11 January 2016
EMA/PRAC/75116/2016
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 30 November – 3 December 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 Chair opened the 30 November-3 December 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 – List of participants). 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 Chair welcomed Leonor Chambel, replacing Magda Pedro, as the new alternate for Portugal. The Chair also noted that Simona Kudeliene has become the new alternate for Lithuania. The PRAC wished both new alternates well in their new roles.

1.2. Agenda of the meeting of 30 November-3 December 2015

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

1.3. Minutes of the previous meeting on 3-6 November 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 3-6 November 2015 were published on the EMA website on 8 January 2016 (EMA/PRAC/799709/2015).

2. EU referral procedures for safety reasons: urgent EU procedures

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

3. EU referral procedures for safety reasons: other EU referral procedures

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. 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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for fusafungine-containing products to review the benefit risk of fusafungine following an increase in the reporting rate of serious allergic reactions including anaphylactic reactions in paediatric and adult populations, as well as its potential role in promoting antibiotic resistance. For background information, see PRAC minutes September 2015.

Summary of recommendation(s)/conclusions

The PRAC discussed the responses from the Paediatric Committee (PDCO) on the clinical use of fusafungine-containing products in paediatric patients together with the conclusion reached by the Rapporteurs. The PRAC agreed on a list of outstanding issues (LoOI) to be addressed by the MAH in accordance with a revised timetable (EMA/PRAC/550970/2015 rev1). In addition, the Committee adopted a list of questions for the Scientific Advisory Group anti-infectives (SAG-AI) organised on 21 January 2016. The PRAC was invited to provide nominations of experts for the SAG-AI by 21 December 2015.

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(8) of Regulation (EC) No 726/2004, based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Tysabri (natalizumab) to review the risk estimates and diagnosis of progressive multifocal leukoencephalopathy (PML) before the development of clinical symptoms and anti-JCV (John Cunningham virus) antibodies in the light of further evidence and scientific progress, in order to better define the risk of PML and identify measures to further minimise it. For background information, see PRAC minutes May 2015, PRAC minutes September 2015, PRAC minutes October 2015 and PRAC minutes November 2015.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusions reached by the Scientific Advisory Group on Neurology (SAG-N) held on 6 November 2015. The Committee adopted a second list of outstanding issues (LoOI) to the MAH and a revised timetable for the procedure (EMA/PRAC/293314/2015 rev3).

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

None

4. Signals assessment and prioritisation[1]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Adalimumab – HUMIRA (CAP)

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of glomerulonephritis (GN)
EPITT 18528 – New signal
Lead Member State(s): SE

Background

Adalimumab is a tumour necrosis factor alpha (TNF-α) inhibitor indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatric

[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

arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease and ulcerative colitis under certain conditions.

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

Following several publications[2] highlighting a possible causal role of anti-TNF alpha in the new onset/exacerbation of glomerular disease, a signal of glomerulonephritis was identified by the EMA, based on 13 supportive 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 variable time to onset, that a positive de-challenge and positive re-challenge was observed in one case of glomerulonephritis and acute renal failure, and that in another case the patient did not have any renal disease before starting adalimumab, and that several potential mechanisms have been postulated, the PRAC agreed to request the MAH of Humira to provide a cumulative review of all reported cases of glomerulonephritis in association with adalimumab.

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should submit to the EMA, within 60 days, a cumulative review of all reported cases of glomerulonephritis in association with adalimumab. Efforts should be made to collect information on time to onset, concomitant medication and medical history. The review should include results from clinical trials, post-marketing experience, registries and the literature. The MAH should discuss the possible aetiology, including the potential role of adalimumab, for each reported case, as well as the incidence of reported cases as compared to the expected incidence of glomerulonephritis disorders in the intended population, based on experience from clinical studies and the registries in place. The MAH should also discuss the need for any potential amendment to the product information and/or the risk

[2] Jahan N, et al. Out of the frying pan and into the fire: rapidly progressive glomerulonephritis secondary to adalimumab. Am. J. Kidney Dis. 2015;65 (4):A44. - EudraVigilance
Piga M, et al. Biologics-induced autoimmune renal disorders in chronic inflammatory rheumatic diseases: systematic literature review and analysis of a monocentric cohort. Autoimmun Rev. 2014 Aug;13 (8):873-9
Wei SS, et al. Adalimumab (TNFα inhibitor) Therapy exacerbates IgA glomerulonephritis acute renal injury and induces lupus autoantibodies in a psoriasis patient. Case Rep Nephrol. 2013;2013:812781
Nishimura K, et al. Tumor necrosis factor-á inhibitor-induced antiglomerular basement membrane antibody disease in a patient with rheumatoid arthritis. J Rheumatol. 2012 Sep;39(9):1904-5
Tosovský M, et al. Case 1-2012: ANCA associated glomerulonephritis in combination with IgG4-positive mediastinal mass in a patient with ankylosing spondylitis treated with TNF alpha inhibitors. Acta Medica (Hradec Kralove). 2012;55(1):42-6. PubMed PMID: 22696935
Kolluru S, et al. Collapsing glomerulopathy following treatment of rheumatoid arthritis with adalimumab, an anti-TNF alpha monoclonal antibody. Am J Kidney Dis (AJKD), Abs 135. 2012;59 (4):A48- A48. - EudraVigilance
Gupta A, et al. Development of the nephrotic syndrome during treatment of Crohn's disease with adalimumab. J Clin Gastroenterol. 2011 Mar;45(3)
Chen T, et al. Permanent renal loss following tumor necrosis factor alpha antagonists for arthritis. Rheumatology International 2010;30:1077-1079. - EudraVigilance
Fournier A, et al. [Antineutrophil cytoplasmic antibody associated vasculitis in a patient treated with adalimumab for a rheumatoid arthritis]. Nephrol Ther. 2009 Dec;5(7):652-7. (French) – EudraVigilance
Simms R, et al. ANCA-associated renal vasculitis following anti-tumor necrosis factor alpha therapy. Am J Kidney Dis. 2008 Mar;51(3)
Stokes MB, et al. Development of glomerulonephritis during anti-TNF-alpha therapy for rheumatoid arthritis. Nephrol Dial Transplant. 2005 Jul; 20(7):1400-6

management plan and make a proposal accordingly for the changes to the relevant sections within this discussion.

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

4.1.2. Dabigatran – PRADAXA (CAP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Signal of pulmonary alveolar haemorrhage
EPITT 18516 – New signal
Lead Member State(s): DK

Background

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

The exposure for Pradaxa, a centrally authorised medicine containing dabigatran, is estimated to have been more than 4,199,015 patient-years worldwide, in the period from first authorisation in 2008 until February 2015.

During routine signal detection activities, a signal of pulmonary alveolar haemorrhage was identified by the EMA, based on 35 supportive 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 that bleeding is not unexpected due to the mechanism of action of dabigatran and that the reported causality is definite in 6 cases, the PRAC agreed to request the MAH for Pradaxa to provide a cumulative review of cases of pulmonary alveolar haemorrhage in association with dabigatran.

Summary of recommendation(s)

- The MAH for Pradaxa (dabigatran) should submit to the EMA, in the next PSUR (DLP: 18/03/2016) (PSUSA/00000918/201603), a cumulative review of cases of pulmonary alveolar haemorrhage in association with dabigatran. The review should include the identification of any risk factors and consist of literature, preclinical and in vitro data as well as clinical trials. The MAH should also discuss the need for any potential amendment to the product information and/or risk management plan and make a proposal accordingly for the changes to the relevant sections within this discussion.

4.1.3. Flucloxacillin (NAP); paracetamol (NAP)

Applicant: various

PRAC Rapporteur: Margarida Guimarães

Scope: Signal of metabolic acidosis following administration of flucloxacillin in association with paracetamol
EPITT 18514 – New signal
Lead Member State(s): PT

Background

Flucloxacillin is a narrow-spectrum beta-lactam antibiotic of the penicillin class. It is used to treat infections caused by susceptible Gram-positive bacteria such as chest, ear, nose and throat (e.g. tonsillitis, sinusitis, pneumonia), skin and soft tissue (e.g. boils, burns, wounds, abscesses, infected eczema, infected acne) and other infections including those of the heart (endocarditis), bones and joints (osteomyelitis), membranes of the brain (meningitis), gastro-intestinal system (enteritis), blood (septicaemia), and the kidney, bladder or urethra. It can also be used to prevent infections during major surgical procedures, particularly in heart or orthopedic surgery.

Paracetamol has analgesic and antipyretic activities believed to be mediated principally through its inhibition of prostaglandin synthesis in the central nervous system.

A signal of metabolic acidosis following administration of flucloxacillin in association with paracetamol was identified by Portugal, based on information provided by the MAH of flucloxacillin (Stragen) following identification of 3 literature case reports of metabolic acidosis with flucloxacillin. Portugal confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the cases reported in EudraVigilance and from the literature. Although flucloxacillin does not appear as the primary cause of metabolic acidosis (in all identified cases other co-suspected drugs were involved and all the concerned patients had additional risk factors), the role of flucloxacillin in the occurrence of pyroglutamic acidosis cannot be excluded and can be explained at molecular level by its action in the gamma glumatyl cycle. This action could be potentially significant when flucloxacillin is associated with drugs acting at a different point on the gamma-glutamyl cycle, such as paracetamol. However considering that there are some limitations with the reported cases, the PRAC agreed that further analysis of this signal would be needed, including both EudraVigilance data and literature searches for metabolic acidosis cases associated with flucloxacillin and other penicillins of the beta-lactamase resistant group: dicloxacillin, cloxacillin, oxacillin and nafcillin.

The PRAC appointed Margarida Guimarães as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed that the PRAC Rapporteur should perform an additional analysis of this signal including both EudraVigilance data and literature searches for metabolic acidosis in association with flucloxacillin. Furthermore, the analysis should be extended to penicillins of the beta-lactamase resistant group (ATC code J01CF): dicloxacillin, cloxacillin, oxacillin and nafcillin. The PRAC Rapporteur will circulate an assessment report on this signal.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

Applicant: Hospira UK Limited (Inflectra), Janssen Biologics B.V. (Remicade), Celltrion Healthcare Hungary Kft (Remsima)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of thyroid gland disorders
EPITT 18530 – New signal
Lead Member State(s): SE, UK

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 exposure for Remicade, a centrally authorised medicine containing infliximab, is estimated to have been more than 4,227,014 patient-years worldwide, in the period from first authorisation in 1999 until August 2013.The exposure for Inflectra, a centrally authorised medicine containing infliximab, is estimated to have been more than 1,759 patient-years worldwide, in the period from first authorisation in 2013 until January 2015. The exposure for Remsima, a centrally authorised medicine containing infliximab, is estimated to have been more than 5,037 patient-years worldwide, in the period from first authorisation in 2013 until January 2015.

Following the publication by *Pascart et al.*[3], a signal of thyroid gland disorders was identified by the EMA, based on 24 cases retrieved from EudraVigilance. Sweden 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 the literature. Taking into account that positive de-challenge was observed in some cases and positive re-challenge in one case and that a biological mechanism is plausible, the PRAC agreed to request the MAH of Remicade to provide a cumulative review of all reported cases of thyroid disorders in association with infliximab, from clinical trials, post-marketing experience, including from the registries in place, and the literature.

