



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 08-11 June 2015

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

In accordance with the Agency's health and safety policy, delegates were 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, the 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 on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).



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1. Introduction

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

The Chairperson opened the 8-11 June 2015 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Isabelle Robine, replacing Arnaud Batz, as the new member for France as well as Corinne Féchant, replacing Patrick Maison, as the new alternate for France. The PRAC Chair also welcomed Jan Neuhauser, replacing Harald Herkner, as the new member for Austria. The PRAC noted that Marianne Lunzer was replacing Jan Neuhauser as the new alternate for Austria.

1.2. Adoption of agenda of the meeting of 8-11 June 2015

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

1.3. Adoption of minutes of the previous meeting of 4-7 May 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 4-7 May 2015 were published on the EMA website on 25 June 2015 ([EMA/PRAC/59170/2015](#)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

3.1.1. Canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP); dapagliflozin – FORXIGA (CAP); dapagliflozin, metformin – XIGDUO (CAP); empagliflozin - JARDIANCE (CAP); empagliflozin, metformin – SYNJARDY (CAP)

Applicant: AstraZeneca AB (Forxiga, Xigduo), Boehringer Ingelheim International GmbH (Jardiance, Synjardy), Janssen-Cilag International N.V. (Invokana, Vokanamet)

PRAC Rapporteur: Menno van der Elst; PRAC Co-rapporteurs: Valerie Strassmann, Qun-Ying Yue

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

Background

Canagliflozin, dapagliflozin and empagliflozin are sodium-glucose co-transporter-2 (SGLT2) inhibitors, and alone or in combination with metformin, a biguanide, are indicated in adults aged 18 years and older with type 2 diabetes mellitus under certain conditions.

The European Commission sent a letter of [notification](#) dated 10/06/2015 of a referral under Article 20 of Regulation (EC) No 726/2004 for the review of SGLT2 inhibitors-containing products following a safety signal of diabetic ketoacidosis (DKA) (for background, see under 4.1.3. New signals).

Discussion

The PRAC noted the notification letter from the European Commission requesting a review of all available data for SGLT2 inhibitors-containing products regarding DKA and assessment of its impact on the benefit/risk balance for these medicinal products. The PRAC discussed a list of questions to be addressed by the relevant MAHs as well as a timetable for conducting the review. The PRAC also agreed that based on the available information, the most effective risk minimisation at this stage was targeted communication to healthcare professionals via a DHPC as agreed within the signal procedure. It was considered that temporary measures were not necessary.

The PRAC appointed Menno van der Elst as Rapporteur and Valerie Strassmann and Qun-Ying Yue as Co-Rapporteurs for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions to the MAHs of SGLT2 inhibitors-containing products ([EMA/PRAC/390892/2015](#)) and a timetable for the procedure ([EMA/PRAC/391289/2015](#)).

3.2. Ongoing procedures

- 3.2.1. Inhaled corticosteroids (ICS)-containing medicinal products indicated in the treatment of chronic obstructive pulmonary disease: beclomethasone (NAP); beclomethasone, formoterol (NAP); budesonide (NAP); budesonide, formoterol – BIRESP SPIROMAX (CAP); BUDESONIDE FORMOTEROL TEVA (CAP); DUORESP SPIROMAX (CAP); VYALER SPIROMAX (CAP); flunisolide, salbutamol (NAP); fluticasone (NAP); fluticasone, salmeterol (NAP); fluticasone, vilanterol – RELVAR ELLIPTA (CAP); REVINTY ELLIPTA (CAP) – EMEA/H/A-31/1415
-

Applicant: Glaxo Group Ltd, Teva Pharma B.V., Teva Pharmaceuticals Europe, various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Jan Neuhauser

Scope: Review of the benefit-risk balance following notification by the European Commission 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 for inhaled corticosteroids (ICS)-containing medicines indicated in the treatment of chronic obstructive pulmonary disease (COPD) alone or in combination with a long acting beta₂ acting agonist (LABA) is ongoing (see [PRAC minutes June 2015](#)). The PRAC was informed of a request from a MAH for an extension of the agreed procedure timetable.

Summary of recommendation(s)/conclusions

The PRAC noted the request for an extension of the timetable for the procedure on ICS-containing products indicated in the treatment of COPD. The PRAC considered that it was appropriate to extend the timetable by one month, in agreement with the Rapporteurs ([EMA/PRAC/290163/2015 Rev. 1](#)).

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 prioritisation¹

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Anakinra - KINERET (CAP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Torbjorn Callreus

Scope: Signal of thrombocytopenia

EPITT 18337 – New signal

Lead Member State: DK

Background

Anakinra is an interleukin inhibitor indicated in adults for the treatment of the signs and symptoms of rheumatoid arthritis (RA) in combination with methotrexate, with an inadequate response to methotrexate alone.

The post-marketing exposure for Kineret, a centrally authorised medicine containing anakinra, is estimated to have been more than 63,758 patient-years worldwide, in the period from first authorisation in 2002 until May 2013.

During routine signal detection activities, a signal of thrombocytopenia was identified by the EMA, based on nine 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 four cases with positive de-challenge and the case with positive re-challenge, and considering the temporal association and that the inhibition of interleukin 1 β could be a potential mechanism, the PRAC agreed to request the MAH to submit a cumulative review of cases of thrombocytopenia in association with anakinra.

