; elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP) - EMEA/H/C/002574/LEG 014.1; emtricitabine – EMTRIVA (CAP) - EMEA/H/C/000533/LEG 049.1; emtricitabine, tenofovir disoproxil – TRUVADA (CAP) - EMEA/H/C/000594/LEG 043.1; emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/LEG 031.1; etravirine – INTELENCE (CAP) - EMEA/H/C/000900/LEG 048.1; fosamprenavir – TELZIR (CAP) - EMEA/H/C/000534/LEG 076.1; indinavir – CRIXIVAN (CAP) - EMEA/H/C/000128/LEG 039.1; lamivudine – EPIVIR (CAP) - EMEA/H/C/000107/LEG 052.1, LAMIVUDINE VIIV (Art 58) - EMEA/H/W/000673/LEG 007.1; lamivudine, zidovudine – COMBIVIR (CAP) - EMEA/H/C/000190/LEG 038.1; lopinavir, ritonavir –ALUVIA (Art 58) - EMEA/H/W/000764/LEG 031.1, KALETRA (CAP) - EMEA/H/C/000368/LEG 118.1; nevirapine – VIRAMUNE (CAP) - EMEA/H/C/000183/LEG 061.1; rilpivirine – EDURANT (CAP) - EMEA/H/C/002264/LEG 026.1; ritonavir – NORVIR (CAP) - EMEA/H/C/000127/LEG 049.1; saquinavir – INVIRASE (CAP) - EMEA/H/C/000113/LEG 065.1; stavudine – ZERIT (CAP) - EMEA/H/C/000110/LEG 060.1; tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/LEG 270.1; tipranavir - APTIVUS (CAP) - EMEA/H/C/000631/LEG 068.1

Applicant: 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)

PRAC Rapporteur (lead): Qun-Ying Yue; PRAC Co-Rapporteur: Isabelle Robine; Julie Williams

Scope: Review of class labelling on mitochondrial dysfunction, lactic acidosis and lipodystrophy
Action: For adoption of advice to CHMP

Background

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are a class of antiretroviral agents indicated for the treatment of patients affected by the human immunodeficiency virus (HIV) under certain conditions.

In the context of the ongoing procedures initiated in July 2014 reviewing the new evidence with respect to mitochondrial toxicity, lactic acidosis and lipodystrophy of relevant antiretroviral medicines and their impact on the product information, the PRAC reviewed the assessments and was requested to provide advice to the CHMP. For further background, see PRAC minutes March 2015.

Summary of advice and conclusion(s)

Following the PRAC advice dated March 2015 to consult the Scientific Advisory Group (SAG) HIV/viral diseases, the Committee was provided with a preliminary feedback from the SAG held on 7 September 2015. With regard to the reviews on lipodystrophy and on lactic acidosis, the PRAC discussed the proposals to update the product information and the regulatory way forward which will be further revised based on the SAG recommendation. As for the review of mitochondrial toxicity, the PRAC acknowledged that supplementary information on the MITOC[71] study was deemed necessary before drawing any conclusions. A full report from the SAG HIV/viral diseases will be provided to PRAC in October 2015 where the Committee will confirm the next milestones.

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

MAH(s): GlaxoSmithKline Biologicals S.A. (Cervarix), Sanofi Pasteur MSD SNC (Gardasil), Merck Sharp & Dohme Limited (Silgard)

PRAC Rapporteurs: Jean-Michel Dogné (Cervarix), Qun-Ying Yue (Gardasil, Silgard)

Scope: PRAC consultation on the preliminary results of a pharmacoepidemiological study on the safety-in-use of human papillomavirus vaccines (HPV)
Action: For adoption of advice to CHMP

Background

Human papillomavirus vaccines are indicated for the prevention of premalignant genital (cervical, vulvar and vaginal) lesions and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) types. Other indications include the active immunisation against premalignant lesions and cancer affecting the anus as well as against genital warts *(condyloma acuminata)* causally related to specific HPV types.

The PRAC was presented the preliminary results of a pharmacoepidemiology study conducted jointly by the French Medicines Agency (ANSM) and the French National Health Insurance Fund (CNAMTS) comparing the incidence of autoimmune conditions in a large cohort of girls aged 13 to 16 years given HPV vaccines with the incidence in girls of the same age group not given the vaccines.

Summary of advice

[71] European study sponsored by the Collaborative Committee for Mitochondrial Toxicity in Children [MITOC]

- Based on the available data, the PRAC noted that the results showed no overall increase in the risk of autoimmune conditions amongst girls given HPV vaccination. The increased incidence of GBS amongst those exposed to HPV vaccine compared with those not exposed was also noted. Nevertheless, the limited information available did not allow the PRAC to draw conclusions on the level of evidence for this observed increase.

10.3.3. Saxagliptin – ONGLYZA (CAP) – EMEA/H/C/001039/LEG 038.1; saxagliptin, metformin - KOMBOGLYZE (CAP) – EMEA/H/C/002059/LEG 015.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: PRAC consultation on the assessment of data on mortality from the SAVOR study
Action: For adoption of advice to CHMP

Background

Saxagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated in adult patients aged 18 years and older for the treatment of type 2 diabetes mellitus under certain conditions. Saxagliptin in combination with metformin, a biguanide, is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets.

In May 2015, the CHMP requested advice from the PRAC, based on the newly available FDA analyses relating to the SAVOR[72] study and on the assessment of the MAH's responses to a CHMP list of questions. In September 2015, the PRAC provided further advice to the CHMP following the assessment of the MAH's responses to a second list of questions.

Summary of advice

- Based on the review of the MAH's responses to a second list of questions and the CHMP's assessment, the PRAC agreed that the MAH's responses provide some explanations about the results of all-cause mortality and fatal infections observed in the studies. However, the results of the SAVOR study regarding all-cause mortality and non-cardiovascular (CV) death cannot be dismissed with complete certainty at this stage and the PRAC advised to update the product information accordingly with the study data on mortality.

[72] Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) study: large, randomised, double-blind, placebo-controlled postmarketing study designed to evaluate the cardiovascular effects of Onglyza when added to current type 2 diabetes background therapy in adult patients with type 2 diabetes mellitus at risk for cardiovascular disease

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Androstanolone (NAP)

Applicant: Besins Healthcare (Andractim), various

PRAC Lead: Corinne Fechant

Scope: PRAC consultation on the relevance of the PRAC recommendation on testosterone and cardiovascular safety from the article 31 referral for androstanolone
Action: For adoption of advice to Member States

Background

Androstanolone is a testosterone metabolite indicated for the treatment of male hypogonadism and gynecomastia as well as for the treatment of lichen sclerosus in both men and women.

In 2014, the PRAC reviewed the cardiovascular safety of testosterone-containing products in the framework of a safety referral under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1396). The PRAC concluded, and the CMDh confirmed, that there was no consistent evidence of an increased risk of heart problems associated with testosterone-containing medicines. The PRAC recommended updating the product information in line with the latest evidence, to provide warnings about those who might be at increased risk of heart problems and to make clear that testosterone should only be used when an abnormally low level of the hormone has been confirmed by signs and symptoms and appropriate laboratory tests. In addition, it was recommended to update the product information to reflect that there is limited data on safety and effectiveness of testosterone-containing products in patients over 65 years of age, that testosterone levels decrease with age and that age-specific testosterone reference values do not exist.

Considering that androstanolone is a metabolite of testosterone, France requested PRAC advice on the relevance of reflecting the product information changes concluded in the recent safety referral in the product information of androstanolone-containing products.

Summary of advice

- Based on the currently available information, the PRAC considered that, at present, the available data are insufficient to draw any firm conclusions regarding the similarity or difference in terms of metabolism and clinical impact of the metabolism between testosterone and androstanolone. The PRAC agreed to seek input from the Pharmacokinetics Working Party (PKWP) before concluding its advice to Member States. Further discussion at the PRAC is preliminary scheduled in December 2015.

  See also under 6.3.2.

11.2. Other requests

11.2.1. Antiretroviral medicinal products (NAP)

Applicant: Teva Pharma B.V., Mikle-Pharm GmBH

PRAC Rapporteur: Martin Huber

Scope: PRAC consultation on initial marketing authorisation applications for generic medicinal products and the need for the applicants to participate in the Antiretroviral Pregnancy Registry
Action: For adoption of advice to Member States

Background

Antiretroviral agents are indicated for the treatment of patients affected by the human immunodeficiency virus (HIV) under certain conditions.
The Antiretroviral Pregnancy Registry (APR) was set up to provide an early signal of any major teratogenic effect associated with a prenatal exposure to the antiretroviral medicinal products monitored through the registry. All originator medicinal products participate in the registry and their product information, in particular, section 4.6 entitled 'fertility, pregnancy and lactation' is updated with any relevant information as appropriate.
In the context of the evaluation of marketing authorisation applications for generic medicinal products at national level, Germany sought the advice of the PRAC regarding the relevance for all MAHs and applicants of generic medicinal products to participate in the registry.

Summary of advice

- Based on the review of the available information, the PRAC considered that further information on the APR data collection, participating MAHs and the report generation was necessary before any advice can be reached.

Follow-up discussion at the PRAC is scheduled in October 2015.

11.2.2. Quetiapine (NAP) - NL/H/PSUR/0021/005

Applicant: AstraZeneca (Seroquel), various

PRAC Lead: Sabine Straus

Scope: PRAC consultation on a PSUR worksharing procedure regarding a signal of possible misuse and abuse
Action: For adoption of advice to Member States

Background

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

In May 2014, the PRAC discussed a signal of possible misuse and abuse following communication with the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and an analysis conducted in EudraVigilance. The PRAC considered the

seriousness and potentially life-threatening nature of possible misuse and abuse of quetiapine and the MAH of the originator product (Seroquel) was requested to provide in the PSUR (DLP: 31/07/2014), a cumulative review for both the immediate release (IR) and the extended release (XR) formulations. For further background, see PRAC minutes May 2014.