The PRAC appointed Ulla Wändel Liminga as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Remicade (infliximab) should submit to the EMA, within 60 days, a cumulative review of all reported cases of thyroid disorders in association with infliximab, from clinical trials, post-marketing experience, including from the registries in place, and the literature. The MAH should discuss a possible role of infliximab in the development of these events, considering a possible pathophysiology, such as by causing an autoimmune disorder, predisposing to viral infections or direct thyrotoxic effects. Additionally, the MAH should comment on the different background incidences for thyroid disorders in the indicated populations. The MAH should also discuss the

[3] Pascart T, Ducoulombier V, Roquette D, Perimenis P, Coquerelle P, Maury F, Baudens G, Morel G, Deprez X, Flipo RM, Houvenagel E. Autoimmune thyroid disorders during anti-TNF alpha therapy: coincidence, paradoxical event or marker of immunogenicity? Joint Bone Spine. 2014 Jul;81(4):369-70

need for any potential amendment to the product information and/or risk management plan and if appropriate make a proposal accordingly for changes to the relevant sections.

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

4.1.5. Olanzapine –ZYPREXA (CAP), ZYPREXA VELOTAB (CAP); olanzapine pamoate – ZYPADHERA (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)
EPITT 18534 – New signal
Lead Member State(s): FI

Background

Olanzapine is an atypical antipsychotic used for the treatment of schizophrenia, for the treatment of moderate to severe manic episodes and for the prevention of recurrence in patients with bipolar disorder. As a suspension for injection, it is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or manic episodes, when oral therapy is not appropriate.

The exposure for Zyprexa and Zyprexa Velotab, centrally authorised medicines containing olanzapine, is estimated to have been more than 27,470,600 patient-years of exposure worldwide, in the period from first authorisation until March 2015. The exposure for Zypadhera, a centrally authorised medicine containing olanzapine pamoate, is estimated to have been more than 35,400 patient-years worldwide, in the period from first authorisation in 2008 until March 2014.

During routine signal detection activities, a signal of drug reaction with eosinophilia and systemic symptoms (DRESS) was identified by the EMA, based on 23 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account the 6 well-documented cases with positive de-challenge including 5 with a positive patch test, the PRAC agreed to request the MAH for Zyprexa, Zyprexa Velotab and Zypadhera (olanzapine) to provide a cumulative review of all cases of DRESS and related terms associated with olanzapine/olanzapine pamoate.

Summary of recommendation(s)

- The MAH for Zyprexa, Zyprexa Velotab and Zypadhera (olanzapine) should submit to the EMA, within 60 days, a cumulative review of all cases of Drug Reaction with Eosinophilia Systemic Symptoms (DRESS) and related terms associated with olanzapine/olanzapine pamoate. The cumulative review should include information from spontaneous reports, literature cases and any relevant studies. The review should also cover all other available data including relevant disease registry data. The MAH should discuss the need for any potential amendment to the product information and/or the

risk management plan and make a proposal accordingly for the changes to the relevant sections of the product information and/or risk management plan within this discussion.

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

4.1.6. Vismodegib - ERIVEDGE (CAP)

Applicant: Roche Registration Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of angioedema
EPITT 18526 – New signal
Lead Member State(s): SE

Background

Vismodegib is an inhibitor of the Hedgehog pathway which leads via signalling through the smoothened transmembrane protein (SMO) to the activation and nuclear localisation of glioma-associated oncogene (GLI) transcription factors and induction of Hedgehog target genes. It is indicated for the treatment of adult patients with symptomatic metastatic basal cell carcinoma and locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

The exposure for Erivedge, a centrally authorised medicine containing vismodegib, is estimated to have been more than 4,493 worldwide, in the period from first authorisation in 2013 until July 2015.

During routine signal detection activities, a signal of angioedema 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. Taking into account that the time to onset ranged from 2 to 12 days, that symptoms improved or recovered after treatment discontinuation and administration of anti-allergic treatment, and the precaution for signs and symptoms of angioedema in the EU package leaflet of sonidegib[4], the PRAC agreed to request the MAH for Erivedge (vismodegib) to provide a cumulative review of evidence regarding angioedema, covering clinical studies, post-marketing data and the literature.

Summary of recommendation(s)

- The MAH for Erivedge (vismodegib) should submit to the EMA, within 60 days, a cumulative review of evidence regarding angioedema covering clinical studies, post-marketing data and the literature. The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan and make a proposal accordingly for the changes to the relevant sections within this discussion.

[4] Of the same substance class as vismodegib

- 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 that the MAH should submit their responses in the next PSUR (DLP: 29/01/2016) (PSUSA/00010140/201601) instead of within 60 days as originally agreed by the PRAC.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. 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
EPITT 18258 – Follow-up to September 2015

Background

For background information, see PRAC minutes April 2015, PRAC minutes June 2015 and PRAC minutes September 2015. Consulted MAHs provided 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) which were assessed by the Rapporteur.

Discussion

The PRAC considered the comments received following the consultation on the update of the product information of post-menopausal hormone replacement therapy products regarding the risk of ovarian cancer. The PRAC concluded that the results of the meta-analysis published in the Lancet[5] on the risk of ovarian cancer associated with the use of post-menopausal hormone replacement therapy products provide sufficiently strong evidence to justify a revision of the product information (special warnings and precautions, undesirable effects of the SmPC and the package leaflet).

Summary of recommendation(s)

- The MAHs for post-menopausal hormone replacement therapy products (all medicinal products containing oestrogens, including tibolone, or combined oestrogens-progestagens, which are not pharmaceutical forms for vaginal use) should submit to EMA or to the relevant EU national competent authorities (NCAs) as applicable, within 90 days, a variation to amend the current warning on ovarian cancer in the special warnings and precautions for use and undesirable effect sections of the SmPC.

[5] 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, Volume 385, Issue 9980, 1835 – 1842, February, 13, 2015

For the full PRAC recommendations, see EMA/PRAC/788914/2015 published on the EMA website.

4.3.2. Human fibrinogen, human thrombin – TACHOSIL (CAP) - EMEA/H/C/000505/SDA/041

Applicant: Takeda Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of intestinal obstruction
EPITT 18373 – Follow-up to November 2015

Background

For background information, see PRAC minutes July 2015 and PRAC minutes November 2015. The MAH submitted a proposed wording to update the product information in relation to the risk of intestinal obstruction, together with a draft direct healthcare professional communication (DHPC) and a communication plan which were assessed by the Rapporteur.

Discussion

The PRAC considered the MAHs' proposal to update the product information, draft DHPC and communication plan. Taking into account all the available evidence from EudraVigilance, the literature and the data submitted by the MAH, the PRAC concluded that the MAH should submit a variation to update its product information (warnings and precautions for use, undesirable effects and special precautions for disposal and other handling sections of the SmPC and the package leaflet).

Summary of recommendation(s)

- The MAH for TachoSil (human fibrinogen, human thrombin) should submit to EMA, within 30 days, a variation to include a new warning relating to formation of adhesion to gastrointestinal tissues leading to gastrointestinal obstruction, to add intestinal obstruction and adhesions as new undesirable effects and that failure to adequately clean adjacent tissues may cause adhesions. An updated RMP should be submitted by the MAH within this variation to include gastrointestinal obstruction as an important identified risk.
- The MAH should distribute a DHPC according to the text and communication plan agreed with the PRAC and CHMP.

For the full PRAC recommendations, see EMA/PRAC/788914/2015 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 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. Daclizumab - EMEA/H/C/003862

Scope: Treatment of multiple sclerosis

5.1.2. Dexamethasone - EMEA/H/C/004071, Orphan

Applicant: Laboratoires CTRS, Hybrid

Scope: Treatment of symptomatic multiple myeloma in combination with other medicinal products

5.1.3. Emtricitabine, tenofovir alafenamide - EMEA/H/C/004094

Scope: Treatment of human immunodeficiency virus (HIV)

5.1.4. Glycopyrronium bromide - EMEA/H/C/003883

Scope: Treatment of sialorrhoea

5.1.5. Infliximab - EMEA/H/C/004020

Scope: Treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis

5.1.6. Ixazomib - EMEA/H/C/003844, Orphan

Applicant: Takeda Pharma A/S

Scope: Treatment of multiple myeloma

5.1.7. Ixekizumab - EMEA/H/C/003943

Scope: Treatment of moderate to severe plaque psoriasis

5.1.8. Rociletinib - EMEA/H/C/004053

Scope (accelerated assessment): Treatment of patients with mutant epidermal growth factor receptor (EGFR) non-small cell lung cancer (NSCLC)

5.1.9. Trifluridine, tipiracil - EMEA/H/C/003897

Scope: Treatment of colorectal cancer

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

See Annex I.14.2.

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

See also Annex I. 14.3.

5.3.1. Fentanyl – INSTANYL (CAP) - EMEA/H/C/000959/X/0030/G

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Isabelle Robine

Scope: Grouped variation to replace the current multi-dose nasal spray by a new improved child resistant multi-dose nasal spray. Addition of a new packsize of 30 doses for each current strength (50 micrograms/dose, 100 micrograms/dose and 200 micrograms/dose). Tightening of the assay release limit of the multi-dose finished product to 98.0%-102.0%. Reduction of the shelf life for all strengths of the multi-dose finished product to 24 months. Additionally, the MAH took the opportunity to include an editorial change, to change the wording of the specification footnote regarding the droplet size distribution test

Background

Fentanyl is an opioid analgesic indicated as a nasal spray for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain.

The CHMP is evaluating a type II variation for Instanyl, a centrally authorised product containing fentanyl, to replace the current multi-dose nasal spray by a new improved child resistant multi-dose nasal spray including a dose counter and a lock-out system and to add a new pack size, together with a reduction in the shelf life for all strengths. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. For further background, see also PRAC minutes February 2015.

Summary of advice

- The RMP version 16.2 for Instanyl (fentanyl) in the context of the variation under evaluation by the CHMP was considered acceptable provided that satisfactory responses to the request for supplementary information are submitted.
- The PRAC considered that the new child resistant multi-dose nasal spray should limit the risk for medication errors and did not support the dissemination of a direct healthcare professional communication (DHPC) to HCPs as the educational materials for patients and for healthcare professionals will provide information on how to use this new device. In addition, the MAH should update the RMP to include the newly identified risk of accidental exposure of 'other people including children to the drug expelled in the patient's proximity during priming'. Finally, a picture of the electronic multidose spray was considered necessary on the outer carton of the electronic multidose system to further differentiate it from the currently authorised presentation.

5.3.2. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0004

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information on toxic epidermal necrolysis (TEN) and encephalitis. The Package Leaflet is updated accordingly

Background

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb),indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults as well as for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

The CHMP is evaluating a type II variation procedure for Opdivo, a centrally authorised product containing nivolumab, to update the safety information on toxic epidermal necrolysis (TEN) and encephalitis. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 2.1 for Opdivo (nivolumab) in the context of the variation under evaluation by the CHMP was considered acceptable.
- The MAH should ensure that the safety concern 'TEN, including fatal outcomes' is added to the educational materials, namely a management guide for HCPs and a patient alert card regarding these adverse reactions, whose content and format (including communication media, distribution modalities, and any other aspects of the programme) should be agreed with the relevant NCAs prior to the launch of the medicinal product in each EU Member State. The PRAC also concurred that at present, there is no need to disseminate a direct healthcare professional communication (DHPC) to HCPs in order to communicate the risk of TEN as the product information contains this information.