Summary of recommendation(s)

- The MAH for Kineret (anakinra) should submit to the EMA, within 60 days, a cumulative review of cases of thrombocytopenia in association with anakinra. The MAH should include clinical data from all sources including clinical trials and relevant literature and evaluate the biological plausibility for a possible causal association. The MAH should also discuss the need for any potential amendment to the product information and/or to the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

4.1.2. Boceprevir – VICTRELIS (CAP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Isabelle Robine

Scope: Signal of hyponatraemia

EPITT 18350 – New signal

Lead Member State: FR

Background

Boceprevir is a protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

The post-marketing exposure for Victrelis, a centrally authorised medicine containing boceprevir, is estimated to have been more than 29,977 patient-years worldwide, in the period from first authorisation in 2011 until November 2014.

Following the publication of one case of hyponatraemia attributed to boceprevir², a signal of hyponatraemia was identified by the EMA during routine signal detection activities, based on a total of four cases retrieved from EudraVigilance (including one case reported in the literature) and published case. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the literature and from case reports in EudraVigilance. Taking into account that diagnosis of drug-induced hyponatraemia can be easily overlooked notably in cirrhotic patients, that hyponatremia with very low sodium levels is a serious adverse reaction to be rapidly managed and that there was one case with positive re-challenge (a literature case), the PRAC agreed to request the MAH of Victrelis to provide a cumulative review of cases of hyponatraemia in association with boceprevir.

Summary of recommendation(s)

- The MAH for Victrelis (boceprevir) should submit to the EMA, within 60 days, a cumulative review of cases of hyponatraemia in association with boceprevir. This analysis should include a review of all data derived from clinical development, post-marketing and literature. The underlying mechanism of potential boceprevir-induced hyponatraemia should be discussed. The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

² Hedrick KT, Just SM, Kahn DR. Probable boceprevir-induced hyponatremia in a patient with chronic hepatitis C. *Am J Health Syst Pharm* 2015 Mar 15;72(6):449-52. Doi: 10.2146/ajhp140025

4.1.3. Canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP); dapagliflozin – FORXIGA (CAP); dapagliflozin, metformin – XIGDUO (CAP); empagliflozin – JARDIANCE (CAP); empagliflozin, metformin – SYNJARDY (CAP)

Applicant: AstraZeneca AB (Forxiga, Xigduo), Boehringer Ingelheim International (Jardiance, Synjardy), Janssen-Cilag International N.V. (Invokana, Vokanamet)

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of diabetic ketoacidosis (DKA)

EPITT 18375 – New signal

Lead Member States: DE, ES, SE

Background

Canagliflozin, dapagliflozin and empagliflozin are sodium-glucose co-transporter-2 (SGLT2) inhibitors, and alone or in combination with metformin, a biguanide, are indicated in adults aged 18 years and older with type 2 diabetes mellitus under certain conditions.

The post-marketing exposure for Forxiga, a centrally authorised medicine containing dapagliflozin, is estimated to have been more than 121,119 patient-years worldwide, in the period from first authorisation in 2012 to October 2014. The post-marketing exposure for Invokana, a centrally authorised medicine containing canagliflozin, is estimated to have been more than 544,915 patients-years worldwide, in the period from first authorisation in 2013 to March 2015. The post-marketing exposure for Jardiance, a centrally authorised medicine containing empagliflozin, is estimated to have been more than 6,388 patient-years worldwide, in the period from first authorisation in April 2014 until October 2014.

Following the issue of a [safety warning by the FDA on SGLT2 inhibitors and the risk of ketoacidosis](#) in May 2015, a signal of diabetic ketoacidosis (DKA) was identified by the EMA during routine signal detection activities, based on 96 cases retrieved for canagliflozin, 46 cases retrieved for dapagliflozin and 5 cases retrieved for empagliflozin from EudraVigilance. Sweden, Germany and Spain confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from EudraVigilance and from the literature. Having considered the seriousness of ketoacidosis, the potential for delayed diagnosis and management of atypical cases without significantly elevated glucose values, the PRAC agreed that the MAHs should distribute a joint direct healthcare professional communication (DHPC) for the class including the combination products according to the text and communication plan agreed with the CHMP. In addition, a thorough evaluation of the issue will be undertaken as part of a referral procedure under Article 20 of Regulation (EC) No 726/2004 triggered during the current PRAC plenary meeting (see **Error! Reference source not found.**New EU referral procedures).

The PRAC appointed Valerie Strassmann as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs should distribute a DHPC according to the text and communication plan agreed with the PRAC and CHMP.
- Taking into account the available evidence, considering the seriousness of ketoacidosis and the potential for delayed diagnosis and management of atypical cases without

significantly elevated glucose values, a thorough evaluation of the issue should be undertaken as part of a referral procedure under Article 20 of Regulation (EC) 726/2004.

4.1.4. Enfuvirtide – FUZEON (CAP)

Applicant: Roche Registration Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of amyloidoses
EPITT 18347– New signal
Lead Member State: SE

Background

Enfuvirtide is a fusion inhibitor indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV)-1 infected patients under certain conditions.

The post-marketing exposure for Fuzeon, a centrally authorised medicine containing enfuvirtide, is estimated to have been more than 72,010 patient-years worldwide, in the period from first authorisation in 2003 until March 2015.

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

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account that amyloidosis is a rare, potentially serious condition, often undiagnosed or misdiagnosed, as well as the four cases of cutaneous amyloidosis and the reported case of renal amyloidosis, the PRAC agreed to request the MAH to provide a cumulative review of cases of amyloidosis in association with enfuvirtide.

Summary of recommendation(s)

- The MAH for Fuzeon (enfuvirtide) should submit to the EMA, by 10 July 2015 in the framework of the ongoing PSUR procedure (DLP: 12/03/2015) (PSUSA/00001217/201503), a cumulative review of cases of amyloidosis in association with enfuvirtide. The MAH should include data on cutaneous and systemic amyloidosis (including possible cases reported as renal failure/acute kidney injury), from all sources including clinical trials, literature and post marketing data including spontaneous reports. The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan as applicable.