In the context of the evaluation of the PSUR worksharing procedure, Netherlands requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC agreed that the MAH for Seroquel should conduct a detailed review of the totality of the available literature regarding quetiapine associated with misuse and abuse, including a discussion on the risk factors of misuse and abuse. The MAH should also provide the country of origin for all cases and further justify why some cases were identified as serious. Based on these analyses, the MAH should propose to update the product information accordingly as appropriate.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC assessors training course – draft agenda

Action: For discussion

At the organisational matters teleconference on 24 September 2015, the EMA Secretariat presented to the PRAC the draft agenda for the 2015 PRAC assessors training course due to take place in November 2015.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

12.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

12.3.1. Post-authorisation efficacy studies (PAES) – regulatory and procedural questions and answers document

Action: For discussion

At the organisational matters teleconference on 24 September 2015, the EMA Secretariat presented the draft regulatory and procedural questions and answers (Q&A) document on post-authorisation efficacy study (PAES) developed in parallel of the draft scientific guidance on PAES. This Q&A document is aimed at clarifying practical implementation aspects of the imposition of PAES in accordance with the Commission Delegated Regulation (EU) No 357/2014 which came into force in 30 April 2014 and will complement the existing EMA post-authorisation procedural advice for users of the centralised procedure. It focuses on the imposition of PAES, submission and assessment of draft protocols and on the

submission and assessment of final study results. This draft document was previously presented to CHMP, CAT and the CMDh in July 2015 and will be published promptly.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

12.6. Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2016 - development

Action: For discussion

At the organisational matters teleconference on 24 September 2015, the EMA Secretariat presented to the PRAC a short update on the development of the draft 2016 PRAC work plan.

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

12.10. Periodic safety update reports (PSURs) & Union reference date (EURD) list

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Margarida Guimarães
Action: For discussion

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and welcomed the progress being made.

12.10.3. PSURs repository

None

12.10.4. Union reference date list – consultation on the draft list

Action: For adoption

The PRAC endorsed the draft revised EURD list version September 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 September 2015, the updated EURD list was adopted by the CHMP and CMDh at their September 2015 meeting and published on the EMA website on 06/10/2015, 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)

12.11. Signal management

12.11.1. Signal management – feedback from Signal Management Review Technical (SMART) Working Group

PRAC lead: Sabine Straus
Action: For discussion

At the organisational matters teleconference on 24 September 2015, the PRAC was updated on the outcome of the September 2015 SMART Working Group (SMART WG). The SMART WG discussed concurrent submission of safety variations by the innovator and generic medicinal products as requested by the PRAC in the context of signal assessment and following agreement at the level of CMDh and EMA levels on the timelines recommended by the PRAC for submission of variations. This agreement is valid provided that the PRAC recommendation is made at the substance level and provides with the exact wording to be implemented in the product information, that the MAH of the innovator product has been consulted beforehand on the proposed wording during the signal procedure and ahead of the final PRAC recommendation and that the text of the product information update agreed by the PRAC is translated in all EU languages and published on the EMA website. The SMART WG also discussed the handling of MAH's signals (follow-up from the July 2015 SMART WG). Further reflection is needed on signal confirmation and it will be taken into account in the ongoing revision of GVP module IX on 'Signal Management'. Some aspects on the level of

access of EudraVigilance by MAHs were also discussed, this will be taken into account as part of the ongoing revision of the EudraVigilance access policy. Finally, the PRAC was updated on the signal detection workshop that EMA organises in December 2015.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

12.12.3. List of products under additional monitoring – consultation on the draft list

Action: For adoption

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

Post-meeting note: The updated additional monitoring list was published on 30/09/2015 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

12.13.1.1. EudraVigilance stakeholder change management plan

Action: For discussion

At the organisational matters teleconference on 24 September 2015, the EMA Secretariat presented to the PRAC the draft EudraVigilance stakeholder change management plan. In accordance with Regulation (EC) 726/2004 as amended, EMA should set up and maintain a Pharmacovigilance database and data processing network (EudraVigilance database) indeed in support of the EudraVigilance auditable requirements which were endorsed by the EMA management board in December 2013. The document details the changes applied to EudraVigilance and to the process of reporting individual case safety reports (ICSR) and suspected unexpected serious adverse reactions (SUSAR) that will be implemented as part of the 'EudraVigilance auditable requirements' project. It details the IT and business changes made at stakeholder level and its intended audience is the national competent authorities, MAHs, clinical trials sponsors and EMA. This change management plan includes key milestones such as the publication of the revised EudraVigilance access policy in Q1 2016, the EudraVigilance audit planned in Q2/Q3 2016, followed by the acceptance by EMA of R3 format messages mid-2017, implementation if the ICSR routing change and the revised EudraVigilance access policy. PRAC delegates were invited to provide comments by 23 September 2015. A follow-up discussion is planned at PRAC in October 2015.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

12.14.1.1. Good Pharmacovigilance Practice (GVP) Module V and Risk Management Plans template for industry - updates

Action: For discussion

At the organisational matters teleconference on 24 September 2015, the EMA Secretariat presented to the PRAC an update on the ongoing revision of the GVP module V on Risk Management systems including the comments received from the PRAC. Some changes in terms of terminology, principles and responsibilities as well as on the RMP structure have been implemented. In parallel the RMP template for industry has also been revised to get aligned with the ongoing GVP module V revision. The draft revised GVP module V, once adopted by Project and Maintenance Group 2, will be released for a 2 months public consultation.

12.14.1.2. Summaries of risk management plans (RMP) - report on pilot testing

Action: For discussion

At the organisational matters teleconference on 24 September 2015, the EMA Secretariat presented to the PRAC an analysis of the 1-year pilot phase on the publication of RMP summaries. The pilot started in March 2014 for all the new medicines authorised since March 2014. 84 RMP summaries have been published so far and the analysis showed an interest from various stakeholders in these published RMP summaries, however expectations were various based on the category of stakeholders. These RMP summaries should be living documents (updated throughout the product life-cycle) according to the stakeholders feedback received. Based on this analysis, the EMA Secretariat will consider how to simplify the process, the content and structures of these RMP summaries as well as publishing them at the same time as the EPAR.

12.14.2. Tools, educational materials and effectiveness measurement of risk minimisations

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

12.15.2. Post-authorisation Safety Studies – non-imposed PASS

None

12.15.3. Post-authorisation Safety Studies and additional monitoring imposed to originator products - applicability to generic products

Action: For discussion

At the organisational matters teleconference on 24 September 2015, the EMA Secretariat presented to the PRAC a proposal for a systematic reflection when imposing a PASS on an originator product on the consequences for the generics medicines already authorised, under evaluation or to be filed in the coming months or years and whether there is a scientific rationale for also imposing a PASS on generics. A proposal of criteria where a PASS should also be imposed on the generics will be developed by EMA and presented to the PRAC in the coming months. This was welcomed by the PRAC.

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

13. Any other business

13.1. Good Pharmacovigilance Practice (GVP) Chapter P.II. on biologicals

PRAC lead: Sabine Straus, Philip Bryan
Action: For discussion
The topic was deferred to the October 2015 PRAC meeting.

13.2. Good Practice Guide (GPG) on medication errors - GPG on recording, coding, reporting and assessment of medication errors (GPG I); GPG on risk minimisation and prevention of medication errors (GPG II) and GPG on risk minimisation and prevention of medication errors, addendum on risk minimisation strategy for high

strength and fixed combination insulin products (GPG II Addendum)

PRAC lead: Filip Babylon
Action: For adoption

The EMA Secretariat presented to the PRAC the three draft revised Good Practice Guide (GPG) on medication errors following the public consultation:

- GPG on recording, coding, reporting and assessment of medication errors (GPG I),
- GPG on risk minimisation and prevention of medication errors (GPG II),
- GPG on risk minimisation and prevention of medication errors, addendum on risk minimisation strategy for insulin medicinal products high-strength and fixed combination (GPG II Addendum).

The PRAC was presented an overview of the key topics following the public consultation along some specific questions to be addressed by the PRAC. The PRAC endorsed the three drafts revised GPG on medication errors.

13.3. Good Pharmacovigilance Practice (GVP) Module XII on safety-related actions on authorised medicinal products

Action: For discussion

At the organisational matters teleconference on 24 September 2015, the EMA Secretariat presented to the PRAC the draft GVP module on safety-related actions on authorised medicinal products. The PRAC suggested integrating the feedback from Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE)'s work package 8 on lifecycle pharmacovigilance into this module. Considering the comments raised by the PRAC, a follow-up discussion is scheduled in October 2015.

14. Annex I – Risk Management Plans

14.1. Medicines in the pre-authorisation phase

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

14.1.1. Aripiprazole - EMEA/H/C/004021

Generic

Scope: Treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.2. Blinatumomab - EMEA/H/C/003731, Orphan

Applicant: Amgen Europe B.V.

Scope: Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.3. Brivaracetam - EMEA/H/C/003898

Scope: Treatment of partial-onset seizures
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.4. Carfilzomib - EMEA/H/C/003790, Orphan

Applicant: Amgen Europe B.V.

Scope: Treatment of multiple myeloma
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.5. Cinacalcet - EMEA/H/C/004014

Generic

Scope: Treatment of secondary hyperparathyroidism and hypercalcaemia
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.6. Dapaglifozin - EMEA/H/C/004161

Scope: Treatment of diabetes mellitus type 2
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.7. Dapaglifozin, metformin - EMEA/H/C/004162

Scope: Treatment of diabetes mellitus type 2
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.8. Efmoroctocog alfa - EMEA/H/C/003964, Orphan

Applicant: Biogen Idec Ltd

Scope: Treatment of haemophilia A
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.9. Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - EMEA/H/C/004042

Scope: Treatment of human immunodeficiency virus (HIV)-1
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.10. Eptifibatide - EMEA/H/C/004104

Generic

Scope: Prevention of early myocardial infarction
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.11. Etanercept - EMEA/H/C/004007

Biosimilar

Scope: Treatment of arthritis
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.12. Fentanyl - EMEA/H/C/002715

Scope: Treatment of acute moderate to severe post-operative pain
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.13. Ferric maltol - EMEA/H/C/002733

Scope: Treatment of iron deficiency anaemia
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.14. Glycerol phenylbutyrate - EMEA/H/C/003822, Orphan

Applicant: Horizon Therapeutics Limited

Scope: Treatment of patients with urea cycle disorders
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.15. Human fibrinogen, human thrombin - EMEA/H/C/003914

Scope: Supportive treatment for improvement of haemostasis and as a suture support in vascular surgery
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.16. Levodopa, carbidopa - EMEA/H/C/002611

ScopeL: Treatment of Parkinson's disease
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.17. Lumacaftor, ivacaftor - EMEA/H/C/003954, Orphan

Applicant: Vertex Pharmaceuticals (U.K.) Ltd.