5.3.3. Paliperidone – PALIPERIDONE JANSSEN (CAP) - EMEA/H/C/004066/X/0007/G

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variation consisting of an extension application to introduce four new strengths of a once-every-3-month paliperidone injection formulation (175 mg, 263 mg, 350 mg and 525 mg). In addition, extension of indication to revise the injection frequency to ' once-every-3-months' following prior adequate treatment with paliperidone for at least four months. Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 are updated. The Package Leaflet and RMP are updated accordingly. In addition, section 1 of SmPC is updated to change the name of the medicinal product from 'Paliperidone Janssen' to 'Trevicta'. Finally, deletion of authorised dosage strengths (i.e. Paliperidone Janssen 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 150 mg / 100 mg - EU/1/14/971/001-006)

Background

Paliperidone is a selective blocking agent of monoamine effects indicated for the maintenance treatment of schizophrenia in adult patients under certain conditions.

The CHMP is evaluating a grouping of type II variations for Paliperidone Janssen (now Trevicta), a centrally authorised product containing paliperidone, including a line extension to introduce four new strengths of an injection formulation for administration every three months following prior adequate treatment with paliperidone for at least four months, and to revise the injection frequency accordingly. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 7.0 for Paliperidone Janssen (paliperidone) in the context of the variation under evaluation by the CHMP was considered acceptable provided that satisfactory responses to the request for supplementary information are submitted.
- The MAH should revise the safety specifications by deleting some sufficiently characterised important identified and potential risks.

5.3.4. Pioglitazone – ACTOS (CAP) - EMEA/H/C/000285/WS/0848, GLUSTIN (CAP) - EMEA/H/C/000286/WS/0848; pioglitazone, glimepiride – TANDEMACT (CAP) - EMEA/H/C/000680/WS/0848; pioglitazone, metformin – COMPETACT (CAP) - EMEA/H/C/000655/WS/0848, GLUBRAVA (CAP) - EMEA/H/C/000893/WS/0848

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Update of section 4.4 of the SmPC based on results of two long term observational cohort studies assessing bladder cancer risk with pioglitazone. The RMP is updated accordingly

Background

Pioglitazone is a thiazolidinedione, indicated alone or in combination with glimepiride, a sulfonylurea antidiabetic or with metformin, a biguanide, and is indicated in the treatment of type 2 diabetes mellitus under certain conditions.

The CHMP is evaluating a type II worksharing variation procedure for Actos, Competact, Glustin, Glubrava and Tandemact, centrally authorised products containing pioglitazone (and combinations with glimepiride or metformin) to update the safety information based on results of long term observational cohort studies[6] assessing the risk of bladder cancer with pioglitazone. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMPs[7] for Actos, Competact, Glustin, Glubrava and Tandemact (pioglitazone and combinations) in the context of the variation under evaluation by the CHMP could be acceptable provided that satisfactory responses to the request for supplementary information are submitted.
- In order to facilitate further review of the studies results, the MAH should address questions relating to the heterogeneity observed in between and within databases as well as the full results for all pooled datasets and sensitivity analyses.

6. Periodic safety update reports (PSURs)

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

See also Annex I. 15.1.

[6] Results for study AD-4833/EC445: PROspective pioglitAzone clinical trial in macro Vascular Events extension study; results for study AD4833-403: cohort study of pioglitazone and cancer incidence in patients with diabetes mellitus; Results for the pan european multi database bladder cancer risk characterisation study (er12-9433)
[7] RMP versions 22 for Actos, Glustin, Competact and Glubrava. RMP version 20 for Tandemact

6.1.1. Decitabine – DACOGEN (CAP) - PSUSA/09118/201505

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

Decitabine is a cytidine deoxynucleoside analogue indicated for the treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dacogen, a centrally authorised medicine containing decitabine, 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 Dacogen (decitabine) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a complete cumulative review of organising pneumonia and other subtypes of interstitial lung disease events with a clear analysis of diagnostic criteria, and of the causality associated to decitabine and/or other underlying factors. The MAH should comment on the appropriate wording for the special warnings and precautions section of the SmPC in relation to such cases. The MAH should also provide a complete cumulative review of cardiac disorder events and evaluate if any update to the product information is necessary regarding these events. Finally the MAH should closely monitor new cases of interstitial lung disease (ILD).

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. Epoetin theta – BIOPOIN (CAP), EPORATIO (CAP) - PSUSA/01240/201504

Applicant: Teva GmbH; Ratiopharm GmbH

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

Epoetin theta is a recombinant erythropoietin indicated for the treatment of symptomatic anaemia associated with chronic renal failure in adult patients as well as for the treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Biopoin and Eporatio, centrally authorised medicines containing epoetin theta, 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 Biopoin and Eporatio (epoetin theta) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include in the special warnings and precautions and undesirable effects sections that cases of neutralising anti erythropoietin antibody-mediated pure red cell aplasia (PRCA) associated with epoetin theta therapy have been reported in the post marketing setting. Therefore the current terms of the marketing authorisation(s) should be varied[8].
- In the next PSUR, the MAH should closely monitor any new adverse events (AEs) of allergic/hypersensitivity reactions or thromboembolic events which might be potentially related to the use of Terumo K-Pack II needles. The MAH should also continue to closely monitor cases of hypertensive disorders, shunt thrombosis in haemodialysis patients, thromboembolic events in cancer patients, pure red cell aplasia caused by neutralising anti-epoetin theta antibodies, increased cardiovascular risk in renal anaemia patients, tumour growth progression, increased mortality in cancer patients, hypo-responsiveness and off-label use in the paediatric population. Medication errors should continue to be monitored through routine pharmacovigilance activities but reports should be better documented in order to distinguish quality issues from handling errors. Moreover, the MAH should indicate for each report which kind of device has been used and specify the handling stage when the issue occurred. A cumulative review of medication errors should be presented in the next PSUR.

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

6.1.3. Ketoconazole – KETOCONAZOLE HRA (CAP) - PSUSA/10316/201505

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Viola Macolic Sarinic

Scope: Evaluation of a PSUSA procedure

Background

Ketoconazole is a steroidogenesis inhibitor indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ketoconazole HRA, a centrally authorised medicine containing ketoconazole, 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 Ketoconazole HRA (ketoconazole) in the approved indication remains unchanged.

[8] 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

- Nevertheless, the product information should be updated to include apixaban, cabazitaxel, cabozantinib and dabrafenib in the 'interactions and recommendations for co-administration' table in the interaction with other medicinal products and other forms of interaction section. Therefore the current terms of the marketing authorisation(s) should be varied[9].
- In the next PSUR, the MAH should provide a cumulative review of all cases involving increased transaminases and/or bilirubin values, along with all available data, whether or not the values were within the reference range, in order to assess the hepatotoxic effect of Ketoconazole HRA. The MAH should closely monitor cases of drug ineffectiveness and to present them in next PSUR along with their overview. The MAH should also carefully assess each reported case of cardiac disorder, and perform the necessary follow-up. Finally the MAH should provide the date of distribution of the Direct Healthcare Professional Communication (DHPC) in every country where ketoconazole HRA was launched.

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. Linagliptin – TRAJENTA (CAP) - PSUSA/01886/201505

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Linagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Trajenta, a centrally authorised medicine containing linagliptin, 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 Trajenta (linagliptin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include bullous pemphigoid as a new undesirable effect with a not known frequency. Therefore the current terms of the marketing authorisation(s) should be varied[10].

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.

[9] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[10] 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

6.1.5. Linagliptin, metformin – JENTADUETO (CAP) - PSUSA/09214/201505

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Linagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated in combination with metformin, a biguanide, for the treatment type 2 diabetes mellitus in adults under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jentadueto, a centrally authorised medicine containing linagliptin, 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 Jentadueto (linagliptin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include bullous pemphigoid as a new undesirable effect with a not known frequency. Therefore the current terms of the marketing authorisation(s) should be varied[11].

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

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

See also Annex I. 15.2.

6.2.1. Capecitabine – CAPECITABINE ACCORD (CAP), CAPECITABINE MEDAC (CAP), ECANSYA (CAP), XELODA (CAP), NAP - PSUSA/00531/201504

Applicant: Accord Healthcare Ltd; Medac Gesellschaft fuer klinische Spezialpraeparate m.b.H; Krka d.d. Novo mesto; Roche Registration Limited, various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU) indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, for the treatment of metastatic colorectal cancer, for first-line treatment of advanced gastric

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

cancer in combination with a platinum based regimen and finally in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Capecitabine Accord, Capecitabine Medac, Ecansya and Xeloda, centrally authorised medicines containing capecitabine, and nationally authorised medicines containing capecitabine, 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 capecitabine-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- The MAH Roche should be requested to submit to EMA, within 90 days, a variation to include 'fingerprint loss' as a new undesirable effect in the product information. The variation should include a review of the frequency, information on temporary and persistent fingerprint loss, ways to inform patients about this risk, treatment options and additional guidance on how patients should deal with this risk.
- In the next PSUR, all the MAHs should closely monitor cases of cerebrovascular disorders, gastrointestinal ischaemia, and dihydropyrimidine dehydrogenase deficiency. In addition, the MAHs should provide a review of all cases of capecitabine monotherapy associated with myocardial infarction and similar unlisted terms and provide a causality assessment. The MAHs should also further analyse the risk of hypertriglyceridemia and potential diminished efficacy with concomitant use of proton pump inhibitors.
  The MAHs Krka and Accord should provide the available literature regarding dermatomyositis (including paraneoplastic dermatomyositis), pancreatitis and thyroid disorder/dysfunction.
- All the MAHs should be requested to remove pancreatitis from the list of important potential risks in the next RMP update.

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

6.2.2. Methylthioninium chloride – METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP), NAP - PSUSA/02029/201505

Applicant: Provepharm SAS, various

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Methylthioninium chloride is a heterocyclic aromatic chemical agent used as an antidote indicated for the acute symptomatic treatment of medicinal and chemical product-induced methaemoglobinaemia.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Methylthioninium Chloride Proveblue, a centrally authorised medicine containing methylthioninium chloride, and nationally authorised medicines containing methylthioninium chloride, 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 methylthioninium chloride-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include injection site pain and pain in extremity as new undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[12].

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. PSUR procedures including nationally authorised products (NAPs) only

See also Annex I. 15.3.

6.3.1. Amlodipine besilate, ramipril (NAP) - PSUSA/00000181/201503

Applicant: various

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Amlodipine besilate is a calcium channel blocker and ramipril is an angiotensin-converting enzyme (ACE) inhibitor. In combination, the product is indicated for the treatment of hypertension in adult patients adequately controlled with the individual substances given concurrently.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing amlodipine besilate/ramipril, 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 amlodipine besilate/ramipril-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the interactions with trimethoprim (including its fixed dose combination with sulfamethoxazole), mammalian target of rapamycin (mTOR) inhibitors, tacrolimus or clarithromycin in the

[12] 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

interaction with other medicinal products and other forms of interaction section and to include the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and extrapyramidal disorders as new undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[13].

- In the next PSUR, triggered by the publication by *Kajiwara A et al.*14, all the MAHs should investigate the potential safety issue of an increased risk of vasodilation-related adverse symptoms caused by dihydropyridine calcium channel blockers in younger females by stratifying the case reports according to age group < 50 years versus > 50 years and according to sex retrospectively. Following the publication by *Li W et a*l.[15], all the MAHs should investigate the potential safety issue of breast cancer and discuss it within the next PSUR.
- The MAHs which have an RMP in place, should in the next update - to be submitted within an upcoming regulatory procedure - amend the list of important identified risks to include: hypersensitivity reactions including angioedema, anaphylactic reactions and severe skin reactions, concomitant use of angiotensin-converting-enzyme-inhibitors, angiotensin II receptor blockers or aliskiren, liver disorders including acute hepatic failure, cholestatic or cytolytic hepatitis, blood disorders including haematological abnormalities and electrolyte disturbances, renal disorders including impaired renal function and acute renal failure, gastrointestinal disorders including pancreatitis, cardiac disorders, neurological disorders, foetotoxicity; amend the list of important potential risks to include: syndrome of inappropriate antidiuretic hormone secretion, drug-drug interaction potential; amend the list of missing information to include fertility, pregnancy and lactation and use in children and adolescents under 18 years.