4.1.5. HMG-CoA reductase inhibitors: Atorvastatin (NAP), fluvastatin (NAP), lovastatin (NAP), simvastatin (NAP), pitavastatin (NAP), pravastatin (NAP), rosuvastatin (NAP); fenofibrate, simvastatin - CHOLIB (CAP); fenofibrate, pravastatin - PRAVAFENIX (CAP)

Applicant: various

PRAC Rapporteur: No need for appointment

Scope: Signal of lichenoid drug eruption
EPITT 18299 – New signal
Lead Member States: CZ, DE, ES, FR, IE, NL, UK

Background

Atorvastatin, fluvastatin, lovastatin, simvastatin, pitavastatin, pravastatin, rosuvastatin are 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors commonly known as statins and widely used for treating dyslipidaemia including treatment of primary hypercholesterolaemia or mixed dyslipidaemia under certain conditions and treatment of homozygous familial hypercholesterolaemia under certain conditions.

During routine signal detection activities, a signal of lichenoid drug eruption was identified by the Netherlands, based on thirteen reports retrieved from the Netherlands Pharmacovigilance centre (Lareb) including five literature cases. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed all the available information on the reported cases of lichenoid drug eruption. Taking into account that only a few cases have been reported compared to the extensive exposure to statins, the background rate of lichen planus and the uncertainties with regard to the establishment of a causal relationship in the actual cases reviewed, the PRAC considered that the MAHs of HMG-CoA reductase inhibitor-containing products should continue to monitor adverse events of lichenoid drug eruption as part of routine safety surveillance. In addition, this signal should be further monitored and reviewed within the evaluation of the next PSURs for HMG-CoA reductase inhibitor-containing products to gather further evidence.

Summary of recommendation(s)

- MAHs for HMG-CoA reductase inhibitor-containing products should continue to monitor events of lichenoid drug eruption as part of routine safety surveillance, including next PSURs.

4.1.6. Nalmefene - SELINCRO (CAP)

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Signal of suicidal ideation
EPITT 18333 – New signal
Lead Member State: DE

Background

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

The post-marketing exposure for Selincro, a centrally authorised medicine containing nalmefene, is estimated to have been more than 12,167 patient-years worldwide, in the period from first authorisation in 2013 until February 2015.

During routine signal detection activities, a signal of suicidal ideation was identified by the EMA, based on seventeen cases retrieved from EudraVigilance and reported as being important medical events. 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. As there are cases in support of a potential causal relationship (including two reports describing a positive re-challenge) and considering that suicidal ideation is a serious event, the PRAC agreed to request the MAH for Selincro to submit a cumulative review of cases of depression and suicide/self-injury associated with nalmefene within the ongoing PSUR procedure.

Summary of recommendation(s)

- The MAH for Selincro (nalmefene) should submit to the EMA, by 12 August 2015 within the ongoing PSUR procedure (DLP: 24/02/2015) (PSUSA/00010120/201502) a cumulative review of cases of depression and suicide/self-injury associated with nalmefene. The MAH should include data from all sources including clinical trials, spontaneous reports and relevant literature evaluating the biological plausibility for a possible association. Different drop-out rates should be taken into account when interpreting results from clinical trials. The MAH should also discuss the need for any potential amendments to the product information and/or the risk management plan as applicable.

4.1.7. Oxybutynin – KENTERA (CAP)

Applicant: Nicobrand Limited

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of psychiatric disorders

EPITT 18342 – New signal

Lead Member State: BE

Background

Oxybutynin is a competitive antagonist of acetylcholine at post-ganglionic muscarinic receptors indicated for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency such as may occur in adult patients with unstable bladder.

The post-marketing exposure for Kentera, a centrally authorised medicine containing oxybutynin, is estimated to have been more than 391,000 patient-years worldwide, in the period from first authorisation in 2004 until February 2011.

During routine signal detection activities, a signal of psychiatric disorders was identified by the EMA, based on thirteen 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 seven cases were reported with a positive de-challenge and that hospitalisation was required in six cases, the PRAC agreed to request the MAH for Kentera to provide a

cumulative review of cases of psychiatric disorders in association with oxybutynin transdermal forms.

Summary of recommendation(s)

- The MAH for Kentera (oxybutynin) should submit to the EMA, within 60 days, a cumulative review of cases of psychiatric disorders in association with oxybutynin transdermal forms. Particular consideration should be given to elderly patients and off-label use in children. The cumulative review should include data from all sources, including reports from post-marketing, clinical trials and the literature. The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.8. Pertuzumab – PERJETA (CAP)

Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope: Signal of acute renal failure

EPITT 18322 – New signal

Lead Member State: DK

Background

Pertuzumab is a recombinant humanised monoclonal antibody indicated for use in combination with trastuzumab and docetaxel in adult patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

The post-marketing exposure for Perjeta, a centrally authorised medicine containing pertuzumab, is estimated to have been more than 39,459 patients worldwide, in the period from first authorisation in 2013 until December 2014.

During routine signal detection activities, a signal of acute renal failure was identified by the EMA, based on six 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. The PRAC agreed that while the reported cases of acute renal failure do not provide strong evidence, the additional information from clinical trials and non-clinical data provides sufficient evidence that diarrhoea, including severe diarrhoea, occurs frequently in patients taking pertuzumab and that this may lead to dehydration and subsequent hypovolemic renal failure if not treated. As the relationship between exposure to pertuzumab and acute kidney injury is being addressed in the ongoing PSUR procedure, the PRAC agreed that if regulatory action was needed it should be taken within the PSUR procedure.