Scope: Treatment of cystic fibrosis
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.18. Mepolizumab - EMEA/H/C/003860

Scope: Treatment of asthma
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.19. Mercaptamine - EMEA/H/C/003769, Orphan

Applicant: Orphan Europe S.A.R.L.

Scope: Treatment of cystinosis
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.20. Mercaptamine - EMEA/H/C/004038, Orphan

Applicant: Lucane Pharma

Scope: Treatment of corneal cystine deposits
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.21. Octocog alfa - EMEA/H/C/004147; EMEA/H/C/003825

Scope: Treatment and prophylaxis of haemophilia A
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.22. Parathyroid hormone - EMEA/H/C/003861, Orphan

Applicant: NPS Pharma Holdings Limited

Scope: Treatment of hypoparathyroidism
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.23. Pemetrexed - EMEA/H/C/003788

Generic

Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.24. Pemetrexed - EMEA/H/C/004072

Generic

Scope: Treatment of unresectable malignant pleural mesothelioma
metastatic non-small cell lung cancer
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.25. Pemetrexed - EMEA/H/C/004109

Hybrid

Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.26. Pemetrexed - EMEA/H/C/003970

Generic

Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer (excluding predominantly squamous cell histology)
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.27. Pemetrexed - EMEA/H/C/003905

Generic

Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.28. Recombinant L-asparaginase - EMEA/H/C/002661, Orphan

Applicant: Medac Gesellschaft fuer klinische Spezialpraeparate GmbH

Scope: Treatment for B/T cell lymphoblastic leukaemia (ALL) or B/T cell lymphoblastic lymphoma (LBL) in combination
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.29. Sacubitril, valsartan - EMEA/H/C/004062

Scope: Treatment of heart failure (NYHA class II-IV)
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.1.30. Talimogene laherparepvec - EMEA/H/C/002771

ATMP[73]

Scope: Treatment of adults with melanoma that is regionally or distantly metastatic
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.2. Medicines in the post-authorisation phase – PRAC-led procedure

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.

14.2.1. Bazedoxifene – CONBRIZA (CAP) - EMEA/H/C/000913/II/0038

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

[73] Advanced-therapy medicinal product

Scope: Submission of an updated RMP version 4.3 in order to reclassify the risks currently listed as potential risks
Action: For adoption of PRAC AR

14.2.1. Filgrastim – FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/WS0779/0029/G, ZARZIO (CAP) - EMEA/H/C/000917/WS0779/0030/G

Applicant: Sandoz GmbH

PRAC Rapporteur: Julie Williams

Scope: Submission of long term safety and immunogenicity data in additional studies EP06-302 to address post authorisation measure MEA 005. Submission of an updated RMP (version 11.0) to include two important potential risks (extramedullary haematopoiesis and venous thrombotic events) following the request from PSUR13 assessment
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.2.2. Filgrastim – NIVESTIM (CAP) - EMEA/H/C/001142/II/0033

Applicant: Hospira UK Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP (version 9.0) following PRAC recommendations dated 12 March 2015 following the completion of the renewal procedure of Nivestim (EMA/PRAC/153431/2015)
Action: For adoption of PRAC AR

14.2.3. Infliximab – INFLECTRA (CAP) - EMEA/H/C/002778/II/0030

Applicant: Hospira UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of an updated RMP in order to add/delete safety concerns in line with the reference product, Remicade and update the status of the category 3 studies, including the change of due date for Post-Authorisation Measure MEA 011 study CT-P13 3.4 (submission of Week 6 clinical study report (CSR)) from May 2015 to December 2016
Action: For adoption of PRAC AR

14.2.4. Infliximab – REMSIMA (CAP) - EMEA/H/C/002576/II/0025

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of a revised RMP to include newly identified safety concerns (acute hypersensitivity reaction (including anaphylactic shock); merkel cell carcinoma; melanoma) in line with the RMP for the reference product Remicade, deletion of potential risks (bowel stenosis, stricture, obstruction (in Crohn's Disease)) in line with the RMP for the reference product Remicade, addition of pharmacological class risks as newly identified class risks, update of category 3 studies to reflect current status and to change the due date for MEA 011 study CT-P13 3.4 (week 6 clinical study report (CSR)) from May 2015 to December 2016
Action: For adoption of PRAC AR

14.2.5. Influenza vaccine (split virion, inactivated) – IDFLU (CAP) - EMEA/H/C/000966/WS/0763/0038; INTANZA (CAP) - EMEA/H/C/000957/WS/0763/0040

Applicant: Sanofi Pasteur, Sanofi Pasteur MSD SNC

PRAC Rapporteur: Miguel-Angel Macia

Scope: Submission of a revised RMP (version 9.0) to update the strategy of the enhanced safety surveillance in EEA during 2015-2016 influenza season, the status of GID47 updated and details on clinical study report, results of THIN study and the table of risk minimisation measures updated according to the PRAC assessment report of the RMP 8.0
Action: For adoption of PRAC AR

14.2.6. Meningococcal group B vaccine (rDNA, component, adsorbed) – BEXSERO (CAP) - EMEA/H/C/002333/II/0033

Applicant: Novartis Vaccines and Diagnostics S.r.l.

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a revised RMP in order to replace study V72_39OB to monitor the use of Bexsero during pregnancy using the vaccines in pregnancy surveillance system, with study V72_82OB using the United States pregnancy registry
Action: For adoption of PRAC AR

14.2.7. Oseltamivir – TAMIFLU (CAP) - EMEA/H/C/000402/II/0114

Applicant: Roche Registration Ltd

PRAC Rapporteur: Kirsti Villikka

Scope: Proposal of 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)'
Action: For adoption of PRAC AR

14.2.8. Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/II/0154/G

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Submission of an updated RMP (version 19.0): to remove the pharmacokinetic (PK) sub-study of the category 3 study GSUS-174-0144, to change the agreed due date of the category 3 study GS-US-236-0103, to update in Part II of the antiretroviral pregnancy registry exposure in line with EMA request. In addition, the RMP is updated to reflect the milestones for category 3 studies GS-US-174-0115 and GS-US-174-0144 in line with those already agreed in the paediatric investigation plan (PIP). Finally, the MAH took the opportunity of this procedure to update studies and exposure data as well as update status/milestones of several studies
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3. Medicines in the post-authorisation phase – CHMP-led procedure

14.3.1. Abiraterone – ZYTIGA (CAP) - EMEA/H/C/002321/II/0035/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variations: submission of clinical study reports (CSRs) associated with four studies listed in the RMP as required additional pharmacovigilance activities to address the important identified risk of cardiac disorders: 1) interim analysis CSR for study ABI-PRO-3002: phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (JNJ-212082) plus prednisone in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer; 2) final CSR for study JNJ-212082-JPN-201: phase 2 study of JNJ-212082 (abiraterone acetate) in metastatic castration-resistant prostate cancer patients who are chemotherapy-naïve; 3) final CSR for study JNJ-212082-JPN-202: phase 2 study of JNJ-212082 (abiraterone acetate) in metastatic castration-resistant prostate cancer patients who have received docetaxel-based chemotherapy; 4) final analysis CSR for study 212082BCA2001: randomized, open-label study of abiraterone acetate (JNJ-212082) plus prednisone with or without exemestane in postmenopausal women with ER+ metastatic breast cancer progressing after letrozole or anastrozole therapy. An updated EU RMP (version 11.0) is submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.2. Abiraterone – ZYTIGA (CAP) - EMEA/H/C/002321/II/0036/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variations: submission of clinical study reports (CSRs) associated with four studies listed in the RMP as required additional pharmacovigilance activities to address missing information in non-white patients: 1) final analysis CSR for study ABI-PRO-3001: phase 3, randomized, double-blind, placebo-controlled study for abiraterone acetate (JNJ-212082) plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy; 2) final analysis CSR for study 212082PCR3001: open-label study of abiraterone acetate in subjects with metastatic castration-resistant prostate cancer who have progressed after taxane-based chemotherapy; 3) final CSR and addendum for study 212082PCR2007: phase 2 open-label study of abiraterone acetate (JNJ-212082) and prednisolone in patients with advanced prostate cancer who have failed androgen deprivation and docetaxel-based chemotherapy; 4) final CSR for study JNJ-212082-JPN-102: phase 1 study of JNJ-212082 (abiraterone acetate) in chemotherapy-naïve patients with castration-resistant prostate cancer. In addition, interim analysis CSR for study ABI-PRO-3002: phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (JNJ-212082) plus prednisone in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer is discussed with regard to missing information for use of ZYTIGA in non-white patients. An updated EU RMP (version 11.0) is submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.3. Aflibercept – EYLEA (CAP) - EMEA/H/C/002392/II/0021

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: Extension of indication to include a new indication for adult for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 are updated. The Package Leaflet is updated accordingly. In addition, some editorial changes are proposed in section 5.1 of the SmPC, in Annex II and in the Package Leaflet
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.4. Alipogene tiparvovec - GLYBERA (CAP) - EMEA/H/C/002145/II/0038

Applicant: UniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: Update of section 5.1 of the SmPC based on the final clinical study report (CSR) for study CT-AMT-011-05, a retrospective clinical records review study undertaken to generate further long-term follow-up data on the incidence and severity of acute pancreatitis episodes in lipoprotein lipase deficiency (LPLD) subjects who previously participated in clinical studies with alipogene tiparvovec or AMT-10
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.5. Ambrisentan – VOLIBRIS (CAP) - EMEA/H/C/000839/II/0041

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include an expanded therapeutic indication for the treatment of pulmonary arterial hypertension (PAH). 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
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.6. Aprepitant – EMEND (CAP) - EMEA/H/C/000527/X/0049/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication for the treatment of chemotherapy-induced nausea and vomiting (CINV) in paediatric patients (12 to 17 years) for the 80 mg and 125 mg hard capsules. In addition, update of SmPC sections 4.2 and 5.3 of the 165 mg hard capsule label. Furthermore, addition of a new pharmaceutical form (powder for oral suspension) for the 125 mg strength. Finally, update of sections 5.1 and 5.2 of the SmPC to reflect the paediatric results for prevention of post-operative nausea and vomiting (PONV) in the clinical sections of the 40 mg hard capsules product information. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.7. Atanazavir – REYATAZ (CAP) - EMEA/H/C/000494/II/0096