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. Carmustine (powder and solvent for solution for infusion) (NAP) - PSUSA/00010349/201504

Applicant: various

PRAC Lead: Corinne Fechant

Scope: Evaluation of a PSUSA procedure

Background

Carmustine is an alkylating antineoplastic agent indicated for the treatment of several malignant neoplasms in monotherapy or in combination with other antineoplastic medicines and/or further therapeutic measures (radiation therapy, operation) such as brain tumours, multiple myeloma, second line therapy in Hodgkin's lymphoma and non-Hodgkin's

[13] Update of SmPC sections 4.5 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

[14] Kajiwara A et al. Younger females are at greater risk of vasodilation-related adverse symptoms caused by dihydropyridine calcium channel blockers: results of a study of 11,918 Japanese patients. Clin Drug Investig. 2014 Jun;34(6):431–5

[15] Li W, Shi Q, Wang W, Liu J, Li Q, Hou F. PLoS. Calcium channel blockers and risk of breast cancer: a meta-analysis of 17 observational studies. ONE. 2014;9(9):e105801

lymphoma, tumours of gastrointestinal tract and malignant melanoma in combination with other neoplastic medicines.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing carmustine (powder and solvent for solution for infusion), 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 carmustine (powder and solvent for solution for infusion)-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include additional information on pulmonary toxicity also manifested as pneumonitis and interstitial disease in post-marketing experience. Therefore the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAHs should closely monitor cases of convulsions, provide a complete discussion and analysis of new cases, and discuss the need to consequently update the SmPC. The MAHs should closely monitor the use of high doses of carmustine, provide an analysis of its use if different from the marketing authorisation recommendations, and assess the risks associated with this use. The MAHs should discuss whether further actions should be taken.

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. Dihydroergocristine (NAP) - PSUSA/00001071/201504

Applicant: various

PRAC Lead: Margarida Guimaraes

Scope: Evaluation of a PSUSA procedure

Background

Dihydroergocristine is a partial agonist of alpha-adrenoreceptors indicated for the treatment of circulatory conditions in otorhinolaryngology (vertigo, tinnitus), the treatment of symptoms of chronic vascular cerebral disorders and age-related cognitive deterioration and for the treatment of chronic cerebrovascular disease (vertigo, memory disorders, difficult concentration, mood changes).

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

Summary of recommendation(s) and conclusions

[16] 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

- Based on the review of the data on safety and efficacy, and where the European Community decision (EC) on the referral procedure for ergot derivative medicinal products (EMEA/H/A-31/1325) was implemented, the risk-benefit balance of dihydroergocristine-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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

6.3.4. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/201504

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Influenza vaccine (surface antigen, inactivated) is an inactivated vaccine containing purified surface antigens of influenza viruses type A and B, propagated in embryonated chicken eggs, and inactivated with formaldehyde, indicated for prophylaxis of influenza from six months of age, especially in those who run an increased risk of associated complications.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing influenza vaccine (surface antigen, inactivated), 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 influenza vaccine (surface antigen, inactivated)-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on anxiety-related reactions including vasovagal reactions (syncope), hyperventilation or stress-related reactions, which can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH Novartis NVI should comment on and explain the context in which some adverse drug reactions were observed, considering that a quite high number of cases reported during the interval period. The MAH is requested to closely monitor non-febrile convulsions that are not listed in the current core data sheet.

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.

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

6.3.5. Metformin (NAP) - PSUSA/00002001/201504

Applicant: various

PRAC Lead: Corinne Fechant

Scope: Evaluation of a PSUSA procedure

Background

Metformin is a biguanide indicated for the treatment of type 2 diabetes mellitus (T2DM) as monotherapy or in combination with other oral antidiabetic agents or with insulin.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing metformin, 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 metformin-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should focus with a critical analysis of the following events: haemolytic anemia, hepatic disorders, encephalopathy, pemphigoid/pemphigus, angioedema, and monitor closely the risk during pregnancy and in utero exposure. The following issues should be kept under close monitoring: lactic acidosis with or without renal impairment, renal impairment with eGFR[18]<45 ml/min, leucocytoclastic vasculitis, vitamin B12 deficiency and megalobastic anemia, interaction with cimetidine and other OCT[19]1 and OCT2 inhibitors, interaction with acarbose, thyroxin/thyrotropin, phenprocoumon, pyrimethamine, clozapine, suicide attempt, tolerability in specific populations (e.g. children, elderly), liver disorders, serious skin reactions, encephalopathy.
- The MAH for Glucophage should be requested to submit to relevant National Competent Authorities within 6 months, a cumulative review of pregnancy cases reported. The analysis should be provided in accordance with the 'Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data' (EMEA/CHMP/313666/2005). In the review, the MAH should mention and discuss any information regarding the metabolic control of the pregnant diabetic women exposed to metformin and potential impact on pregnancy outcome. A specific focus on off label use of metformin for the treatment of polycystic ovary syndrome should be also discussed in the context of pregnancy occurring while treated for this disease. The MAH should provide a comprehensive review of data from clinical trials (including both MAH sponsored and non-sponsored studies), pharmacoepidemiological studies, including any pregnancy registries and all relevant published literature. The MAH should submit all available scientific evidence on the risk of coadministration of metformin with OCT1 and OCT2 transporters and its combinations with inhibitors of these transporters (e.g.

[18] Estimated glomerular filtration rate
[19] Organic cation transporter

cimetidine, dolutegravir, crizotinib, olaparib, daclatasvir, vandetanib) including a proposal for a variation to update the product information.

- Due to the current discrepancies between metformin-containing medicinal products in Europe, a wider review of the risk of lactic acidosis and on its use in renally impaired patients should be considered.

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.

Post-meeting note: the Dutch Medicines Agency (MEB) sent a letter of notification dated 25/01/2016 of a referral under Article 31 of Directive 2001/83/EC to the CHMP for the review of metformin-containing medicinal products with respect to the risk of lactic acidosis and use in patients with renal failure (EMA/50029/2016).

6.3.6. Ofloxacin (systemic use) (NAP) - PSUSA/00002203/201504

Applicant: various

PRAC Lead: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

Ofloxacin is a fluoroquinolone antibiotic (gyrase inhibitor). Ofloxacin (systemic use) is indicated for the treatment of urinary tract infections, male or female genital infections, skin and soft-tissue infections, bone and joint infections, abdominal and biliary tract infections, ear, nose, throat infections, respiratory tract infections, prevention of infections due to ofloxacin susceptible pathogens in patients with a significant reduction in resistance to infections (e.g. in neutropenic states) and in treatment of septicaemia.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing ofloxacin (systemic use), 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 ofloxacin (systemic use)-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include uveitis, severe liver injury and exfoliative dermatitis as undesirable effects with a not known frequency. Therefore the current terms of the marketing authorisation(s) should be varied[20].

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.

[20] 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

6.3.7. Ofloxacin (topical use) (NAP) - PSUSA/00002204/201504

Applicant: various

PRAC Lead: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

Ofloxacin is a fluoroquinolone antibiotic (gyrase inhibitor). Ofloxacin 0.3% is indicated for the treatment of external ocular infections in adults and children that are caused by ofloxacin-sensitive organisms in the following conditions: conjunctivitis, blepharitis, blepharoconjunctivitis, keratoconjunctivitis, keratitis, dacryocystitis, meibomianitis, hordeolum, and postoperative infection. Ofloxacin 1.5 mg/0.5 mL ear drops, solution is indicated for the topical treatment of chronic suppurative otitis media in adults and children over 12 years of age with perforated tympanic membranes and acute otitis media in paediatric patients over one year and older with tympanostomy tubes.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing ofloxacin (topical use), 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 ofloxacin (topical use)-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) for ofloxacin (otic formulation)-containing medicinal products should be maintained.
- Nevertheless, the product information for ofloxacin (ophthalmic formulation)-containing medicinal products should be updated to remove the warning on Stevens-Johnson syndrome in the special warnings and precautions section and to include Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) as a new undesirable effect with an unknown frequency and amend the same section regarding periorbital oedema (including eyelid oedema) to list it under another MedDRA SOC[21]. Therefore the current terms of the marketing authorisation(s) of ofloxacin (ophthalmic formulation) containing medicinal products 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.

6.3.8. Paracetamol (intravenous formulation) (NAP) - PSUSA/00002311/201505

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

[21] Medical Dictionary for Regulatory Activities System Organ class
[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 CMDh for adoption of a position

Background

Paracetamol (intravenous (IV) formulation) is a para-aminophenol derivative with analgesic and antipyretic properties indicated for the short-term treatment of moderate pain.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing paracetamol, 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 paracetamol-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should assess the effectiveness of the measures implemented to minimize the risks of confusion between milligrams and millilitres leading to overdose in children and underweight patients. The MAHs should provide a cumulative review and analysis of the cases reported for paracetamol for infusion and following literature review for paracetamol (any formulation) for the following issues: agranulocytosis, rhabdomyolysis, convulsions and paraesthesia, sleep disorders and delirium, pancreatitis, gastric haemorrhage, respiratory disorders, cardiac arrhythmias, cases of interaction between flucloxacillin and paracetamol as well as metabolic acidosis. Based on the analysis of cases, the MAHs should discuss the need for amending the product information accordingly.

  In future PSURs, each MAH should also provide additional analyses, on one hand, an analysis of the cases of renal disorders and on the other hand, an analysis of hepatobiliary disorders and abnormal liver functions. Both should contain a distinction between the cases which occurred in a context of therapeutic dosage and those in a context of overdose. In addition all the MAHs should review the scientific evidence available and discuss at the time of the next PSUR the relevance of maintaining the contraindication in patients with severe hepatocellular insufficiency. All the MAHs should continue reporting in PSURs on the latest scientific evidences on the risk of endocrine disruption with paracetamol.
- Regarding the recent articles by *Veyckemans et al.*[23] questioning the adequate posology recommendation to be used in children less than <10 kg, the next steps will be discussed with the CMDh.
- The MAHs which have an RMP in place should include hypotension and medication errors (overdose due to confusion between ml and mg in neonates, and overdose in underweight adult patients) as important identified risks in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP.

[23] Veyckemans F. Posologie du paracétamol IV chez le nouveau-né et le nourrisson de moins de 10kg; Annales francaises d'anesthesie et de reanimation (Impact Factor: 0.84); 03/2014; 21(9). DOI: 10.1016/j.annfar.2014.01.001
Veyckemans F, Anderson BJ, Wolf AR, Allegaert K. Intravenous paracetamol dosage in the neonate and small infant. Br J Anaesth. 2014 Feb;112(2):380-1. doi: 10.1093/bja/aet559

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 procedures

See Annex I. 15.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[24]

7.1.1. Afamelanotide – SCENESSE (CAP) - EMEA/H/C/PSP/0033

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Draft protocol for a retrospective chart review study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued the use of Scenesse. The second primary objective of the study should be the assessment of the compliance with risk minimisation recommendations and the controlled access programme for patients receiving Scenesse

Background

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

A protocol for a retrospective chart review study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued the use of Scenesse, and assessing compliance with risk minimisation recommendations and the controlled access programme for patients receiving Scenesse, 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 1 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that that the design of the study did not fulfil the study objectives. A number of concerns regarding the study objectives, the study design, the milestones, the setting and the variables should be resolved before the final approval of the study protocol. The PRAC therefore recommended that:
- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 60 days-assessment timetable will be applied.