Summary of recommendation(s)

- No regulatory action was considered necessary based on this study report; however the MAH should continue to further evaluate the signal of acute kidney injury within the ongoing PSUR procedure (PSUSA/00010125/201412).

4.2. New signals detected from other sources

4.2.1. Pregabalin - LYRICA (CAP)

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of hyponatremia and syndrome of inappropriate antidiuretic hormone (SIADH)

EPITT 18334 – New signal

Lead Member States: NL

Background

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

The post-marketing exposure for Lyrica, a centrally authorised medicine containing pregabalin, is estimated to have been more than 28,530,369 patient-years worldwide, in the period from first authorisation in 2004 until January 2015.

During routine signal detection activities, a signal of hyponatremia and syndrome of inappropriate antidiuretic hormone (SIADH) was identified by Spain, based on twelve cases retrieved in the Spanish safety database. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in the Spanish safety database, EudraVigilance and in the literature. Taking into account the available information, the PRAC agreed to request the MAH of Lyrica to provide a cumulative review of cases of hyponatraemia/SIADH in association with pregabalin.

Summary of recommendation(s)

- The MAH for Lyrica (pregabalin) should submit to the EMA, by 12 August 2015 in the framework of the ongoing PSUSA procedure (DLP: 31/05/2015) (PSUSA/00002511/201501), a cumulative review of cases of hyponatraemia/SIADH in association with pregabalin. The MAH should include data from all sources including clinical and pre-clinical studies, on-going studies, registries, literature and spontaneous reports. The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan as applicable.

4.3. Signals follow-up and prioritisation

- ### 4.3.1. Atypical antipsychotics: Aripiprazole – ABILIFY (CAP) - EMEA/H/C/000471/SDA/073, ABILIFY MAINTENA (CAP) - EMEA/H/C/002755/SDA/006; asenapine – SYCREST (CAP) - EMEA/H/C/001177/SDA/017; clozapine (NAP); lurasidone – LATUDA (CAP) -

EMA/H/C/002713/SDA/004; olanzapine - ZYPADHERA (CAP) - EMA/H/C/000890/SDA/023, ZYPREXA (CAP) - EMA/H/C/000115/SDA/044, ZYPREXA VELOTAB (CAP) - EMA/H/C/000287/SDA/037; paliperidone – INVEGA (CAP) – EMA/H/C/000746/SDA/023, XEPLION (CAP) - EMA/H/C/0002105/SDA/012; quetiapine (NAP); risperidone (NAP); sertindole (NAP); ziprasidone (NAP); zotepine (NAP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of acute renal failure
EPITT 18102 – Follow-up to November 2014

Background

For background information, see [PRAC minutes November 2014](#). The MAHs replied to the request for information on the signal of acute renal failure and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. Having considered the available evidence from clinical trials, spontaneous cases as well as the literature, the PRAC agreed that there is no evidence of a causal relationship between atypical antipsychotics and direct nephrotoxic effects.

As also discussed in the *Hwang et al.* study³ however, acute renal failure may occur secondary to pre- and post-renal injuries (such as neuroleptic malignant syndrome, rhabdomyolysis, hypotension or urinary retention). These factors are already addressed in current product information of atypical antipsychotics. There might be differences between the medicinal products regarding the risk of acute renal failure.

The PRAC acknowledged possible limitations of the *Hwang et al.* study but agreed that the study provides valuable data on the elderly, a population not usually exposed in clinical trials. In the elderly population the number of cases of acute renal failure in clinical trials is limited and comorbidities, concomitant medication and the frailty of the population should be taken into consideration. Given the available data and the differences in pharmacology and safety profile of the atypical antipsychotics, the PRAC considered that no conclusion on this topic could be drawn at this stage. Therefore, the PRAC recommended that the MAHs of atypical antipsychotics should continue to carefully monitor events of acute kidney injury as part of routine safety surveillance and provide a comprehensive discussion in future PSURs.

Summary of recommendation(s)

- The MAHs of atypical antipsychotics should continue to carefully monitor these events of acute kidney injury (including acute renal failure) as part of routine safety surveillance and provide a comprehensive discussion in future PSURs.
- The PRAC agreed to seek advice from the Geriatric Expert Group (GEG) on the signal in the light of different patterns of usage of atypical antipsychotics in the elderly.

³ Hwang YJ, Dixon SN, Reiss JP, Wald R, Parikh CR, Gandhi S, Shariff SZ, Pannu N, Nash DM, Rehman F, Garg AX. Atypical antipsychotic drugs and the risk for acute kidney injury (AKI) and other adverse outcomes in older adults. *Annals of Internal Medicine*, 2014 Aug 19;161(4):242-8

4.3.2. Clopidogrel – ISCOVER (CAP), PLAVIX (CAP); prasugrel – EFIENT (CAP)

Applicant: Eli Lilly Nederland B.V. (Efient), Sanofi-aventis groupe (Iscover), Sanofi Clir SNC (Plavix)

PRAC Rapporteur: Margarida Guimarães

Scope: Signal of safety of dual antiplatelet therapy
EPITT 18184 – Follow-up to January 2015

Background

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

Discussion

The PRAC further discussed this signal and the additional information provided by the MAH of Plavix/Iscover regarding the results of the dual antiplatelet therapy (DAPT) study published in the New England Journal of Medicine (NEJM) in November 2014 and on randomised clinical studies of clopidogrel with or without aspirin. Taking into consideration the strength of the available evidence from the DAPT trial as well as the new information provided by the MAH for Plavix/Iscover, the PRAC agreed that the likelihood of a causal relationship between treatment with clopidogrel and increased all-cause mortality, cardiovascular mortality or non- cardiovascular mortality is not sufficiently robust, and therefore, no further actions were deemed necessary at this point in time. Any new evidence will be reviewed.