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Isabelle Robine

Scope: Update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 5.1 and 5.2 of the SmPC in order to provide important information and guidance to prescribers when they consider using unboosted atazanavir (ATV) in line with international guidelines based on study INDUMA/AI424-136. In addition, the MAH took the opportunity to make a minor change in section 4.7 of the SmPC for increased clarity, and minor editorial changes to the SmPC and Package Leaflet. RMP version 9 has been submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.8. Bivalirudin – ANGIOX (CAP) - EMEA/H/C/000562/II/0062

Applicant: The Medicines Company UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to update the posology instructions and update the warning of use of bivalirudin in case of haemorrhage. The Package Leaflet is updated accordingly

Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.9. Capecitabine – XELODA (CAP) - EMEA/H/C/000316/II/0067

Applicant: Roche Registration Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.3 and 4.4 of the SmPC in order to delete the contraindication regarding patients with known dihydropyrimidine dehydrogenase (DPD) and add information with regard to patients with DPD deficiency. The package leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.10. Ceftaroline fosamil – ZINFORO (CAP) - EMEA/H/C/002252/II/0021

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report of the multicentre, randomised, double-blind, comparative study to evaluate the efficacy and safety of ceftaroline fosamil (600 mg every 8 hours) versus vancomycin plus aztreonam in the treatment of patients with complicated bacterial skin and soft tissue infections with evidence of systemic inflammatory response or underlying comorbidities. A revised RMP (version 14) is submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.11. Dabigatran – PRADAXA (CAP) - EMEA/H/C/000829/II/0082

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final study report for study 1160.166: exploratory study to investigate the pharmacokinetics and effects of dabigatran etexilate in patients with stable severe renal disease (DabiRenal). A revised RMP (version 31.1) is submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.12. Dabigatran – PRADAXA (CAP) - EMEA/H/C/000829/II/0085

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Update of sections 4.2 and 5.1 of the SmPC to add a recommendation to ensure Pradaxa is taken with a meal and/or a proton pump inhibitor such a pantoprazole in case of gastrointestinal symptoms (GIS), based on the results of study 1160.128; a prospective, open label study evaluating the efficacy of two management strategies on GIS in non-valvular atrial fibrillation (NVAF) patients. The Package Leaflet (including the patient alert card) has been updated accordingly. A revised RMP (version 31.2) is submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.13. Daclatasvir – DAKLINZA (CAP) - EMEA/H/C/003768/II/0008/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to update the safety information based on the final results of clinical study AI444043. In addition, update

of section 4.5 of the SmPC in order to update the safety information based on the final results of clinical study AI444093. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.14. Daclatasvir – DAKLINZA (CAP) - EMEA/H/C/003768/II/0010/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the safety information based on the final results of clinical study AI444216 (ALLY-2): phase 3 evaluation of daclatasvir plus sofosbuvir in treatment-naive and treatment experienced chronic hepatitis C (genotype 1, 2, 3, 4, 5, or 6) subjects co-infected with human immunodeficiency virus (HIV). The Package Leaflet is updated accordingly. In addition, update of sections 4.2, 4.4, 4.8, 5.1, 5.2 in order to update the safety information based on the final results of clinical study AI444215 (ALLY-1): phase 3 evaluation of daclatasvir, sofosbuvir, and ribavirin in genotype 1-6 chronic hepatitis C infection subjects with cirrhosis who may require future liver transplant and subjects post-liver transplant. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.15. Deferasirox – EXJADE (CAP) - EMEA/H/C/000670/II/0045

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Corinne Fechant

Scope: Update of section 4.4 of the SmPC based on the results from studies CICL670A2425, CICL670A2426 and CICL670AFR01T and the patient survey. The Package Leaflet and Annex II are updated accordingly. Updated RMP version 11 has been submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.16. Diphtheria (D) tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) – HEXACIMA (CAP) - EMEA/H/C/002702/WS/0789; HEXAXIM (Art 58) - EMEA/H/W/002495/WS/0789; HEXYON (CAP) - EMEA/H/C/002796/WS/0789

Applicant: Sanofi Pasteur

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.8 of the SmPC, upon request by the PRAC following the assessment of PSUSA/10091/201410, to include the adverse drug reactions: 'convulsion with or without fever' and 'anaphylactic reaction'. The Package Leaflet is updated accordingly. A revised RMP (version 10.0) was submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.17. Dolutegravir – TIVICAY (CAP) - EMEA/H/C/002753/II/0014/G

Applicant: ViiV Healthcare

PRAC Rapporteur: Julie Williams

Scope: Update of section 5.1 of the SmPC in order to include additional, long-term efficacy and safety data from week 144 of the Phase III study ING114467 (SINGLE) and week 96 of the Phase IIIb study ING114915 (FLAMINGO). An updated RMP (version 6.0) has been submitted accordingly

Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.18. Dolutegravir, abacavir, lamivudine – TRIUMEQ (CAP) - EMEA/H/C/002754/II/0015/G

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Update of section 5.1 of the SmPC in order to include additional, long-term efficacy and safety data from week 144 of the Phase III study ING114467 (SINGLE) and week 96 of the Phase IIIb study ING114915 (FLAMINGO). An updated RMP (version 6.0) has been submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.19. Eculizumab – SOLIRIS (CAP) - EMEA/H/C/000791/II/0077

Applicant: Alexion Europe SAS

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.3 and 4.4 of the SmPC to add the serogroup B vaccine in addition to the serogroups A, C, W135 and Y. In addition, update of section 4.4 of the SmPC to remove the reference to tetravalent or conjugated vaccines. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.20. Emtricitabine – EMTRIVA (CAP) - EMEA/H/C/000533/WS/0792; tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/WS0792 tenofovir disoproxil, emtricitabine – EVIPLERA (CAP) - EMEA/H/C/002312/WS0792; TRUVADA (CAP) - EMEA/H/C/000594/WS0792 tenofovir disoproxil, emtricitabine, efavirenz – ATRIPLA (CAP) - EMEA/H/C/000797/WS0792 tenofovir disoproxil, emtricitabine, elvitegravir, cobicistat – STRIBILD (CAP) - EMEA/H/C/002574/WS0792

Applicant: Bristol-Myers Squibb and Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.4 of the SmPC in order to delete the human immunodeficiency virus (HIV) class label wording for mitochondrial dysfunction following the review of existing data on mitochondrial toxicity including the Mitochondrial Toxicity in Children (MITOC) Study. The Package Leaflet of Viread, Truvada and Emtriva were updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.21. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/II/0063/G

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC in order to add safety information regarding severe skin reactions with systemic symptoms. The Package Leaflet and the RMP (version 10.0) are updated accordingly. In addition, update of the RMP in alignment with the RMP for the mono-component rilpivirine (RPV) by deleting an important missing information safety concern (drug-drug interactions) and update the RMP to amend the potential risk safety concern (off-label use) to reflect the use for the product and not the single component RPV

Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.22. Etanercept – ENBREL (CAP) - EMEA/H/C/000262/II/0184

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.6 of the SmPC in order to update the information on the effects of etanercept on pregnancy and lactation. The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to update the RMP in reference to past approved variations
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.23. Etravirine – INTELENCE (CAP) - EMEA/H/C/000900/II/0042

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Isabelle Robine

Scope: Update of sections 4.2, 4.4, 5.1 and 5.2 of the SmPC in order to update the safety information of the TMC114HIV3015 study. In addition, the MAH took the opportunity to include information on the removal of gastric lavage in section 4.9 of the SmPC
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.24. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/II/0065/G

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information based on review of all available safety data. The Package Leaflet and RMP are updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.25. Human fibrinogen, human thrombin – EVICEL (CAP) - EMEA/H/C/000898/II/0032

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2 and 4.8 of the SmPC in order to update the safety information and the frequencies of adverse drug reactions (ADR) already reported in the Product Information based on the final study report for a prospective, single-arm, observational, non-interventional study for Evicel when used as an adjunct to haemostasis in vascular surgery. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.26. Human normal immunoglobulin - KIOVIG (CAP) - EMEA/H/C/000628/II/0065/G

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.4 of the SmPC in order to include further information to avoid thromboembolic events and renal complications and to update information on aseptic meningitis syndrome. New information is also provided on possible false positive testing of assays used for diagnosis of fungal infections depending on detection of beta-D-glucans. In

addition, update of section 4.8 of the SmPC in order to update the safety information and to change frequencies of existing adverse drug reactions as revealed in several clinical studies in which Kiovig was used as investigational medicinal product. The Package Leaflet is updated accordingly. Finally, the MAH took the opportunity to update the RMP in reference to the new warning for the false positive testing for ß-d-glucan and including the changes requested during assessment of procedure EMEA/H/C/0000628/II/0056.
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.27. Human rotavirus, live attenuated – ROTARIX (CAP) - EMEA/H/C/000639/II/0078

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.28. Human thrombin, human fibrinogen – TACHOSIL (CAP) - EMEA/H/C/000505/II/0057

Applicant: Takeda Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication for the use of Tachosil as suture line sealing in dura mater closure. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC and the Package leaflet are updated
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.29. Infliximab – REMICADE (CAP) - EMEA/H/C/000240/II/0191

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 to add a warning on possible causal relationship between infliximab and cervical cancer and 4.8 of the SmPC in order to add cervical cancer with frequency category 'rare' as a new adverse drug reaction (ADR) identified from post marketing experience. These updates address LEG 135.7. The Package Leaflet is updated accordingly. An updated RMP (version 12.0) has been submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.30. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/002494/II/0027

Applicant: Vertex Pharmaceuticals (U.K.) Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Extension of indication to include the treatment of cystic fibrosis in patients aged 18 years and older who have a R117H mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Consequently, changes are proposed to sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet is updated accordingly

14.3.31. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/002494/X/0034/G

Applicant: Vertex Pharmaceuticals (U.K.) Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Line extension to include a new pharmaceutical form (granules) in two new strengths (50 mg and 75 mg unit doses) to enable administration of Kalydeco to patients aged 2 to less than 6 years of age. Consequently, changes to SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.2 are proposed to provide clarity and relevant updates in line with the proposed paediatric extension application. The Package Leaflet is updated accordingly

14.3.32. Insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/II/0009

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 5.1 of the SmPC based on the results from 26-week trials assessing efficacy and safety of Xultophy compared to insulin glargine in patients with type 2 diabetes mellitus inadequately controlled on insulin glargine and metformin. Consequently, sections 4.4 and 4.8 of the SmPC have also been updated. The Package Leaflet and RMP are updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.33. Liraglutide – VICTOZA (CAP) - EMEA/H/C/001026/II/0032