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

See Annex I.16.2

[24] In accordance with Article 107n of Directive 2001/83/EC
[25] 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

7.3. Results of PASS imposed in the marketing authorisation(s)[26]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[27]

7.4.1. Agomelatine – THYMANAX (CAP) - EMEA/H/C/000916/II/0028; VALDOXAN (CAP) - EMEA/H/C/000915/II/0030 (without RMP)

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

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of the final study report for PASS study CLE-20098- 068: an observational cohort study to evaluate the safety of agomelatine in standard medical practice in patients with depressive illness. A prospective, observational (non-interventional), international, multicentre cohort study to fulfil a post-authorisation measure (MEA 006)

Background

Thymanax and Valdoxan are centrally authorised medicines containing agomelatine, a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist indicated for the treatment in adults of major depressive episodes.

The MAH committed to perform a non-interventional PASS: study CLE-20098-068, a prospective, observational cohort study, as listed in the RMP. The Rapporteur assessed the final results of study CLE-20098- 068, an observational cohort study to evaluate the safety of agomelatine in standard medical practice in patients with depressive illness.

Summary of advice

- The PRAC discussed the final results from study CLE-20098-068 which evaluated the safety of agomelatine in standard medical practice in patients depressive illness with a focus on hepatobiliary disorders, suicidality, skin disorders, elderly patients and patients with known renal disorders. The PRAC noted that the results from this study indicate non-compliance with the recommended hepatic transaminases monitoring schedule in clinical practice. The MAH did not perform any differentiation in frequency of non-compliance with transaminases monitoring between prescriber groups (psychiatrists versus general practitioners) or between different settings (hospitals, clinics and private practices). If any difference could be found, this might be valuable information concerning more targeted use of educational materials vis a vis the prescribers with the lowest grade of compliance. As part of the request for supplementary information, the MAH should discuss if such data could be provided based on the current study results. In addition, the MAH should comment on how compliance with agomelatine treatment was monitored in the study, provide information on the main characteristics of the cohort of patients with decreased renal function, and perform a post hoc subgroup analysis of patients ≥ 75 years old to investigate whether the incidence of adverse events was higher in this group compared with elderly patients aged 65-75 years.

[26] In accordance with Article 107p-q of Directive 2001/83/EC
[27] 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

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[28]

7.5.1. Ketoconazole – KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/MEA/004.1

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Viola Macolic Sarinic

Scope: Final report from named patient basis programme in France (ATU de cohorte): to further characterize the risk of hepatotoxicity in terms of frequency, symptoms in a real life use, potential risk factors, and consequences

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.

The MAH had committed to perform a PASS, a named patient basis programme in France (ATU[29] de cohorte), to further characterize the risk of hepatoxicity in terms of frequency of adverse drug reactions, symptoms in real life use, potential risk factors, and consequences. Interim results of the PASS looking into hepatoxicity and QT interval prolongation/Torsade de Pointes were assessed by the Rapporteur and discussed by the PRAC.

Summary of advice

- The PRAC discussed the MAH's responses to the list of questions raised in June 2016 on the interim analysis of the data collected in the named patient basis programme in France as well as the final study report of the named patient basis programme. The PRAC agreed that the comments raised as part of this named patient basis programme in France should be taken into account when developing the ERCUSYN[30] PASS protocol (see PRAC minutes May 2015 and PRAC minutes September 2015) and in future PSURs. In particular, from the safety data presented, the PRAC agreed that no conclusion could be drawn regarding QT prolongation, and the MAH was requested to ensure that physicians involved in the ERCUSYN study will be properly informed on how and in which units the QT values should be expressed, emphasising the need for the corrected QT value to be reported.
- The PRAC did not fully support the MAH's causality assessment regarding the involvement of Ketoconazole HRA in the occurrence of liver injury. Nevertheless, the PRAC supported the MAH's conclusions that liver injury occurred during the first months of treatment, but it was acknowledged that a complete data analysis for all patients was not performed due to the lack of reference ranges of local laboratories. In the ERCUSYN study protocol, the MAH should clearly state which values of liver enzymes are mandatory for assessment and need to be collected. Furthermore, the MAH should obtain all reference ranges and define clear guidelines and necessary steps for obtaining relevant missing data, if applicable. The PRAC stressed the need for all participating physicians to be aware of the importance of liver function monitoring and of providing the appropriate data.

[28] In line with the revised variations regulation for any submission before 4 August 2013
[29] 'Autorisation temporaire d'utilisation'
[30] European registry on Cushing's syndrome

7.6. Others

7.6.1. Gadoversetamide – OPTIMARK (CAP) - EMEA/H/C/000745/ANX/014.6

Applicant: Mallinckrodt Deutschland GmbH

PRAC Rapporteur: Rafe Suvarna

Scope: From R/012: Responses to request for supplementary information / response to outcome of teleconference from 27 July 2015 to evaluate options for protocol amendments of study no. ALS-Gd64/001

Background

Gadoversetamide is a chelate containing gadolinium indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver. It provides contrast enhancement and facilitates visualisation and helps with the characterization 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.

As part of a referral procedure under Article 31 of Directive 2001/83/EC completed in 2010 (EMEA/H/A-31/1097), the CHMP agreed that further clinical studies were warranted to assess the retention of gadolinium in bone and skin. Studies were initiated, in particular, ALS-Gd64-001[31] led by a consortium of MAHs, including the MAH for Optimark (gadoversetamide). For further background, see PRAC minutes May 2015 and PRAC minutes July 2015. At its current plenary meeting, the PRAC discussed the proposed amendments to the study protocol for ALS-Gd64-001.

Summary of advice

- The PRAC agreed to replace the separate study subgroups for moderate and severe renal impairment patients with a single combined subgroup for patients with at least moderate renal impairment. The PRAC also agreed with other proposals for protocol amendments and conditions for submission of interim analyses.
- The PRAC considered that the MAH should submit to the EMA, within 60 days, an updated version of the protocol and should provide the latest site initiation and patient recruitment figures together with detailed actions undertaking to increase the number of study sites, expand the study to include additional countries, target specific specialist sites and to provide additional site training. The MAH should provide details of the timelines for these actions and should discuss the anticipated impact on recruitment, with quantitative estimates of additional recruitment where possible. In addition, details of the revisions made to the protocol and the other actions to improve recruitment should be recorded in the RMP.

See also under 11.2.1. Gadolinium-containing contrast agents (GdCAs)

7.7. New Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

[31] Exploratory evaluation of the potential for long-term retention of Gadolinium in the bones of patients who have received Gadolinium based Contrast Agents according to their medical history

7.8. Ongoing Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

7.9. Final Scientific Advice (Reports and Scientific Advice letters)

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

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

See Annex I. 17.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders connected with human centrally authorised products

The PRAC agreed the list of planned pharmacovigilance inspections 2015-1018, second revision, reviewed according to a risk based approach. This list is subsequently due for adoption at CHMP.

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.

9.3. Others

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

10.3.1. Mitoxantrone (NAP) – EMA/H/A-30/1399

Applicant: Meda Pharma GmbH and associated companies (Novantrone)

PRAC Lead: Sabine Straus

Scope: PRAC consultation on the need for additional risk minimisation measures regarding the risk of leukaemia and cardiotoxicity as part of an ongoing referral procedure under Article 30 of Directive 2001/83/EC

Background

Mitoxantrone is a synthetic anthracenedione antineoplastic agent, indicated for the treatment of a number of malignancies, including breast carcinoma, acute leukaemia, and non-Hodgkin's lymphoma. It is also indicated for the treatment of prostate cancer in combination with corticosteroids and its immunosuppressant and immunomodulatory properties provide a rationale for use of mitoxantrone in active multiple sclerosis (MS).

The CHMP is evaluating a referral procedure for Novantrone (mitoxantrone) under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst nationally authorised product information with a view to harmonise this across the European Union. The CHMP requested PRAC advice on the need for a risk management plan and the potential need for risk minimisation measures, focusing on the MS indication.

Summary of advice

- Based on the available data, the PRAC considered that the risks of cardiomyopathy and leukaemia associated with mitoxantrone are well known. Nevertheless, it was considered that additional risk minimisation measures were needed to ensure physicians' awareness of the possible risks and highlight the importance of complying with the monitoring requirements, as included in the SmPC, as well as patients' understanding of the risks and of the monitoring needs during and after treatment. Therefore the PRAC recommended the development of educational materials, to be included in a RMP to ensure a consistent minimum standard of management of the risks of mitoxantrone. In addition, the PRAC advised that the adherence to the risk minimisation measures should be monitored via a post-authorisation study.

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

Lead member: Corinne Fechant

Scope: PRAC consultation on the applicability of the PRAC recommendation of the 2014 referral procedure on testosterone and cardiovascular safety under Article 31 of Directive 2001/83/EC to androstanolone

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 2014 PRAC conclusions on 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), France requested PRAC advice in September 2015 on the relevance of reflecting the product information changes concluded in this referral procedure in the product information of androstanolone-containing products. Before concluding its advice to Member States, the PRAC agreed to consult the Pharmacokinetics Working Party (PKWP). For further background, see PRAC minutes September 2015.

Summary of advice

- Based on the PKWP's responses to the PRAC list of questions, and the available information on androstanolone in the literature, the PRAC concurred that the administration of androstanolone is associated with an impact on several surrogate parameters that might be associated with an increased cardiovascular risk. In addition, as highlighted by the PKWP, the PRAC agreed that there was no evidence for a substantial difference in the totality of risk factors between testosterone and androstanolone based on a comparison of the pharmacokinetics (PK)/pharmacodynamics (PD) properties of the two substances, taking also into account the same mechanism of action. Therefore, the PRAC concluded that Member States should request the MAH of androstanolone-containing products to submit a national type II variation to NCAs to implement for androstanolone the product information changes concluded for testosterone-containing products in the framework of the referral procedure.

11.2. Other requests

11.2.1. Gadolinium-containing contrast agents (GdCA): Gadobenate dimeglumine; gadobutrol; gadodiamide; gadopentetic acid dimeglumine, gadoteric acid (intra-articular formulation); gadoteric acid (intravenous and intravascular formulations); gadoteridol; gadoxetic acid disodium (NAP)

Applicant: various

Lead member: Rafe Suvarna

Scope: PRAC consultation on a post-authorisation measure to conduct further clinical studies to assess the retention of gadolinium in bone resulting from the 2010 referral procedures under Article 20 of Regulation (EC) 726/2004 and Article 31 of Directive 2001/83/EC for gadolinium-containing contrast agents

Background

Gadolinium-containing contrast agents (GdCAs) are used intravenously as an enhancement for magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). A referral procedure under Article 31 of Directive 2001/83/EC, completed in 2010 (EMEA/H/A-31/1097), focused on measures to minimise the risk of nephrogenic systemic fibrosis (NSF) in specific patient groups, and investigation of concerns regarding accumulation of gadolinium in bone and skin tissue. As part of the outcome of the referral procedure, the CHMP agreed that further clinical studies were warranted to assess the retention of gadolinium in bone and skin. Studies were initiated, ALS-Gd64-001[32] led by a consortium of MAHs, including the MAH for Optimark (gadoversetamide), and GMRA-102 concerning two products authorised by national procedures. Due to slow rates of patient recruitment for both studies, revised protocols are being discussed. In May 2015, the UK requested PRAC advice on the issue of recruitment for study GMRA-102. For further background, see PRAC minutes May 2015 and PRAC minutes July 2015.
At its current plenary meeting, the PRAC discussed the proposed amendments to the study protocols for ALS-Gd64-001 and GMRA-102.