Summary of recommendation(s)

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

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

Applicant: Bayer, Sanofi, various

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of retinal detachment
EPITT 15914 – Related to June 2014

Background

For background information, see [PRAC minutes April 2013](#) and [PRAC minutes June 2014](#). Following the last discussion at the PRAC, a self-controlled case series analysis (SCCS) was conducted by the French Agency, ANSM. The final results of this new study were critically reviewed by the Rapporteur.

Discussion

The PRAC discussed the assessment of the newly available study from ANSM and agreed that the study shows a small increase in the risk of retinal detachment within ten days of systemic fluoroquinolone intake. The study addresses many of the limitations of prior studies. However, further clarifications and analyses from the study authors would be helpful to confirm the importance of these findings, before concluding on the need for

further regulatory measures. In addition, more complete information on spontaneous reports is considered necessary. The originator MAHs of fluoroquinolone-containing systemic preparations should provide and discuss available case reports of retinal detachment, retinal scar, retinal tear, and retinoschisis in association with systemic fluoroquinolone intake.

Summary of recommendation(s)

- The MAHs for fluoroquinolone-containing medicinal products for systemic use (Angelini, Bayer, Delta, Gerda, MSD, Pierre Fabre, Rottapharm, S.F. and Sanofi-Aventis) should submit to the PRAC, within 60 days, a cumulative review of cases of retinal detachment, retinal scar, retinal tear, chorioretinal scar, and retinoschisis in association with systemic fluoroquinolone intake.
- The authors of the recent ANSM study should be requested to provide answers to the list of questions adopted by the PRAC within 60 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

Applicant: Pfizer Limited (Duavive), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of increased risk of ovarian cancer
EPITT 18258 – Follow-up to April 2015

Background

For background information, see [PRAC minutes April 2015](#). The PRAC Rapporteur further assessed the new published meta-analysis⁴, focusing on hormone replacement therapy medicinal products containing oestrogens or oestrogens and progestogens in combination.

Discussion

The PRAC considered that the new large meta-analysis performed by the Collaborative Group on Epidemiological Studies of Ovarian Cancer provides strong evidence to justify a revision of the current product information of hormone replacement therapy (HRT) medicinal products containing oestrogens or oestrogens and progestogens in combination regarding the risk of ovarian cancer. However, the PRAC agreed that several aspects of the meta-analysis need to be clarified before an updated wording of the product information can be finalised.

Therefore, to further progress a proposal to update the product information of these products, the PRAC requested the principal investigators of the study to provide additional information via reply to a list of questions. The PRAC also requested EMA to analyse Intercontinental Marketing Services (IMS) healthcare data on the pattern of use of hormone replacement therapy medicinal products containing oestrogens or oestrogens and progestogens in several Member States.

⁴ Collaborative group on epidemiological studies of ovarian cancer. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies; Collaborative Group on Epidemiological Studies of Ovarian Cancer; The Lancet, February, 13, 2015

Summary of recommendation(s)

- The principal investigator of the meta-analysis was requested to provide to EMA additional information in a list of questions adopted by the PRAC.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.5. Teriparatide – FORSTEO (CAP) – EMEA/H/C/000425/SDA/051

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Signal of angina pectoris
EPITT 18203 – Follow-up to February 2015

Background

For background information, see [PRAC minutes February 2015](#). The MAH replied to the request for information on the signal of angina pectoris and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's response including data from the published literature, non-clinical data, clinical data, and post-marketing data. The PRAC noted that the available data did not support a plausible mechanism of action by which teriparatide may cause or precipitate angina and in the majority of post-marketing reports the patients' medical history or concomitant medicines may provide an alternative explanation for the observed angina. Overall, the PRAC considered that given the reassuring pre-clinical and clinical study data, the absence of literature reports associating angina with teriparatide, and the lack of convincing data from post-marketing sources, the available evidence does not support a causal relationship between teriparatide and angina. Having considered this, the PRAC agreed that the MAH for Forsteo should continue to monitor angina pectoris events as part of routine safety surveillance.

Summary of recommendation(s)

- The MAH for Forsteo (teriparatide) should continue to monitor reports of angina pectoris as part of routine safety surveillance.

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

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

Scope: Treatment of cystinosis

5.1.2. Sebelipase alfa - EMEA/H/C/004004, Orphan

Applicant: Synageva BioPharma Ltd

Scope: Treatment of lysosomal acid lipase (LAL) deficiency

5.1.3. Sonidegib - EMEA/H/C/002839

Scope: Treatment of basal cell carcinoma (BCC)

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

See also Annex I 14.2.

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

Applicant: Sanofi Pasteur, Sanofi Pasteur MSD SNC

PRAC Rapporteur: Miguel-Angel Macia

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

Background

Influenza vaccine (split virion, inactivated) is indicated for the prophylaxis of influenza in adults up to 59 years of age, especially in those who run an increased risk of associated complications.

The PRAC is evaluating a type II variation procedure for IDflu and Intanza, centrally authorised influenza vaccines, to update the RMP to reflect, in particular, the strategy of the enhanced safety surveillance (ESS)⁵ in the European Economic Area (EEA) during the 2015-2016 influenza season. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP version 9.0 for IDflu and Intanza (influenza vaccine (split virion, inactivated)) in the context of the variation under evaluation by the PRAC and CHMP could be considered acceptable provided that satisfactory responses to the first list of questions detailed in the adopted assessment report are submitted.