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report from the liraglutide 10-week juvenile toxicity study. Consequently, an updated RMP is submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.34. Lomitapide – LOJUXTA (CAP) - EMEA/H/C/002578/X/0016

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Line extension to add three new strengths: 30 mg, 40 mg and 60 mg hard capsules
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.35. Macitentan – OPSUMIT (CAP) - EMEA/H/C/002697/II/0007/G

Applicant: Actelion Registration Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of final study report for studies AC-055C301/DUAL-1 and AC-055C302/DUAL-2, two completed Phase 3 studies in patients with digital ulcers associated with systemic sclerosis. An updated RMP has been submitted accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.36. Nintedanib – OFEV (CAP) - EMEA/H/C/003821/WS/0766; VARGATEF (CAP) - EMEA/H/C/002569/WS/0766

Applicant: Boehringer Ingelheim Pharma GmbH & Co. KG

PRAC Rapporteur: Leonidas Klironomos

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to include further information related to patients with hepatic impairment based on the clinical study reports

(CSRs) of studies 1199.37, 1199.39 and 1199.200. A revised RMP was provided as part of the application; RMP version 2.0 for Ofev and RMP version 3.0 for Vargatef
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.37. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0001

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been revised accordingly. Further, Annex II has been updated to include a post-authorisation efficacy study as a new obligation in line with the agreed Annex II for Nivolumab BMS. In addition, the MAH took the opportunity to make editorial changes in the SmPC, Annex II, labelling and Package Leaflet. A revised RMP (version 2.0) is provided accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.38. Perampanel – FYCOMPA (CAP) - EMEA/H/C/02434/II/0023

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.5 and 5.2 in order to update the safety information based on the results of a mass balance study
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.39. Pyronaridine, artesunate – PYRAMAX (Art 58) - EMEA/H/W/002319/II/0002

Applicant: Shin Poong Pharmaceutical Co.

PRAC Rapporteur: Isabelle Robine

Scope: Update of SmPC section 4.1 to remove restrictions on repeated course of treatment in any individual and use only in areas of low transmission with evidence of artesmisinin resistance, based on further clinical experience. Consequent changes in SmPC sections 4.2, 4.4, 4.8 and the Package Leaflet are also included. In addition, update of SmPC Section 4.2 in relation to dosing in mild to moderate renal impairment
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.40. Pyronaridine, artesunate – PYRAMAX (Art 58) - EMEA/H/W/002319/X/0008/G

Applicant: Shin Poong Pharmaceutical Co.

PRAC Rapporteur: Isabelle Robine

Scope: Line Extension to add a new paediatric formulation 60 mg/20 mg granules for oral suspension. The product information for Pyramax 180 mg/60 mg film coated tablets has also been updated with data submitted for the line extension
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.41. Ramucirumab – CYRAMZA (CAP) - EMEA/H/C/002829/II/0003

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include a new indication for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with progression after platinum-based chemotherapy for Cyramza. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.42. Ramucirumab – CYRAMZA (CAP) - EMEA/H/C/002829/II/0004

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the use of Cyramza in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.43. Retigabine – TROBALT (CAP) - EMEA/H/C/001245/R/0036

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.44. Sofosbuvir – SOVALDI (CAP) - EMEA/H/C/002798/II/0015

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report to investigate the safety and efficacy of GS-7977 and ribavirin for 24 weeks in subjects with recurrent chronic hepatitis C virus (HCV) post liver transplant (GS-US-334-0126). The submission of this study fulfils MEA 005. An updated RMP (version 3.0) is proposed accordingly
Action: For adoption of PRAC Assessment Report

14.3.45. Thiotepa – TEPADINA (CAP) - EMEA/H/C/001046/II/0021

Applicant: Adienne S.r.l. S.U.

PRAC Rapporteur: Corinne Fechant

Scope: Update of section 4.8 of the SmPC to add the new adverse drug reaction (ADR) 'toxic skin reactions' with an unknown frequency. The Package Leaflet is updated accordingly. A revised RMP version 12 was provided as part of the application
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.46. Trametinib – MEKINIST (CAP) - EMEA/H/C/002643/II/0006/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.5 and 5.2 of the SmPC in order to update the safety information based on new preclinical data provided to fulfil four nonclinical post-authorisation measures (REC 001, MEA 004, MEA 005 and MEA 006). Moreover, an updated RMP (version 10) has been submitted
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.47. Trametinib – MEKINIST (CAP) - EMEA/H/C/002643/II/0007

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2 and 5.3 of the SmPC in order to update the safety information based on new preclinical data from an oral juvenile toxicity study in rats. Moreover, an updated RMP (version 10) has been submitted
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.48. Trastuzumab – HERCEPTIN (CAP) - EMEA/H/C/000278/II/0092

Applicant: Roche Registration Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of SmPC sections 4.4, 4.8 and 5.1 to reflect the results of a new study report BO22227 (Hannah) regarding non inferior trastuzumab exposure and clinical efficacy of a q3w regimen of Herceptin subcutaneous (SC) compared to Herceptin intravenous (IV). An updated RMP has been provided
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.49. Trastuzumab – HERCEPTIN (CAP) - EMEA/H/C/000278/II/0093

Applicant: Roche Registration Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to update the safety information of Herceptin 600 mg solution for injection (EU/1/00/145/002 and EU/1/00/145/003) in line with the interim report of study MO28048 (SafeHER) submitted. The RMP is updated accordingly
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

14.3.50. Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0023

Applicant: Roche Registration Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.5 of the SmPC in order to update the drug-drug interaction information following finalisation of study GO28394 (phase I, open-label, multicentre, 3-period, fixed sequence study to investigate the effect of vemurafenib on the pharmacokinetics of a single dose of digoxin in patients with BRAFV600 mutation-positive metastatic malignancy – MEA 013)
Action: For adoption of PRAC RMP AR, PRAC RMP assessment overview and advice to CHMP

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 in the outcome of the relevant PSUR/PSUSA procedure(s).

15.1. PSUR procedures including centrally authorised products only

15.1.1. Aclidinium bromide – BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/09005/201501

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.2. Aflibercept – ZALTRAP (CAP) - PSUSA/10019/201502

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.3. Ataluren – TRANSLARNA (CAP) - PSUSA/10274/201501

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.4. Axitinib – INLYTA (CAP) - PSUSA/10022/201501

Applicant: Pfizer Limited

PRAC Rapporteur: Ingebjørg Buajordet

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.5. Bevacizumab – AVASTIN (CAP) - PSUSA/00403/201502

Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.6. Cobicistat – TYBOST (CAP) - PSUSA/10081/201502

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.7. Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil – STRIBILD (CAP) - PSUSA/10082/201502

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.8. Colistimethate sodium – COLOBREATHE (CAP) - PSUSA/09112/201502

Applicant: Forest Laboratories UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.9. Copper (^{64}Cu) chloride – CUPRYMINA (CAP) - PSUSA/10040/201502

Applicant: SparkleSRL

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.10. Dabrafenib – TAFINLAR (CAP) - PSUSA/10084/201502

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.11. Daclatasvir – DAKLINZA (CAP) - PSUSA/10295/201501

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.12. Dapagliflozin, metformin – XIGDUO (CAP) - PSUSA/10294/201501 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.13. Degarelix – FIRMAGON (CAP) - PSUSA/00944/201502 (with RMP)

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Corinne Fechant

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.14. Dexamethasone – OZURDEX (CAP) - PSUSA/00985/201501 (with RMP)

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.15. Dolutegravir - TIVICAY (CAP) - abacavir, dolutegravir –TRIUMEQ (CAP) - PSUSA/10075/201501 (with RMP)

Applicant: ViiV Healthcare, ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.16. Elosulfase alfa – VIMIZIM (CAP) - PSUSA/10218/201502

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.17. Elvitegravir – VITEKTA (CAP) - PSUSA/02577/201502

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.18. Emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - PSUSA/09142/201502

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.19. Epoetin zeta – RETACRIT (CAP), SILAPO (CAP) - PSUSA/01241/201412

Applicant: Hospira UK Limited, Stada Arzneimittel AG

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.20. Etanercept – ENBREL (CAP) - PSUSA/01295/201502

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.21. Fampridine – FAMPYRA (CAP) - PSUSA/01352/201501 (with RMP)

Applicant: Biogen Idec Ltd.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.22. Human coagulation factor VIII, von Willebrand factor – VONCENTO (CAP) - PSUSA/10102/201502

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure
Action n: For adoption of recommendation to CHMP

15.1.23. Idelalisib – ZYDELIG (CAP) - PSUSA/10303/201503

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.24. Infliximab – INFLECTRA (CAP), REMSIMA (CAP) - PSUSA/10106/201501

Applicant: Hospira UK Limited, Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.25. Ingenol mebutate – PICATO (CAP) - PSUSA/10035/201501

Applicant: Leo Pharma A/S

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.26. Ivacaftor – KALYDECO (CAP) - PSUSA/09204/201501

Applicant: Vertex Pharmaceuticals (U.K.) Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.27. Lipegfilgrastim – LONQUEX (CAP) - PSUSA/10111/201501

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.28. Lixisenatide – LYXUMIA (CAP) - PSUSA/10017/201501

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.29. Lomitapide – LOJUXTA (CAP) - PSUSA/10112/201501

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.30. Loxapine – ADASUVE (CAP) - PSUSA/10113/201502

Applicant: Alexza UK Ltd.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.31. Meningococcal group B vaccine (rDNA, component, adsorbed) – BEXSERO (CAP) - PSUSA/10043/201501

Applicant: Novartis Vaccines and Diagnostics S.r.l.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.32. Mifamurtide – MEPACT (CAP) - PSUSA/02059/201503 (with RMP)

Applicant: Takeda France SAS

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.33. Mixture of polynuclear iron(iii)-oxyhydroxide, sucrose and starches – VELPHORO (CAP) - PSUSA/10296/201502

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.34. Modified vaccinia ankara virus – IMVANEX (CAP) - PSUSA/10119/201501

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.35. Nilotinib – TASIGNA (CAP) - PSUSA/02162/201501

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.36. Nitisinone – ORFADIN (CAP) - PSUSA/02169/201502

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.37. Nonacog gamma – RIXUBIS (CAP) - PSUSA/10320/201412