Summary of advice

- The PRAC noted that currently, the final results for both studies are expected in June 2016, although it is unlikely that recruitment according to the revised protocols will be completed by this date. Moreover, it was also agreed that the MAH conducting study GMRA-102 could be requested to explore options for expanding recruitment by recruiting patients from additional study sites currently taking part in study ALS-Gd64-001.
- The PRAC agreed to replace the separate study subgroups for moderate and severe renal impairment patients with a single combined subgroup for patients with at least moderate renal impairment. The PRAC also agreed with other proposals for protocol amendments, namely to reduce the minimum time between GdCA exposure and surgery to one month, and to reduce the numbers of patients with multiple exposure to the same GdCA required to complete the studies. In addition, the PRAC agreed with the proposed conditions for submission of interim analyses. Moreover, the PRAC advised

[32]Exploratory evaluation of the potential for long-term retention of gadolinium in the bones of patients who have received gadolinium based contrast agents according to their medical history

that the MAH conducting study GMRA-102 could be requested to explore options for expanding recruitment by recruiting patients from additional study sites currently taking part in study ALS-Gd64-001.

- Finally, the PRAC agreed with the protocol amendments for study GMRA-102. The CHMP will adopt these amendments at its December 2015 plenary meeting with regard to study ALS-Gd64-001. See under 7.6.1. Gadoversetamide

11.2.2. Tramadol, paracetamol (NAP) - PT/H/0919/002/E/001

Applicant: PTR Pharma Consulting, Lda (Tramadol Paracetamol Litexil)

Lead member: Margarida Guimarães

Scope: PRAC consultation on a CMDh procedure evaluated under Article 29(1) of Directive 2001/83/EC following a disagreement between Member States on the risk management plan and the need for a drug utilisation study (DUS)

Background

Tramadol is an opioid analgesic, and in combination with paracetamol, an analgesic, is indicated for the symptomatic treatment of moderate to severe pain.

In the context of an ongoing referral procedure under Article 29(1) of Directive 2001/83/EC recently referred to the CMDh following a disagreement between Member States in relation to a repeat use[33] mutual recognition procedure (MRP) for Tramadol/Paracetamol Lixetil 75 mg/650 mg tablets in view of the strength being twice that of the reference medicinal product, the CMDh requested PRAC advice on the risk management plan and the need for a drug utilisation study (DUS).

Summary of advice

- Based on the review of the available information, the PRAC considered that this combination and dosage of tramadol/paracetamol might raise a concern regarding the possible risk of misuse and/or overdose. The PRAC also noted that medicinal products containing the same combination of substances and strengths have been already authorised in the EU since 2011 and a search in EudraVigilance did not reveal any relevant cases of overdosing/medication errors. Therefore, the PRAC concluded that routine pharmacovigilance activities should be sufficient and considered that risk minimisation activities should be carefully addressed in the RMP in order to minimise or mitigate the important potential risks of misuse and overdose.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

[33] The mutual recognition procedure can be used more than once for subsequent applications to other Member States in relation to the same medicinal product (so called repeat use). Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, Procedures for marketing authorisation, Chapter 2, Mutual Recognition, February 2007 (ENTR/F2/ SM(2007))

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Joint Paediatric Committee (PDCO)-PRAC Working Group - guideline on conduct of pharmacovigilance for medicines used by the paediatric population

PRAC lead: Jolanta Gulbinovič; Amy Tanti

Following the October and November 2015 discussions (see PRAC minutes October 2015 and PRAC minutes November 2015), a further updated draft guideline on the conduct of pharmacovigilance for medicines used by the paediatric population was presented. A follow-up is needed, in particular, on the section related to paediatric off-label use. The guideline is scheduled for further discussion at the January 2016 PRAC meeting.

12.2.2. Paediatric pharmacovigilance - organ maturation tables

The topic was deferred to the January 2016 PRAC meeting.

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

12.3.1. Scientific Advice Working Party (SAWP) – consultation procedure: involving the PRAC outside the pilot for non-imposed PASS protocols

The EMA Secretariat presented to the PRAC a proposal for a consultation procedure on scientific advice requests (i.e. to involve the PRAC outside of the pilot for non-imposed PASS protocols) following receipt of two requests where the input from the PRAC would be welcomed by the Scientific Advice Working Party (SAWP). An outline of the two scientific advice requests together with the questions raised by the MAHs was presented to the PRAC. The PRAC supported the need for such a consultation procedure but would welcome some further details on the process. An update will be presented to the PRAC in February 2016.

12.4. Cooperation within the EU regulatory network

12.4.1. EMA Management Board data gathering initiative

The EMA Secretariat presented to the PRAC the ongoing data gathering initiative agreed at the level of the EMA Management Board. The EMA Secretariat provided feedback on the first phase of the initiative collecting data on the time spent by NCAs and EMA on the conduct of scientific advice. The PRAC was informed that a similar data gathering exercise will start in 2016 for fee generating and non-fee generating procedures.

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

None

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. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst; Margarida Guimarães

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

12.10.2. Periodic safety update

None

12.10.3. Project and Maintenance Group (PMG) 2 - roadmap for PSUR issues: preparation for workshop in January 2016

PRAC lead: Margarida Guimaraes, Menno van der Elst

Following the October 2015 discussion (see PRAC minutes October 2015), the PRAC was updated on the progress made on the scoping paper to clarify fundamental aspects of the new procedure for PSUSAs for nationally approved products (NAPs) only. A workshop for the PSUR action group composed of PRAC and CMDh delegates as well as EMA members is organised in January 2016. Further update is planned at the January 2016 PRAC meeting.

12.10.4. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version December 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 December 2015, the updated EURD list was adopted by the CHMP and CMDh at their December 2015 meetings and published on the EMA website on 21/12/2015, 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

The PRAC was updated on the outcome of the December 2015 SMART Working Group (SMART WG) work stream (WS) 1. The SMART WS1 discussed some proposed improvements to communicate signal PRAC recommendations to MAHs in order to ensure consistency and accuracy. In addition, SMART WS1 presented the achievements made in 2015 and over the last three years, with key objectives for 2016. The PRAC welcomed this overview and thanked the SMART WG for all its work to support PRAC in strengthening and optimising signal management.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Additional monitoring

None

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

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 16/12/2015 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.12.3. Management and reporting of adverse reactions to medicinal products – guidance on monitoring of off label use

Following the July 2015 PRAC meeting (see PRAC minutes July 2015), the EMA secretariat revised the draft guideline format into a Q&A entitled 'management of reports of off-label

use which do not result in harm to patients'. At the current meeting, the PRAC discussed in particular the interpretation of Article 23 (2) of Directive 2001/83/EC. The draft Q&A will be further reviewed before scheduling for adoption at the level of PRAC.

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality - EudraVigilance auditable requirement technical implementation

The EMA Secretariat presented to the PRAC the 'EudraVigilance (EV) audit checklist for technical implementation of the EV auditable requirement functionalities' developed to support the audit of the EV system in August 2016.The checklist describes how EV auditable requirements have been implemented in the EV system. Every auditable functional requirement is further refined into verifiable elements, and for each of them, an explanation is provided on how this is implemented in EudraVigilance system. PRAC delegates were invited to provide any written comments by 6 January 2016.

12.13.2. Activities related to the confirmation of full functionality – EudraVigilance audit tender

The EMA Secretariat launched a call for interest amongst PRAC delegates to participate as a technical adviser in the tender process that will select the company which will perform the audit of the EudraVigilance system in August 2016. PRAC delegates were invited to send their expressions of interests by 6 January 2016.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

12.16. 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

13. Any other business

13.1. Initial marketing authorisation(s) - revised accelerated assessment procedural timetables

The EMA Secretariat presented to the PRAC a proposal for a revised procedural timetable for the evaluation of marketing authorisation applications under accelerated assessment following the input from CHMP and PRAC members. The PRAC discussed some challenges that may be met during such an assessment procedure and therefore requested further clarifications and refinements of the process before its implementation. Further discussion is planned in January 2016 after discussion at the level of the CHMP.

13.2. Pharmacovigilance operation and implementation - proposal for a streamlined governance structure

The topic was deferred to the January 2016 PRAC meeting.

13.3. Strategy on impact of pharmacovigilance

As a follow up to previous PRAC discussions (see PRAC minutes June 2015 and PRAC minutes July 2015), the EMA Secretariat presented to PRAC an update of the draft paper on the PRAC strategy on measuring the impact of the pharmacovigilance activities, including a work plan for deliverables, to be also reflected in the draft 2016 PRAC work plan. The PRAC suggested some amendments. Follow-up discussion is planned in January 2016 with a view to adopting the strategy paper. The EMA Secretariat also took the opportunity to launch a call for expressions of interest to participate in the virtual PRAC interest group (IG) to work on the planned activities for 2016. PRAC delegates were invited to express their interest by 11 January 2016.

13.4. Update on Pharmacovigilance systems and services

The PRAC was updated on the Pharmacovigilance systems and services, in particular, the Article 57 database, EudraVigilance auditable requirements, Medical literature monitoring (MLM), pharmacovigilance fees as well as the PSUR repository. Further information can be found in News bulletin pharmacovigilance programme update - Issue 6 - dated December 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(s) will be made available following the CHMP opinion on their marketing authorisation(s).

14.1.1. Caspofungin - EMEA/H/C/004134

Scope: Treatment of invasive candidiasis and invasive aspergillosis

14.1.2. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) - EMEA/H/C/003982

Scope: Vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib)

14.1.3. Lesinurad - EMEA/H/C/003932

Scope: Treatment of hyperuricaemia

14.1.4. Necitumumab - EMEA/H/C/003886

Scope: Treatment of squamous non-small cell lung cancer (NSCLC)

14.1.5. Rasagiline - EMEA/H/C/004064

Scope: Treatment of idiopathic Parkinson’s disease (PD)

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

Applicant: Actelion Registration Ltd

Scope: Treatment of pulmonary arterial hypertension (PAH)

14.1.7. Sirolimus - EMEA/H/C/003978 - Orphan

Applicant: Santen Oy

Scope: Treatment of adults with chronic non-infectious uveitis of the posterior segement of the eye

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 the variation procedure for the below mentioned medicine(s).