⁵ To comply with the Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines ([EMA/PRAC/222346/2014](#)), and according to PRAC recommendation to MAHs ([PRAC minutes February 2015](#))

- Having reviewed the MAH's proposal for the passive enhanced safety surveillance (ESS) plan for the 2015-2016 influenza season, the PRAC considered that refinements were needed, in particular, the MAH should better define the terms 'signal' and 'valid case'. In addition, an interim analysis report should be submitted to the EMA within 30 days after starting the use of the vaccine in the EU⁶, independently of any signals. The full description of the passive ESS system should be submitted with the final report in order to allow interpretation of the results.

5.2.2. 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 a category 3 study (MEA 099) to replace the agreed 2-year extension of the Danish-Swedish registry (NV25577)

Background

Oseltamivir is a neuraminidase inhibitor indicated for the treatment and prevention of influenza under certain conditions.

The CHMP is evaluating a type II variation procedure for Tamiflu, a centrally authorised product containing oseltamivir, in order to propose a new and alternative study BV29684 assessing the 'safety of prenatal exposure to oseltamivir' as a category 3 study to replace the agreed 2-year extension of the Danish-Swedish registry (NV25577: assessing the safety of oseltamivir exposure in pregnant women in Denmark and Sweden). The extension of this registry was requested by the PRAC in May 2013 after the interim results of the study (period 2008-2010) were examined. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. For further background, see [PRAC minutes January 2015](#) and [PRAC minutes March 2015](#).

Summary of advice

- The RMP version 11 for Tamiflu (oseltamivir) in the context of the variation under evaluation by the PRAC and CHMP could be considered acceptable provided that satisfactory responses to the third list of questions detailed in the adopted assessment report are submitted.
- Having reviewed the MAH's response to the request for supplementary for information, the PRAC considered that the alternative study BV29684 'assessing the safety of prenatal exposure to oseltamivir' was acceptable to replace the agreed 2-year extension of the Danish-Swedish registry (NV25577). The MAH should submit a revised protocol for study BV29684.

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

See also Annex I 14.3.

⁶ defined as the first vaccine dose administered to a vaccinee in any EU country

Applicant: Celgene Europe Limited

PRAC Rapporteur: Corinne Féchant

Scope: Update of sections 4.2 and 4.8 of the SmPC in order to add new dosing information for elderly patients (>75 years) with untreated multiple myeloma receiving thalidomide in combination with melphalan and prednisone (MPT). In addition the MAH is updating the posology with the recommended starting doses for melphalan and prednisone for completeness. The package leaflet is being updated accordingly

Background

Thalidomide is an immunosuppressant indicated in combination with melphalan and prednisone as a first line treatment of patients with untreated multiple myeloma, aged 65 years and over or ineligible for high dose chemotherapy.

The CHMP is evaluating a type II variation procedure for Thalidomide Celgene, a centrally authorised product containing thalidomide, to include new dosing information for elderly patients (above 75 years) with untreated multiple myeloma receiving thalidomide in combination with melphalan and prednisone (MPT) and to update the posology with the recommended starting doses for melphalan and prednisone. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 16.0 for Thalidomide Celgene (thalidomide) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to the first list of questions detailed in the adopted assessment report are submitted.
- The PRAC considered that the MAH should provide further information regarding the IFM⁷ 01/01 study⁸ results, including the cause of early death, and the number and listing of serious adverse events (SAE) in the elderly population (above 75 years). In addition, the MAH should submit a proposal for a Direct Healthcare Professional Communication (DHPC) together with a communication plan in order to communicate concerning the recommendation to reduce the starting dose of thalidomide and melphalan in elderly patients.

6. Periodic safety update reports (PSURs)

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

See also Annex I 15.1.

⁷ Intergroupe Francophone du Myelome

⁸ Multicentre, placebo-controlled, phase III study in which patients ≥ 75 years with newly diagnosed multiple myeloma (NDMM) were randomly assigned to receive a 100 mg daily dose of thalidomide or placebo for 72 weeks, and melphalan/prednisone (MP) on days 1 to 4 of twelve 6-week cycles

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Eliquis, a centrally authorised medicine containing apixaban, 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 Eliquis (apixaban) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include pruritus as a new undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied⁹.
- In the next PSUR, the MAH should provide an updated analysis from the two ongoing non-interventional PASS (studies B0661017 and B0661018) on incidence rates of bleeding events on apixaban versus warfarin initiators. Furthermore, the PRAC noted that a higher proportion of warfarin users had lower CHADS2 (congestive heart failure, hypertension, age over 75 years, diabetes mellitus, and prior stroke or transient ischemic attack or thromboembolism) scores and a medical history of bleeding events. This should be taken into account during the analysis of the collected data for comparison between the two groups. Also the summary of safety concerns should be updated in line with the apixaban EU RMP version 13. Finally, regarding the evaluation of risks and new information, the MAH should include all bleeding events, including gastrointestinal haemorrhages and epistaxis, and present a classification of the haemorrhagic events by SOC¹⁰. Regarding reporting rates for bleeding cases, the MAH should present reporting rates with number of cases instead of number of events and include all bleeding cases in the PSUR analyses.

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

⁹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

¹⁰ MedDRA System Organ Class

6.1.2. Canagliflozin – INVOKANA (CAP) canagliflozin, metformin – VOKANAMET (CAP) - PSUSA/10077/201411

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope of procedure: Evaluation of a PSUSA procedure

Background

Canagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor, and alone or in combination with metformin, a biguanide, is indicated in adults aged 18 years and older with type 2 diabetes mellitus under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Invokana and Vokanamet, a centrally authorised medicine containing canagliflozin and canagliflozin/metformin respectively, 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 Invokana (canagliflozin) and Vokanamet (canagliflozin, metformin) in the approved indications remains favourable.
- Nevertheless, the product information should be updated to add angioedema as an undesirable effect with an unknown frequency and to amend the current wording on urinary tract infections in the undesirable effects section of the SmPC. Therefore the current terms of the marketing authorisations should be varied¹¹.
- In the next PSUR (DLP: 28/09/2015), the MAH should provide further information on cases of hypersensitivity reactions, renal cancer, pancreatitis and fungal infection as well as further information on safety in elderly patients as compared to younger patients.
- The MAH should submit to the EMA, within 60 days, as supplementary information to the ongoing PSUR procedure (PSUSA/00010077/201503), information and discussions on renal impairment and renal failure.