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.38. Palifermin – KEPIVANCE (CAP) - PSUSA/02265/201501 (with RMP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.39. Perampanel – FYCOMPA (CAP) - PSUSA/09255/201501

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.40. Pirfenidone – ESBRIET (CAP) - PSUSA/02435/201502 (with RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.41. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) – PREVENAR 13 (CAP) - PSUSA/09263/201501 (with RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.42. Prasugrel – EFIENT (CAP) - PSUSA/02499/201502 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.43. Pyronaridine, artesunate – PYRAMAX (Art 58) – EMEA/H/W/002319/PSUV/0010

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.44. Rufinamide – INOVELON (CAP) - PSUSA/02671/201501

Applicant: Eisai Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.45. Ruxolitinib – JAKAVI (CAP) - PSUSA/10015/201502

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.46. Silodosin – SILODYX (CAP), UROREC (CAP) - PSUSA/02701/201501

Applicant: Recordati Ireland Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.47. Simoctocog alfa – NUWIQ (CAP) - PSUSA/10276/201501

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.48. Tacrolimus – ENVARSUS (CAP) - PSUSA/10337/201501

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.49. Teduglutide – REVESTIVE (CAP) - PSUSA/09305/201502

Applicant: NPS Pharma Holdings Limited

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.50. Trastuzumab emtansine – KADCYLA (CAP) - PSUSA/10136/201502

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.51. Ulipristal acetate – ESMYA (CAP) - PSUSA/09325/201502

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.1.52. Vismodegib – ERIVEDGE (CAP) - PSUSA/10140/201501

Applicant: Roche Registration Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.2. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

15.2.1. Estradiol, nomegestrol acetate – ZOELY (CAP), NAP - PSUSA/02182/201501

Applicant: Teva B.V., various

PRAC Rapporteur: Corinne Fechant

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.2.2. Nitric oxide – INOMAX (CAP), NAP - PSUSA/02172/201412

Applicant: Linde Healthcare AB, various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CHMP

15.3. PSUR procedures including nationally approved products (NAPs) only

15.3.1. Alpha-1-antitrypsin (NAP) - PSUSA/00108/201412

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.2. Amisulpride (NAP) - PSUSA/00167/201501

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.3. Atovaquone (NAP) - PSUSA/00265/201411

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.4. Azelastine (NAP) - PSUSA/00277/201412

Applicant: various

PRAC Lead: Marianne Lunzer

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.5. Betahistine (NAP) - PSUSA/00389/201412

Applicant: various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.6. Calcitriol (NAP) - PSUSA/00000495/201501

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.7. Celecoxib (NAP) - PSUSA/00616/201412

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.8. Desmopressin (NAP) - PSUSA/00000964/201412

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.9. Enalapril, nitrendipine (NAP) - PSUSA/00001213/201501

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.10. Ethinylestradiol, gestodene (transdermal application) (NAP) - PSUSA/00010145/201502

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Action: For adoption of recommendation to CMDh

15.3.11. 5-Fluorouracil (intravenous application) (NAP) - PSUSA/00000007/201412

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.12. Flupirtine (NAP) - PSUSA/00010225/201501

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.13. Gasiloxe (NAP) - PSUSA/00010283/201501

Applicant: various

PRAC Lead: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.14. Glatiramer (NAP) - PSUSA/00001529/201411

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.15. Magnesium sulphate, sodium sulphate, potassium sulphate (NAP) - PSUSA/00010239/201502

Applicant: various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.16. Reviparin (NAP) - PSUSA/00002634/201501

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.17. Rubella vaccine (live, attenuated) (NAP) - PSUSA/00002670/201501

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.18. Tetanus vaccine (NAP) - PSUSA/00002910/201501

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.3.19. Tobramycin (nebuliser solution) (NAP) - PSUSA/00009316/201412

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure
Action: For adoption of recommendation to CMDh

15.4. Follow-up to PSUR procedures

15.4.1. Arsenic trioxide – TRISENOX (CAP) - EMEA/H/C/000388/LEG 049

Applicant: Teva B.V.

PRAC Rapporteur: Corinne Fechant

Scope: MAH's responses to PSUSA/00000235/201409/0053
Action: For adoption of advice to CHMP

15.4.2. Botulinium B toxin – NEUROBLOC (CAP) - EMEA/H/C/000301/LEG 062

Applicant: Eisai Ltd

PRAC Rapporteur: Magda Pedro

Scope: MAH's response to EMEA/H/C/PSUSA/00000428/201406 following PRAC outcome in February 2015
Action: For adoption of advice to CHMP

15.4.3. Dibotermin alfa – INDUCTOS (CAP) - EMEA/H/C/000408/LEG 070

Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to EMEA/H/C/PSUSA/00001034/201409 as adopted in April 2015
Action: For adoption of advice to CHMP

15.4.4. Iloprost – VENTAVIS (CAP) - EMEA/H/C/000474/LEG 037

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: MAH's response to EMEA/H/C/474/PSUSA/00001724/201409 as adopted in April 2015
Action: For adoption of advice to CHMP

15.4.5. Infliximab – REMICADE (CAP) - EMEA/H/C/000240/LEG 153

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Cumulative review of weight changes in patients treated with Remicade (infliximab)
Action: For adoption of advice to CHMP

15.4.6. Leflunomide – ARAVA (CAP) - EMEA/H/C/000235/LEG 056; LEFLUNOMIDE WINTHROP (CAP) - EMEA/H/C/001129/LEG 023

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to EMEA/H/C/000235/PSUSA/00001837/201409/0064 following PRAC adoption in April 2015
Action: For adoption of advice to CHMP

15.4.7. Mycophenolate mofetil – CELLCEPT (CAP) - EMEA/H/C/000082/LEG 038

Applicant: Roche Registration Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's response to EMEA/H/C/PSUSA/00002099/201405 on Drug Safety Report for Haemolytic Anaemia (DUS 1065479) and Interstitial Lung Disease (DUS 1065477)
Action: For adoption of advice to CHMP

15.4.8. Sirolimus – RAPAMUNE (CAP) - EMEA/H/C/000273/LEG 052

Applicant: Pfizer Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's responses to (EMEA/H/C/PSUSA/00002710/201409) as adopted in May 2015 following PRAC
Action: For adoption of advice to CHMP

15.4.9. Temozolomide – TEMODAL (CAP) - EMEA/H/C/000229/LEG 040

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to (EMEA/H/C/PSUSA/00002886/201407): cumulative review on the concomitant use of live vaccines and temozolomide

Action: For adoption of advice to CHMP

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. Protocols of PASS imposed in the marketing authorisation(s)[74]

16.1.1. Chlormadinone acetate, ethinyl estradiol (NAP) – EMEA/H/N/PSP/0012.2

Applicant: Gideon Richter, various

PRAC Rapporteur: Valerie Strassmann

Scope: Revised joint PASS protocol (following conclusion of Article31 referral procedure for combined hormonal contraceptives with CHMP opinion adopted in November 2013) to study the risk of venous thromboembolism (VTE) associated with chlormadinone/ethinylestradiol (CMA/EE) containing products
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

16.1.2. Dexamfetamine (NAP) – EMEA/H/N/PSP/0018.1

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Julie Williams

Scope: Revised 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
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

16.1.3. Dexamfetamine (NAP) – EMEA/H/N/PSP/0021.1

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

PRAC Rapporteur: Julie Williams

Scope: Revised protocol for a drug utilisation study of dexamfetamine to follow the use of prescribed dexamfetamine in the European Union using multiple data sources
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

16.1.4. Domperidone (NAP) – EMEA/H/N/PSP/0016.1

Applicant: Janssen (Motilium), various

PRAC Rapporteur: Isabelle Robine

Scope: Revised PASS protocol for a study is to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the change in SmPC and the distribution of DHPC. The secondary

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

objective of the study is to characterise the extent to which domperidone is prescribed for conditions that are not labelled
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

16.1.5. Ospemifene – SENSHIO (CAP) - EMEA/H/C/PSP/0023.1

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Revised protocol for a post-authorisation safety study to evaluate the incidence of venous thromboembolism and other adverse events, as agreed in the risk management plan, in vulvar and vaginal atrophy (VVA) patients treated with ospemifene as compared to: 1) patients newly prescribed selective oestrogen receptor modulators (SERMs) for oestrogen-deficiency conditions or breast cancer prevention; 2) the incidence in untreated VVA patients
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[75]

16.2.1. Aflibercept – ZALTRAP (CAP) - EMEA/H/C/002532/MEA 002.2

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's responses to MEA 002.1 [PASS protocol for study OZONE OBS13597] adopted in September 2013
Action: For adoption of advice to CHMP

16.2.2. Apremilast – OTEZLA (CAP) - EMEA/H/C/003746/MEA 005

Applicant: Celgene Europe Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PASS protocol to collect long-term data, as required in the RMP, by using the PsoBest registry
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

16.2.3. Apremilast – OTEZLA (CAP) - EMEA/H/C/003746/MEA 006

Applicant: Celgene Europe Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PASS protocol to investigate several safety concerns, as required in the RMP, using the CPRD (UK) database
Action: For adoption of PRAC Assessment Report, PRAC outcome letter

16.2.4. Bromelain enriched proteolytic enzyme preparation from ananas comosus – NEXOBRID (CAP) - EMEA/H/C/002246/MEA 003.2

Applicant: MediWound Germany GmbH

[75] 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

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a revised PASS protocol (MW2013-06-01) for a drug utilisation study to further evaluate the effectiveness of the risk minimisation activities (including evaluation of educational and training materials)

Action: For adoption of advice to CHMP

16.2.5. Buprenorphine, naloxone – SUBOXONE (CAP) - EMEA/H/C/000697/MEA 023.4

Applicant: RB Pharmaceuticals Ltd

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 023.3 [protocol for safety study PE-US-005-Suboxone mortality study in the UK with the Health Improvement Network database (THIN)], request for supplementary information (RSI) as adopted in March 2013
Action: For adoption of advice to CHMP

16.2.6. Canakinumab – ILARIS (CAP) - EMEA/H/C/001109/MEA/037.3

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA-037.2 [non-interventional study collecting safety and efficacy data from systemic juvenile idiopathic arthritis (SJIA) patients enrolled in Pharmachild JIA registry, revised protocol, study no. CACZ885G2401] as adopted in June 2015
Action: For adoption of PRAC Assessment Report