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

Applicant: Roche Registration Ltd

PRAC Rapporteur: Kirsti Villikka

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

14.2.2. Turoctocog alfa – NOVOEIGHT (CAP) - EMEA/H/C/002719/II/0011/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Revised RMP edition 3 version 1 to include criteria of category 3 study NN7008-3553 PASS, due date for the provision of the final clinical study report (CSR) for study NN7008-3553. In addition, information on ongoing PASS study in Japan NN7008-4105 has been added; clinical trial NN7008-3568 has been removed

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

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

14.3.1. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/II/0089

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.6 of the SmPC in order to update the safety information on the risk of infection associated with live vaccination in infants born to women treated with abatacept during pregnancy. The Package Leaflet is updated accordingly

14.3.2. Abatacept – ORENCIA (CAP) - EMEA/H/C/000701/II/0094/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variation to amend sections 4.8 and 5.1 of the SmPC in order to update the safety information with data from the long-term (LT) final clinical study report for IM101174.In addition, the timelines for study IM101537, aimed at evaluating the effectiveness of risk minimisation measure (alert card) are updated

14.3.3. Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/II/0146

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of non-infectious intermediate, posterior and panuveitis in adult patients. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly

14.3.4. Amifampridine – FIRDAPSE (CAP) - EMEA/H/C/001032/II/0038

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4, 4.5, 5.2 and 5.3 of the SmPC to update the safety information with new data available following the completion of the clinical study report (CSR) REN-002 on renal impairment

14.3.5. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0012

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope:Extension of indication to include the treatment of cystic fibrosis resulting from a nonsense mutation in at least one allele of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Consequently, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP are updated accordingly

14.3.6. Conestat alfa – RUCONEST(CAP) - EMEA/H/C/001223/II/0032

Applicant: Pharming Group N.V

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to remove the requirement for testing all new patients for immunoglobulin E (IgE) antibodies against rabbit epithelium (dander) prior to initiation of treatment and the requirement for repeat testing of IgE antibodies to rabbit dander. The Package Leaflet is updated accordingly. The Annex II is updated to reflect changes to the educational material. The RMP is also updated accordingly

14.3.7. Dabigatran etexilate – 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 the recommendation that Pradaxa should be 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 gastrointestinal symptoms (GIS) in non-valvular atrial fibrillation (NVAF) patients'. The Package Leaflet (including the patient alert card) is updated accordingly. The RMP (version 31.2) is updated accordingly

14.3.8. Darunavir – PREZISTA (CAP) - EMEA/H/C/000707/II/0078

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report of the clinical study GS-US-236-0118: Phase 3 open-label safety study of COBI-containing highly active ARV regimens in HIV-1 infected patients with mild to moderate renal impairment (category 3 study in the RMP) in order to update the relevant information on the RMP

14.3.9. Darunavir, cobicistat – REZOLSTA (CAP) - EMEA/H/C/002819/II/0007

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final study report of the clinical study GS-US-236-0118: Phase 3 open-label safety study of COBI-containing highly active ARV regimens in HIV-1 infected patients with mild to moderate renal impairment (category 3 study in the RMP) in order to update the relevant information on the RMP

14.3.10. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil– STRIBILD (CAP) - EMEA/H/C/002574/II/0054

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.5 of the SmPC in order to update the safety information with the potential drug interaction of ledipasvir/sofosbuvir (LDV/SOF), as well as that of LDV and SOF as single agents with tenofovir disoproxil fumarate (TDF). The Package Leaflet and RMP are updated accordingly

14.3.11. Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/WS/0829; emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/WS/0829; emtricitabine, tenofovir disoproxil – TRUVADA (CAP) - EMEA/H/C/000594/WS/0829; tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/WS/0829

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd., Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Update of section 4.5 of the Viread, Truvada, Atripla and Eviplera SmPCs regarding potential drug interaction of ledipasvir/sofosbuvir (LDV/SOF) as well asthat of LDV and SOF as single agents with tenofovir disoproxil fumarate. The RMP is updated accordingly

14.3.12. Idelalisib – ZYDELIG (CAP) - EMEA/H/C/003843/II/0011

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Extension of indication to include the combination of idelalisib with ofatumumab. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly

14.3.13. Lixisenatide – LYXUMIA (CAP) - EMEA/H/C/002445/II/0013

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update information on patients with congestive heart failure following submission of the final study report for study EFC11319 (ELIXA) in fulfilment of MEA 001

14.3.14. Lixisenatide – LYXUMIA(CAP) - EMEA/H/C/002445/II/0014

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to update the safety information on older patients with type 2 diabetes mellitus inadequately controlled on their current diabetes treatment regimen and on patients with renal impairment following submission of study EFC12703 in fulfilment of MEA 006

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

Applicant: Aegerion Pharmaceuticals

PRAC Rapporteur: Menno van der Elst

Scope: Application for a line extension to include 30 mg, 40 mg and 60 mg hard capsules

14.3.16. Obinutuzumab – GAZYVARO (CAP) - EMEA/H/C/002799/II/0007

Applicant: Roche Registration Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to add the treatment of patients with follicular lymphoma based on the results of the pivotal study GAO4753g. Consequently, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC are udpated. The Package Leaflet and RMP are updated accordingly

14.3.17. Oritavancin – ORBACTIV (CAP) - EMEA/H/C/003785/II/0003

Applicant: The Medicines Company UK Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of sections 4.3, 4.4 and 4.5 of the SmPC in order to include information on the interaction potential between oritavancin and phospholipid-dependent and phospholipid-independent laboratory coagulation tests following the conclusion of two RMP category 3 studies. The Package Leaflet and RMP are updated accordingly

14.3.18. Pazopanib – VOTRIENT (CAP) - EMEA/H/C/001141/II/0032/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Grouped variation to amend section 5.3 of the SmPC in order to update the safety information following completion of two carcinogenicity studies in mice and rats. In addition, the MAH submitted a study on the induction of cytochrome P450 (CYP) mRNA expression in mice. Moreover, the RMP (version 15) is updated accordingly

14.3.19. Pazopanib – VOTRIENT (CAP) - EMEA/H/C/001141/II/0033

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Update of section 4.4 and 5.1 of the SmPC in order to update pharmacogenomics information following the results of a meta-data analysis (study number 201761) of additional clinical trials. In addition, the MAH took the opportunity to add a footnote in Table 3 in section 4.8 of the SmPC to align with Table 2 of the same section. Moreover, the RMP (version 14) is updated accordingly

14.3.20. Perampanel – FYCOMPA (CAP) - EMEA/H/C/002434/X/0025

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Line extension to add a new strength of 0.5 mg/ml (EU/1/12/776/024) and add a new pharmaceutical form, oral solution

14.3.21. 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 the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression after platinum-based chemotherapy. 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

14.3.22. Trastuzumab emtansine – KADCYLA (CAP) - EMEA/H/C/002389/II/0019/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Grouped variation to amend Annex II of the product information to delete the obligation regarding the EMILIA (TDM4370g/BO21977) study (ANX006). Furthermore, update of section 4.8 of the SmPC in order to update frequency of adverse drug reaction as a result of a pool data analysis from several clinical studies. The RMP is updated accordingly, including also changes related to inclusion and deletion of safety concerns in the RMP (enhanced pregnancy programme, evaluation of cardiac safety in patients with baseline left ventricular ejection fraction and efficacy of monotherapy versus trastuzumab associated to docetaxel). In addition, changes of final clinical study report (CSR) due dates for study KRISTINE (BO28408) and KAMILLA (mo28231) have been introduced. The MAH also took the opportunity to update the RMP following requests from previously assessed procedures (MEA011.1 and ANX007)

14.3.23. Trastuzumab emtansine – KADCYLA(CAP) - EMEA/H/C/002389/II/0020/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Grouped variation to amend sections 4.2, 4.4 and 5.2 of the SmPC in order to update the safety information on hepatic impaired patients after analysis of study BO25499 in fulfilment of MEA 009. The Package Leaflet and the RMP are updated accordingly. The due date for the final study report for study BO25499 is also changed retrospectively

14.3.24. Vorapaxar – ZONTIVITY(CAP) - EMEA/H/C/002814/II/0005

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include the treatment of patients with peripheral arterial disease (PAD).As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is also updated accordingly

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, formoterol – BRIMICA GENUAIR (CAP), DUAKLIR GENUAIR (CAP) - PSUSA/10307/201505

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.2. Apixaban – ELIQUIS (CAP) - PSUSA/00226/201505

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.1.3. Basiliximab – SIMULECT (CAP) - PSUSA/00301/201504

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.4. Cobicistat, darunavir – REZOLSTA (CAP) - PSUSA/10315/201505

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

15.1.5. Dalbavancin – XYDALBA (CAP) - PSUSA/10350/201505

Applicant: Durata Therapeutics International B.V.

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

15.1.6. Efavirenz – STOCRIN (CAP), SUSTIVA (CAP) - PSUSA/01200/201504

Applicant: Merck Sharp & Dohme Limited; Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

15.1.7. Fidaxomicin – DIFICLIR (CAP) - PSUSA/01390/201505

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.8. Fluticasone furoate – AVAMYS (CAP) - PSUSA/09154/201504

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

15.1.9. Fluticasone furoate, vilanterol – RELVAR ELLIPTA (CAP), REVINTY ELLIPTA (CAP) - PSUSA/10099/201505

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

15.1.10. Interferon beta-1a – AVONEX (CAP), REBIF (CAP) - PSUSA/09198/201505

Applicant: Biogen Idec; Merck Serono Europe Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.1.11. Lidocaine, prilocaine – FORTACIN (CAP) - PSUSA/10110/201505

Applicant: Plethora Solutions Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

15.1.12. Misoprostol – HEMOPROSTOL (Art 58[34]) –EMEA/H/W/002652/PSUV/0004

Applicant: Linepharma International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.1.13. Nintedanib – VARGATEF (CAP) - PSUSA/10318/201505

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Leonidas Klironomos

Scope: Evaluation of a PSUSA procedure

15.1.14. Pixantrone dimaleate – PIXUVRI (CAP) - PSUSA/09261/201505

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.15. Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) – PREPANDRIX (CAP) Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP) - PSUSA/02281/201505

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.16. Radium Ra^{223} dichloride – XOFIGO (CAP) - PSUSA/10132/201505

Applicant: Bayer Pharma AG

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.17. Rilpivirine – EDURANT (CAP) - PSUSA/09282/201505

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

15.1.18. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP) - PSUSA/09289/201505

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.19. Simeprevir – OLYSIO (CAP) - PSUSA/10255/201505

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.20. Tafamidis – VYNDAQEL (CAP) - PSUSA/02842/201505

Applicant: Pfizer Limited

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.1.21. Tilmanocept – LYMPHOSEEK (CAP) - PSUSA/10313/201505

Applicant: Navidea Biopharmaceuticals Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

15.1.22. Tolvaptan – SAMSCA (CAP) - PSUSA/02994/201505

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.23. Ulipristal – ELLAONE (CAP) - PSUSA/03074/201505

Applicant: Laboratoire HRA Pharma, SA

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.1.24. Vedolizumab – ENTYVIO (CAP) - PSUSA/10186/201505

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

15.2.1. Cytarabine – DEPOCYTE (CAP), NAP - PSUSA/00911/201503

Applicant: Pacira Ltd, various

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.2.2. Tacrolimus – ADVAGRAF (CAP), ENVARSUS (CAP), MODIGRAF (CAP), NAP - PSUSA/02839/201503

Applicant: Astellas Pharma Europe B.V.; Chiesi Farmaceutici S.p.A., various

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

15.3. PSUR procedures including nationally approved products (NAPs) only

15.3.1. Acarbose (NAP) - PSUSA/00000017/201503

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.3.2. Acetylsalicylic acid, bisoprolol (NAP) - PSUSA/00010287/201505

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.3. Artemether, lumefantrin (dispersible tablet) (NAP) - PSUSA/00009060/201504

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.4. Captopril (NAP) - PSUSA/00000535/201504

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.5. Ciprofloxacin hydrochloride, dexamethasone acetate (ear drops, suspension) (NAP) - PSUSA/00010012/201504

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

15.3.6. Dihydroergotamine (NAP) - PSUSA/00001075/201504

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.7. Dihydroergotoxine (NAP) - PSUSA/00001079/201504

Applicant: various

PRAC Lead: Jana Mlada

Scope: Evaluation of a PSUSA procedure

15.3.8. Human anti-D immunoglobulin (NAP) - PSUSA/00001614/201503

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.3.9. Influenza vaccine (split virion, inactivated) (NAP) - PSUSA/00010298/201504

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.3.10. Influenza vaccine (split virion, inactivated, prepared in cell cultures) (NAP) - PSUSA/00010299/201504