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. Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis b (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and Haemophilus influenza type b (Hib) conjugate vaccine (adsorbed) – INFANRIX HEXA (CAP) - PSUSA/01122/201410

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

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

Scope of procedure: Evaluation of a PSUSA procedure

Background

Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis b (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and *Haemophilus influenzae* type b (Hib) conjugate vaccine (adsorbed) is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by *Haemophilus influenzae* type b.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Infanrix Hexa, a centrally authorised medicine containing diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis b (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and *Haemophilus influenzae* type b (Hib) conjugate vaccine (adsorbed), 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 Infanrix Hexa (D-T-Pa-HBV-IPV-Hib conjugate vaccine (adsorbed)) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include upper respiratory tract infection as a new undesirable effect with an uncommon frequency, and bronchitis and thrombocytopenia as new undesirable effects with a rare frequency. Furthermore, the current information on experience with hepatitis B vaccine has been amended in the undesirable effects section of the SmPC to include the following events: allergic reactions mimicking serum sickness, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis and muscular weakness. Therefore the current terms of the marketing authorisation(s) should be varied¹².
- The MAH should submit to the EMA, within 60 days, a detailed discussion on the recently observed increase, mainly in Czech Republic, in the reported cases of regression of psychomotor development. The national reporting patterns, geographical differences in case classifications and any other issues that could influence reporting by patients and physicians should be taken into account. Moreover, the MAH should present a discussion regarding psychomotor development delay including information on case definition and epidemiology of the disorder in the context of vaccination. Moreover, the MAH should discuss if there is a potential biological mechanism for an association between regression of psychomotor development and Infanrix Hexa vaccination. Finally, with respect to the recently reported cases of medication errors and maladministration, the MAH should submit a detailed review and propose further risk minimisation measures regarding the lack reconstitution as appropriate.
- In the next PSUR, the MAH should provide a detailed discussion on the need for collection of further vaccine effectiveness information, the implication of the waning immunity on the vaccination schedule as well as the available data regarding currently circulating *Bordetella pertussis* strains. Moreover, the MAH should provide some clarification regarding reported events of hyperpyrexia, extensive limb swellings (ELS), encephalopathy, autism, Kawasaki's disease, and apparent life threatening event

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

(ALTE). The MAH should provide a detailed description of the search strategy for hypotonic-hyporesponsive episode (HHE) and for lack of efficacy/vaccination failure.

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. Metformin, saxagliptin – KOMBOGLYZE (CAP) - PSUSA/02686/201411

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

Background

Saxagliptin is a dipeptidyl peptidase 4 (DPP4) inhibitor and metformin, a biguanide, and in combination is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Komboglyze (metformin, saxagliptin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add constipation as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied¹³.
- The MAH should align as appropriate the product information of saxagliptin/metformin with the metformin product information once the metformin PSUSA (PSUSA/00002001/201504) has been finalised, should any update to the product information be agreed.

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

6.1.5. Simeprevir – OLYSIO (CAP) - PSUSA/10255/201411

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

Background

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

Simeprevir is a specific inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease, indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Olysio, a centrally authorised medicine containing simeprevir, 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 Olysio (simeprevir) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new warning on the risk of hepatic decompensation and hepatic failure. In addition a new warning on the risk of bradycardia when simeprevir is used in combination with sofosbuvir and amiodarone should be added to the warnings and precautions for use, the interaction with other medicinal products and other forms of interaction and the undesirable effects sections of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied¹⁴.
- In the next PSUR, the MAH should provide a comprehensive cumulative safety review of all seizure events including spontaneous reports, relevant literature reports and clinical and non-clinical data. The MAH should also provide the placebo case details for those that matched the Hy's Law criteria from the Phase 2b and 3 studies and a discussion of how these cases compare to the simeprevir reports in meeting Hy's law, along with providing any interim data available on the interferon free studies, and analysis of any new post-marketing cases and cumulative review of post-marketing reporting for these events to further determine the risk of worsening of hepatic decompensation/ hepatic failure.
- The PRAC considered that changes in the RMP related to the risk of hepatic decompensation and hepatic failure were acceptable. The MAH should include the risk of bradycardia when simeprevir is used in combination with sofosbuvir and amiodarone in the next RMP update. Moreover, revisions of the RMP not related to the PSUR submission (mainly updates on an interventional trial, milestone changes in the Pharmacovigilance plan, among others) were not considered acceptable and were recommended to be taken into account at the next appropriate regulatory procedure.

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

6.1.6. Sofosbuvir – SOVALDI (CAP) - PSUSA/10134/201412

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

¹⁴ Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Background

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sovaldi, a centrally authorised medicine containing sofosbuvir, 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 Sovaldi (sofosbuvir) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to the EMA, within 60 days, justification for the proposed non-clinical models (in vitro/in-vivo) to investigate the potential interaction with amiodarone and sofosbuvir (and other direct-acting antivirals as appropriate).
- In the next PSUR, the MAH should provide more detailed analyses of ongoing and completed clinical trials, in particular relating to the ANRS CO22 HEPATHER¹⁵ study. The MAH should discuss a number of potential signals using data from all relevant sources (e.g. literature, clinical trials, post-marketing reports). These signals include: worsening of hepatic disease, convulsions/epilepsy and pulmonary arterial hypertension. The MAH should also provide an updated cumulative review of the cardiac events cases, including an analysis of any relationship between severity of hepatic dysfunction and the incidence bradycardia, when sofosbuvir is used in combination with amiodarone and other direct acting antivirals. Finally, the MAH should provide a breakdown of cases of medication errors leading to accidental overdose by country of origin and context.