16.2.7. Crizotinib – XALKORI (CAP) - EMEA/H/C/002489/MEA 011.3

Applicant: Pfizer Limited

PRAC Rapporteur: Corinne Fechant

Scope: Revised PASS protocol for study A8081038 to estimate the incidence rate and incidence proportion over a 3-year period of observation for hepatotoxicity, pneumonitis/interstitial lung disease (ILD), QTc prolongation related events, bradycardia, and visual disorder among lung cancer patients receiving crizotinib prescriptions
Action: For adoption of advice to CHMP

16.2.8. Crizotinib – XALKORI (CAP) - EMEA/H/C/002489/MEA 022

Applicant: Pfizer Limited

PRAC Rapporteur: Corinne Fechant

Scope: PASS protocol for studies to evaluate the effectiveness of the patient information brochure (PIB) and therapeutic management guide (TMG). It consists of: 1) study A8081049: cross-sectional study to evaluate the effectiveness of the TMG among physician; 2) study A8081050: a cross-sectional study to evaluate the effectiveness of the PIB among non-small cell lung cancer (NSCLC) patients receiving Xalkori treatment in Europe
Action: For adoption of advice to CHMP

16.2.9. Eliglustat – CERDELGA (CAP) - EMEA/H/C/003724/MEA 005.1

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Drug utilisation study for eliglustat in Europe using electronic healthcare records (final protocol for US DUS study report / ELIGLC06913)
Action: For adoption of advice to CHMP

16.2.10. Eliglustat – CERDELGA (CAP) - EMEA/H/C/003724/MEA 006

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Drug utilisation study for eliglustat in the US population using the MarketScan database (final protocol for US DUS study report / ELIGL C06912)
Action: For adoption of advice to CHMP

16.2.11. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope: MAH's response to MEA 002 [PASS protocol for BI study no. 1245.96] request for supplementary information (RSI) as adopted in May 2015
Action: For adoption of advice to CHMP

16.2.12. Epoetin zeta – RETACRIT (CAP) - EMEA/H/C/000872/MEA 031.1

Applicant: Hospira UK Limited

PRAC Rapporteur: Valerie Strassmann

Scope: PASS protocol for a PASCO II (PMS-830-09-0082): post-authorisation safety cohort observation of Silapo (epoetin zeta) administered subcutaneously for the treatment of renal anaemia
Action: For adoption of advice to CHMP

16.2.13. Florbetaben (^{18}F) – NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.3

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA. 001.2 [revised PASS protocol for study no. FBB-01_03_13] as adopted in April 2015
Action: For adoption of advice to CHMP

16.2.14. Flutemetamol (^{18}F) – VIZAMYL (CAP) - EMEA/H/C/002557/MEA 003.1

Applicant: GE Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA-003 [PASS protocol for a drug utilisation study as an additional pharmacovigilance activity to further characterize the safety concern (GE067-028)] as adopted in March 2015
Action: For adoption of advice to CHMP

16.2.15. Hydrocortisone – PLENADREN (CAP) - EMEA/H/C/002185/MEA 005.1

Applicant: ViroPharma SPRL

PRAC Rapporteur: Qun-Ying Yue

Scope: PASS protocol for study SWE-DUS (study no.: 10918 -404 (SHP617-404): a Swedish, retrospective, study progress reports to be provided on a yearly basis evaluating the pattern of Plenadren use from as part of the PSURs Swedish quality registries
Action: For adoption of advice to CHMP

16.2.16. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/MEA 023.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Updated protocol for a PASS study PCYC-PMR-2060-04: enhanced pharmacovigilance to evaluate the risks of haemorrhage with the administration of ibrutinib

16.2.17. Insulin human – INSUMAN (CAP) - EMEA/H/C/000201/MEA 047.1

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 047 [PASS protocol for study HUBIN-C-06380] as adopted in April 2015
Action: For adoption of advice to CHMP

16.2.18. Liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/MEA 014

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Drug utilisation study (DUS) protocol (study No. NN8022-4241): in-market utilisation of liraglutide used for weight management in Europe: a retrospective medical record review study
Action: For adoption of advice to CHMP

16.2.19. Liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/MEA 015

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Drug utilisation study (DUS) protocol (study No. NN8022-4246): in-market utilisation of liraglutide used for weight management in the UK: a study in the CPRD primary care database
Action: For adoption of advice to CHMP

16.2.20. Sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/MEA 013

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: Drug utilisation study (DUS) protocol (study number GS-EU-337-1820): an observational drug utilisation study of ledipasvir/sofosbuvir and tenofovir disoproxil fumarate with pharmacokinetic enhancer co-administration in adults co-infected with chronic hepatitis C and human immunodeficiency (HIV)-1 infections
Action: For adoption of advice to CHMP

16.2.21. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/MEA 041.4

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Revised paediatric registry protocol: observational safety and effectiveness study of patients with polyarticular juvenile idiopathic arthritis treated with tocilizumab
Action: For adoption of advice to CHMP

16.2.22. Voriconazole – VFEND (CAP) - EMEA/H/C/000387/MEA 091.1

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA-091 [PASS protocol for study A1501103] as adopted in April 2015
Action: For adoption of advice to CHMP

16.3. Results of PASS imposed in the marketing authorisation(s)[76]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[77]

16.4.1. Abacavir – ZIAGEN (CAP) - EMEA/H/C/000252/WS/0769 (without RMP)

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Isabelle Robine

Scope: Submission of final clinical study report (CSR) for mitochondrial toxicity in children (MITOC) study (WE027/WWE112888). The MAH took also the opportunity to respond to a LEG on mitochondrial dysfunction to address the request on revision of class labelling of antiretrovirals on mitochondrial toxicity
Action: For adoption of PRAC Assessment Report

16.4.2. Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS/0807 (without RMP); aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP) – EMEA/H/C/000964/WS/0807 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

[76] In accordance with Article 107p-q of Directive 2001/83/EC
[77] 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

Scope: Submission of final results of the non-interventional (NIS) aliskiren study SPP100A2418 on the incidence of colorectal hyperplasia and gastrointestinal cancer in aliskiren treated patients
Action: For adoption of PRAC Assessment Report

16.4.3. Anidulafungin – ECALTA (CAP) - EMEA/H/C/000788/II/0030 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of final study results of study A8851030: retrospective cohort study of the risk of severe hepatic injury in hospitalised patients treated with echinocandins for candida infections
Action: For adoption of PRAC Assessment Report

16.4.4. Bivalirudin – ANGIOX (CAP) - EMEA/H/C/000562/II/0058 (without RMP)

Applicant: The Medicines Company UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Study report for the study entitled: 'exposure and adverse event assessment (EAEA) for protocol TMC-BIV-07-01 bivalirudin (Angiomax) as a procedural anticoagulant in the paediatric population undergoing intravascular procedures for congenital heart disease' to update information on paediatric population

Action: For adoption of PRAC Assessment Report

16.4.5. Dabigatran – PRADAXA (CAP) - EMEA/H/C/000829/II/0079/G (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final clinical study report (CSR) for study 1160.84: observational cohort study undertaken to evaluate the safety and efficacy of Pradaxa in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) undergoing elective total hip replacement surgery or total knee replacement surgery. An updated RMP (version 31.0) was submitted accordingly
Action: For adoption of PRAC Assessment Report

16.4.6. Etanercept – ENBREL (CAP) - EMEA/H/C/000262/II/0182 (with RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of the final report of the STORK study: retrospective study to evaluate pregnancy outcomes associated with and without etanercept use among pregnant women with chronic inflammatory arthritis or psoriasis, as listed in RMP part III
Action: For adoption of PRAC Assessment Report

16.4.7. Human rotavirus, live attenuated – ROTARIX (CAP) - EMEA/H/C/000639/II/0062 (with RMP)

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report of genetic stability study EPI-ROTA-014 VS BE – 112560 that addresses the post-approval measure ME2 005.2: monitoring for the potential occurrence of genetic drifts and shifts in the vaccine strain in post-marketing settings
Action: For adoption of PRAC Assessment Report

16.4.8. Insulin detemir – LEVEMIR (CAP) - EMEA/H/C/000528/WS/0784 (with RMP) liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/WS/0784; VICTOZA (CAP) - EMEA/H/C/001026/WS/0784 - (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of final results for the database study NN2211-3880: a health care database study using the clinical practice research datalink (CPRD) to evaluate and monitor the safety of liraglutide
Action: For adoption of PRAC Assessment Report

16.4.9. Lamivudine – EPIVIR (CAP) - EMEA/H/C/000107/WS/0769 (without RMP), LAMIVUDINE VIIV (Art 58) - EMEA/H/W/000673/WS/0769 (without RMP); lamivudine, abacavir – KIVEXA (CAP) - EMEA/H/C/000581/WS/0769 (without RMP); lamivudine, abacavir, zidovudine – TRIZIVIR (CAP) - EMEA/H/C/000338/WS/0769 (without RMP); lamivudine, zidovudine – COMBIVIR (CAP) - EMEA/H/C/000190/WS/0769 (without RMP)

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Isabelle Robine

Scope: Submission of final clinical study report (CSR) for mitochondrial toxicity in children (MITOC) study (WE027/WWE112888). The MAH took also the opportunity to respond to a LEG on mitochondrial dysfunction to address the request on revision of class labelling of antiretrovirals on mitochondrial toxicity
Action: For adoption of PRAC Assessment Report

16.4.10. Moroctocog alfa – REFACTO AF (CAP) - EMEA/H/C/000232/II/0127/G (with RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of a post-marketing study in subjects with haemophilia A, study B1831078 and consequential update of the RMP. In addition, introduction of missing information in the RMP as previously agreed with PRAC: 'patients receiving anti-fibrinolytic agents, medications known to influence platelet function and concomitant therapy with immunosuppressive drugs' and 'patients with genetic polymorphisms'
Action: For adoption of PRAC Assessment Report

16.4.11. Raltegravir – ISENTRESS (CAP) - EMEA/H/C/000860/II/0052 (without RMP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of the fifth and final report of the five-year EuroSIDA post-authorisation observational study
Action: For adoption of PRAC Assessment Report

16.4.12. Regorafenib – STIVARGA (CAP) - EMEA/H/C/002573/II/0013 (without RMP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final clinical study report for study 16675 single-centre, open-label, non-randomized, two-period sequential treatment study to assess the effect of neomycin on the pharmacokinetics of regorafenib in healthy male subjects. The data does not require an update of the product information. An updated RMP is included
Action: For adoption of PRAC Assessment Report