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.3.11. Influenza vaccine (surface antigen, inactivated, adjuvanted) (NAP) - PSUSA/00010300/201504

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.3.12. Influenza vaccine (surface antigen, inactivated, virosome) (NAP) - PSUSA/00001746/201504

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.3.13. Metamizole (NAP) - PSUSA/00001997/201504

Applicant: various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

15.3.14. Nadroparin (NAP) - PSUSA/00002104/201503

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.3.15. Nitrendipine (NAP) - PSUSA/00002171/201503

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

15.3.16. Promestriene (cream and vaginal capsules) (NAP) - PSUSA/00009271/201503

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.3.17. Reboxetine (NAP) - PSUSA/00002615/201504

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.4. Follow-up to PSUR procedures

15.4.1. Iloprost – VENTAVIS (CAP) - EMEA/H/C/000474/LEG 037.1

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: MAH's responses to LEG037 following PSUSA/00001724/201409 (special REVEAL registry study analysis) as adopted in September 2015

16. Annex I –Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

16.1. Protocols of PASS imposed in the marketing authorisation(s)[35]

None

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[36]

16.2.1. Alglucosidase alfa – MYOZYME (CAP) - EMEA/H/C/000636/MEA/053.1

Applicant: Genzyme Europe BV

PRAC Rapporteur: Isabelle Robine

Scope: MAH's responses to MEA 053 [evaluation of a PASS protocol for epidemiology study ALGMYC07390: prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions] as adopted in June 2015

16.2.2. Dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/MEA/001.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: MAH's responses to MEA 001 [revised PASS protocol regarding the utilisation of dulaglutide in European countries: a cross-sectional, multi-country and multi-source drug utilisation study using electronic health record databases], as adopted in March 2015

16.2.3. Dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/MEA/002.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: MAH's responses to MEA 002 [revised PASS protocol on the utilisation and safety of dulaglutide in European countries: a modified prescription-event monitoring and network database study (multi-database collaborative research programme of observational studies)] request for supplementary information (RSI) as adopted in March 2015

16.2.4. Empagliflozin – JARDIANCE(CAP) - EMEA/H/C/002677/MEA/002.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Miguel-Angel Macia

[35] In accordance with Article 107n of Directive 2001/83/EC
[36] 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

Scope: MAH's responses to MEA 002.1 [PASS protocol for study 1245.96] request for supplementary information (RSI) as adopted in September 2015

16.2.5. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/MEA/004

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope: Draft protocol for a PASS (study 1245.97) to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes: a multi-database European study

16.2.6. Flutemetamol (^{18}F) – VIZAMYL (CAP) - EMEA/H/C/002557/MEA/002.2

Applicant: GE Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002.1 [PASS protocol, study GE067-027 CPR to assess the effectiveness of the educational training programme] request for supplementary information (RSI) as adopted in July 2015

16.2.7. Panobinostat – FARYDAK (CAP) - EMEA/H/C/003725/MEA/002

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Draft protocol for a non-interventional PASS study (LBH589D2408) of panobinostat use in relapsed or relapsed/refractory multiple myeloma patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent in a real-world setting according to the current EU prescribing information and document adherence to dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of the medication error events

16.2.8. Secukinumab – COSENTYX (CAP) - EMEA/H/C/003729/MEA/002.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's responses to MEA 002 [protocol for a non-interventional, non-imposed PASS to study the comparative safety of approved psoriasis therapies in a national cohort of psoriasis subjects treated by dermatologists/study No. Coronna-PSO-500] as adopted in June 2015

16.2.9. Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/MEA/273

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Draft protocol for PASS study GS-EU-174-1846: a multicentre, non-interventional, retrospective cohort study of patients with chronic hepatitis B and with moderate or severe renal impairment treated with Viread

16.3. Results of PASS imposed in the marketing authorisation(s)[37]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[38]

16.4.1. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP) - EMEA/H/C/000781/II/0043 (without RMP)

Applicant: Instituto Grifols S.A.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final clinical study report (CSR) of the post-authorisation safety study (PASS): study IG1004 performed with Flebogamma DIF 50 mg/ml and 100 mg/ml to assess the tolerability of Flebogamma DIF 100 mg/ml in the clinical practice under routine conditions by comparing the frequency of infusions associated with potentially related adverse events between both strengths (to fulfil and additional pharmacovigilance activity, MEA 009.2)

16.4.2. Retigabine – TROBALT (CAP) - EMEA/H/C/001245/II/0039 (with RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Submission of final results of study PRJ2250 entitled a 'survey of prescriber understanding of specific risks associated with Trobalt'. The RMP is revised to reflect the status and results of the study and associated conclusion on the effectiveness of current risk minimisation measures

16.4.3. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/WS/0839 Saxagliptin / metformin hydrochloride – KOMBOGLYZE (CAP) - EMEA/H/C/002059/WS/0839 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report for an epidemiological study (PASS study category 3 not currently in the RMP) in order to compare the risk of hospitalisation for heart failure between dipeptidyl peptidase-4 inhibitors and sulfonylureas. In addition, a revised RMP (version 9) is submitted including other minor changes

16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[39]

16.5.1. Alglucosidase alfa – MYOZYME (CAP) - EMEA/H/C/000636/MEA/056

Applicant: Genzyme Europe BV

PRAC Rapporteur: Isabelle Robine

[37] In accordance with Article 107p-q of Directive 2001/83/EC
[38] 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
[39] In line with the revised variations regulation for any submission before 4 August 2013

Scope: Interim report from a healthcare pofessional survey that measure the effectiveness of the approved safety information packet (SIP)

16.5.2. Darunavir – PREZISTA (CAP) - EMEA/H/C/000707/MEA/069.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Interim results from PENTA study: an observational study to assess growth abnormalities (height) in human immunodeficiency virus (HIV)-infected children and adolescents on antiretroviral therapy in Europe, with special reference to darunavir (category 3)

16.5.3. Etravirine – INTELENCE (CAP) - EMEA/H/C/000900/MEA/049.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Isabelle Robine

Scope: Submission of second annual report on study TMC125-EPPICC: a pharmacovigilance study to define the long-term safety profile of etravirine in human inmmunodeficiency virus (HIV)-1-infected children and adolescents in Europe

16.5.4. Fampridine – FAMPYRA (CAP) - EMEA/H/C/002097/MEA/017

Applicant: Biogen Idec Ltd.

PRAC Rapporteur: Sabine Straus

Scope: Annual progress report of an observational safety study (protocol no: 218MS401) to collect information on safety and to document the drug utilisation of Fampyra when used in routine medical practice (LIBERATE)

16.5.5. Indacaterol, glycopyrronium bromide – ULTIBRO BREEZHALER (CAP) - EMEA/H/C/2679/MEA 003.3; ULUNAR BREEZHALER (CAP) - EMEA/H/C/3875/MEA 004.2; XOTERNA BREEZHALER (CAP) - EMEA/H/C/3755/MEA 003.3

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: MAH's response to MEA 003.2 [Drug utilisation study – First interim report CQVA 149A2401] request for supplementary information (RSI) as adopted in October 2015

16.5.6. Infliximab – INFLECTRA (CAP) - EMEA/H/C/002778/MEA/008.1; REMSIMA (CAP) - EMEA/H/C/002576/MEA/008.1

Applicant: Hospira UK Limited, Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

Scope: Fifth periodic report for post marketing surveillance of Remsima 100 mg to evaluate safety and efficacy in Korea

16.5.7. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/002494/MEA/023

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Submission of annual interim analysis data for study VX12-770-115 : an ocular safety study of ivacaftor-treated pediatric patients 11 years of age or younger with cystic fibrosis. report L113, version 1.0.

16.5.8. Mannitol – BRONCHITOL (CAP) - EMEA/H/C/001252/ANX/002.7

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002.6 (4th interim interim analysis of the cystic fibrosis (CF) study) as adopted in July 2015

16.5.9. Micafungin – MYCAMINE (CAP) - EMEA/H/C/000734/MEA/013.1

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Annual interim report from an observational database-assisted comparative cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma (protocol number: ISN 9463-CL-140): a multicentre cohort study of the short and long-term safety of micafungin and Other parenteral antifungal agents (MYCOS)

16.5.10. Ustekinumab – STELARA (CAP) - EMEA/H/C/000958/MEA/023.7

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 023.6 [Fifth interval safety registry report (protocol: CNTO1275PSO4005) Nordic Database] request for supplementary information (RSI) as adopted in July 2015

16.6. Others

16.6.1. Elvitegravir – VITEKTA (CAP) - EMEA/H/C/002577/MEA/007.2

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's responses to MEA 007.1 [Feasibility study / drug utilisation study (DUS) GS-EU-183-1335] request for supplementary information (RSI) as adopted in June 2015

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. Alipogene tiparvovec – GLYBERA (CAP) - EMEA/H/C/002145/S/0051 (without RMP)

Applicant: uniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

17.1.2. Cholic acid – ORPHACOL (CAP) - EMEA/H/C/001250/S/0012 (without RMP)

Applicant: Laboratoires CTRS - Boulogne Billancourt

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation

17.1.3. Tocofersolan – VEDROP (CAP) - EMEA/H/C/000920/S/0015 (without RMP)

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

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

17.2. Conditional renewals of the marketing authorisation

None

17.3. Renewals of the marketing authorisation

17.3.1. Belatacept – NULOJIX (CAP) - EMEA/H/C/002098/R/0031 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

17.3.2. Belimumab – BENLYSTA (CAP) - EMEA/H/C/002015/R/0036 (with RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

17.3.3. Boceprevir – VICTRELIS (CAP) - EMEA/H/C/002332/R/0036 (with RMP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Isabelle Robine

Scope: 5-year renewal of the marketing authorisation

17.3.4. Exenatide – BYDUREON (CAP) - EMEA/H/C/002020/R/0031 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

17.3.5. Natalizumab – TYSABRI (CAP) - EMEA/H/C/000603/R/0091 (with RMP)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

17.3.6. Rivastigmine – RIVASTIGMINE ACTAVIS (CAP) - EMEA/H/C/002036/R/0016 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Isabelle Robine

Scope: 5-year renewal of the marketing authorisation

17.3.7. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP) – EMEA/H/C/000674/R/0096 (with RMP)

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

17.3.8. Tobramycin – TOBI PODHALER (CAP) - EMEA/H/C/002155/R/0034 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

18. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 30 November-3 December 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 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
Marina Dimov Di Giusti	Member	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Eva Jirsová	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Isabelle Robine	Member	France	No interests declared	Full involvement
Corinne Fechant	Alternate	France	No restrictions applicable to this meeting	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	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
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	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
Leonor Chambel	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	Full involvement
Dolores Montero Corominas	Member	Spain	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
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Jane Ahlqvist Rastad	Member	Independent scientific expert	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Filip Babylon	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Marco Greco	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Xavier Goossens - Reporting inspector	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Željana Margan Koletić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Sami Paaskoski	Expert - in person*	Finland	No interests declared	Full involvement
Serge Bakchine - SAG chair	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Eleanor Carey	Expert - in person*	Ireland	No interests declared	Full involvement
Anna Marie Coleman	Expert - in person*	Ireland	No interests declared	Full involvement
Zane Stade	Expert - in person*	Latvia	No interests declared	Full involvement
Baukje Schat	Expert - in person*	Netherlands	No interests declared	Full involvement
Lies van Vlijmen	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Niels Vermeer	Expert - in person*	Netherlands	No interests declared	Full involvement
Miroslava Gočová	Expert - in person*	Slovakia	No interests declared	Full involvement
Eva Segovia Muñoz	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Patrick Batty	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the 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/