16.4.13. Tolvaptan – SAMSCA (CAP) - EMEA/H/C/000980/II/0020 (without RMP)

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report for Samsca PASS (FUM 004): a multi-centre multi-national observational post-authorisation safety study to document the drug utilisation of Samsca and to collect information on the safety of Samsca when used in routine medical practice
Action: For adoption of PRAC Assessment Report

16.4.14. Vildagliptin – GALVUS (CAP) - EMEA/H/C/000771/WS/0791, JALRA (CAP) - EMEA/H/C/001048/WS/0791, XILIARX (CAP) - EMEA/H/C/001051/WS/0791 (with RMP) Vildagliptin, metformin – EUCREAS (CAP) - EMEA/H/C/000807/WS/0791, ICANDRA (CAP) - EMEA/H/C/001050/WS/0791, ZOMARIST (CAP) - EMEA/H/C/001049/WS/0791 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final results of PASS study CLAF237A2401 to add the study results and to include the 'rhabdomyolysis' under the current potential risk as 'muscle events/myopathy/rhabdomyolysis, in particular with concurrent statin use' following the PRAC recommendation EMA/PRAC/716523/2014. An updated RMP (version 13.0) is submitted accordingly
Action: For adoption of PRAC Assessment Report

16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[78]

16.5.1. Apixaban – ELIQUIS (CAP) - EMEA/H/C/002148/MEA 012.3

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Second interim report on a drug utilisation study (DUS) to monitor the potential off label use with apixaban: study of the utilisation patterns in Sweden (study B066017) and in the Netherlands (study B066018)
Action: For adoption of advice to CHMP

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

16.5.2. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 004.1 and 005.1 [canagliflozin independent data monitoring committee (IDMC) status reports for the DIA3008 CANVAS study], request for supplementary information (RSI) as adopted in April 2015
Action: For adoption of advice to CHMP

16.5.3. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.3 canagliflozin, metformin – VOKANAMET (CAP) – EMEAH/C/002656/MEA 004.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Six-monthly status report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study as requested in the RMP additional pharmacovigilance activity
Action: For adoption of advice to CHMP

16.5.4. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA 006

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Status report 1 of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity
Action: For adoption of advice to CHMP

16.5.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 004.1 [canagliflozin independent data monitoring committee (IDMC) status reports for the DIA3008 CANVAS study], request for supplementary information (RSI) as adopted in April 2015
Action: For adoption of advice to CHMP

16.5.6. Canagliflozin, metformin – VOKANAMET - EMEA/H/C/002656/MEA 005

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Status report 1 of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity
Action: For adoption of advice to CHMP

16.5.7. Collagenase clostridium histolyticum – XIAPEX (CAP) - EMEA/H/C/002048/MEA 015.1

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Interim clinical study report for study Auxilium B1531005: non-interventional post approval commitment study to evaluate the outcomes of the various treatment options for Dupuytren's contracture
Action: For adoption of advice to CHMP

16.5.8. Efavirenz – SUSTIVA (CAP) - EMEA/H/C/000249/MEA 079.2

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Second annual report for malignant events associated with efavirenz: diagnostic consulting network (DCN) report dated June 2015
Action: For adoption of PRAC Assessment Report

16.5.9. Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/MEA 039.2

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd

PRAC Rapporteur: Martin Huber

Scope: Second annual report for malignant events associated with efavirenz: diagnostic consulting network (DCN) report dated June 2015
Action: For adoption of PRAC Assessment Report

16.5.10. Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/MEA 022.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Interim report of the study measuring the effectiveness of eltrombopag educational materials for hepatitis C associated thrombocytopenia
Action: For adoption of advice to CHMP

16.5.11. Filgrastim – FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007; ZARZIO (CAP) – EMEA/H/C/000917/MEA 007

Applicant: Hexal AG

PRAC Rapporteur: Julie Williams

Scope: Submission of fourth interim report of study EP06-501 after four years of treatment: a non-interventional, prospective, long-term observational study to assess the safety and effectiveness of Zarzio/Filgrastim Hexal administered to healthy unrelated stem cell donors for peripheral blood progenitor cell mobilisation
Action: For adoption of advice to CHMP

16.5.12. Indacaterol – HIROBRIZ BREEZHALER (CAP) - EMEA/H/C/001211/MEA 015.1; ONBREZ BREEZHALER (CAP) - EMEA/H/C/001114/MEA 017.1; OSLIF BREEZHALER (CAP) - EMEA/H/C/002576/MEA 015.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: MAH's response [comments on fourth interim study report of US PASS] to request for supplementary information (RSI) as adopted in March 2015
Action: For adoption of advice to CHMP

16.5.13. Infliximab – INFLECTRA (CAP) - EMEA/H/C/002778/MEA 007

Applicant: Hospira UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Annual safety and efficacy interim analysis for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra in patients with rheumatoid arthritis (EU and Korea)
Action: For adoption of advice to CHMP

16.5.14. Infliximab – INFLECTRA (CAP) - EMEA/H/C/002778/MEA 010

Applicant: Hospira UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Annual safety and efficacy interim analysis for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea)
Action: For adoption of advice to CHMP

16.5.15. Infliximab – REMSIMA (CAP) - EMEA/H/C/002576/MEA 007

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

Scope: Annual safety and efficacy interim analysis for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Remsima in patients with rheumatoid arthritis (EU and Korea)
Action: For adoption of advice to CHMP

16.5.16. Infliximab – REMSIMA (CAP) - EMEA/H/C/002576/MEA 010

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

Scope: Annual report on a registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea)
Action: For adoption of advice to CHMP

16.5.17. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP) - EMEA/H/C/000758/MEA 041.4

Applicant: Novartis Influenza Vaccines Marburg GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Two year interim report on study V58_30OB, an observational study to investigate the safety of Optaflu vaccination in adults in routine clinical care in the UK using the THIN database
Action: For adoption of advice to CHMP

16.5.18. Mannitol – BRONCHITOL (CAP) – EMEA/H/C/001252/ANX 002.6

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Fifth interim analysis of the cystic fibrosis (CF) study
Action: For adoption of advice to CHMP

16.5.19. Tenofovir – VIREAD (CAP) - EMEA/H/C/000419/MEA 256.4

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Interim results for a drug utilisation study (DUS) in human immunodeficiency virus (HIV)-1 and hepatitis B virus (HBV)-infected paediatric patients to follow-up the effectiveness of the risk minimisation measures
Action: For adoption of PRAC Assessment Report

16.5.20. Trastuzumab emtansine – KADCYLA (CAP) - EMEA/H/C/002389/MEA 011.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Second annual interim report on an observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with Herceptin or Perjeta in combination with Herceptin during pregnancy or within 6 months prior to conception
Action: For adoption of advice to CHMP

16.5.21. Vernakalant – BRINAVESS (CAP) - EMEA/H/C/001215/LEG 027

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Follow-up on case report of hypotension
Action: For adoption of advice to CHMP

16.6. Others

16.6.1. Eliglustat – CERDELGA (CAP) - EMEA/H/C/003724/ANX 001

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Concept protocol for a prospective multicentre observational post authorisation safety sub-registry to characterize the long-term safety profile of eliglustat of adult patients with Gaucher disease
Action: For adoption of advice to CHMP

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. Annual reassessments of the marketing authorisation

17.1.1. Amifampridine – FIRDAPSE (CAP) - EMEA/H/C/001032/S/0036 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation
Action: For adoption of advice to CHMP

17.1.2. Laronidase – ALDURAZYME (CAP) - EMEA/H/C/000477/S/0054 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation
Action: For adoption of advice to CHMP

18. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 7-10 September 2015 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Marianne Lunzer	Alternate	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
Marina Dimov Di Giusti	Member	Croatia	No interests declared	Full involvement
Viola Macolić Šarinić	Alternate	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
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Isabelle Robine	Member	France	No interests declared	Full involvement
Corinne Fechant	Alternate	France	No participation in discussions, final deliberations and voting	Human fibrinogen, human thrombin
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Alternate	Greece	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Melinda Palfi	Alternate via telephone*	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
Ruchika Sharma	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Alternate	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	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
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Magda Pedro	Alternate	Portugal	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Miguel-Angel Macia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	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
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Filip Babylon	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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
Valerie Beral	Expert - in person*	Principal investigator	No interests declared	Full involvement
Laurence de Fays	Expert - via telephone*	Belgium	No interests declared	Full involvement
Xavier Goossens	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Flora Musuamba Tshinanu	Expert - via telephone*	Belgium	No interests declared	Full involvement
Mikko Jokisalo	Expert - via telephone*	Finland	No interests declared	Full involvement
Sami Paaskoski	Expert - via telephone*	Finland	No interests declared	Full involvement
Florence Cardona	Expert - via telephone*	France	No interests declared	Full involvement
Carine Condy	Expert - via telephone*	France	No interests declared	Full involvement
Rosemary Dray-Spira	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Marc Martin	Expert - via telephone*	France	No interests declared	Full involvement
Sara Miranda	Expert - via telephone*	France	No interests declared	Full involvement
Wilma Fischer-Barth	Expert - via telephone*	Germany	No interests declared	Full involvement
Bernhardt Sachs	Expert - via telephone*	Germany	No interests declared	Full involvement
Eleanor Carey	Expert - in person*	Ireland	No interests declared	Full involvement
Giuseppe Rosano	Expert - in person*	Italy	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
Zane Stade	Expert - in person*	Latvia	No interests declared	Full involvement
Quirine Fillekes	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Lies van Vlijmen	Expert - in person*	Netherlands	No interests declared	Full involvement
Sophia Venzke	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Inge Zomerdijk	Expert - in person*	Netherlands	No interests declared	Full involvement
Leonor Chambel	Expert - in person*	Portugal	No interests declared	Full involvement
Miriam Verčinská	Expert - in person*	Slovakia	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Annika Folin	Expert - via telephone*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Olle Karlström	Expert - via telephone*	Sweden	No interests declared	Full involvement
Anna Vikerfors	Expert - via telephone*	Sweden	No interests declared	Full involvement
Philip Bryan	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Emma Cornforth	Expert -in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Kathryn Ord	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Andrew Ruddick	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Jane Woolley	Expert - in person*	United Kingdom	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
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in

19. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

20. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as 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 minutes)

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 minutes)

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

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk 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 minutes)

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/