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

6.1.7. Vedolizumab – ENTYVIO (CAP) - PSUSA/10186/201411

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope of procedure: Evaluation of a PSUSA procedure

Background

Vedolizumab is a humanised IgG₁ monoclonal antibody indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF_α) antagonist as well as for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response

¹⁵ Multicentre cohort of hepatitis B virus (HBV) and/or hepatitis C virus (HCV)-infected patients

with, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Entyvio, a centrally authorised medicine containing vedolizumab, 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 Entyvio (vedolizumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to strengthen the current warning on hypersensitivity reactions to include the management of acute hypersensitivity reactions including anaphylaxis, and to include a cross reference to this strengthened warning in the posology and method of administration section. In addition, pain in the extremity should be included as a new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied¹⁶.

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

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

See also Annex I 15.2.

6.2.1. Bosentan – STAYVEER (CAP); TRACLEER (CAP), NAP - PSUSA/00425/201411

Applicant: Actelion Registration Ltd., Marklas Nederlands BV, various

PRAC Rapporteur: Isabelle Robine

Scope of procedure: Evaluation of a PSUSA procedure

Background

Bosentan is a dual endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with World Health Organisation (WHO) functional class II and III under certain conditions and also to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

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

Summary of recommendation(s) and conclusions

¹⁶ Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of bosentan-containing medicinal products in the approved indications remains favourable.
- Nevertheless, the product information should be updated to include nasal congestion as a new undesirable effect with a common frequency. In addition, possible exacerbation of underlying autoimmune hepatitis is added to the already included undesirable effect of aminotransferase elevations associated with hepatitis and/or jaundice. Therefore the current terms of the marketing authorisation(s) should be varied¹⁷.
- In the next PSUR, the MAHs should include pancytopenia in the signal evaluation section and should provide an updated cumulative review. In addition, further cases of hepatic disorders including co-medication with methotrexate, and cases of ascites, should be monitored in the context of the important identified risk of hepatotoxicity in the liver safety updated report.
- Finally, in accordance with the recently approved type II variation [EMA/H/C/000401/II/0066](#), bosentan generic products should update their product information to align it with the product information of Tracleer and Stayveer and include the warning regarding decrease in sperm count, and the updated data on the paediatric population.

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

6.2.2. [Sodium oxybate – XYREM \(CAP\); NAP - PSUSA/02757/201410](#)

Applicant: UCB Pharma Ltd., various

PRAC Rapporteur: Magda Pedro

Scope of procedure: Evaluation of a PSUSA procedure

Background

Sodium oxybate is a central nervous system depressant indicated for the treatment of narcolepsy with cataplexy in adult patients and also in general and paediatric surgery for the induction of anaesthesia and basal narcosis, as narcosis for surgery in elderly patients with hypotension and hypovolaemia in various diagnostic procedures, in gynaecology and in obstetrics as narcosis in case of operative delivery, as general anaesthesia during delivery, and to avoid hypoxia.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xyrem, a centrally authorised medicine containing sodium oxybate and of nationally authorised medicine containing sodium oxybate, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the risk-benefit balance of sodium oxybate-containing medicinal products in the approved indications remains favourable.
- Nevertheless, the product information should be updated to include dry mouth and angioedema as new undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH for Xyrem should continue to closely monitor dyspepsia, stomach discomfort, epigastric discomfort, hypersomnia and loss of consciousness.
- Furthermore, the MAH Nātrija oksibutirāts-Kalceks should include the outcome of the corrective and preventive action (CAPA) assessment by the Latvian competent authority 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.

6.2.3. Tadalafil – ADCIRCA (CAP), CIALIS (CAP); NAP - PSUSA/02841/201410

Applicant: Eli Lilly Nederland B.V., various

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

Background

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) indicated for the treatment of erectile dysfunction in adult males, for the treatment of pulmonary arterial hypertension (PAH) classified as World Health Organisation (WHO) functional class II and III to improve exercise capacity and in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Adcirca and Cialis, centrally authorised medicines containing tadalafil and nationally authorised medicines containing tadalafil, 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 tadalafil-containing medicinal products in the approved indications remains favourable.
- Nevertheless, the product information should be updated to include a new contraindication for the co-administration of PDE5 inhibitors including tadalafil with guanylate cyclase stimulators, such as riociguat as it may cause symptomatic hypotension. Additional information on this contraindication should also be included in

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

the interaction with other medicinal products and other forms of interaction section. Therefore the current terms of the marketing authorisation(s) should be varied¹⁹.

- In the next PSUR, the MAH for Adcirca and Cialis should provide the number of patients enrolled in the four non-interventional studies, provide additional detailed information of the new ongoing study (B022), such as study design, estimated number of patients to be enrolled, and source of the population to be studied. Finally, the MAHs should also closely monitor cases of eye haemorrhages, chorioretinopathy and anaemia.

The PRAC further recommended that the wording on the increased risk of hypotension during concomitant administration with guanylate cyclase stimulators, such as riociguat, should also be reflected in the product information for the other PDE5 inhibitors (including vardenafil, sildenafil, avanafil), and that MAHs of these products shall take due note of this recommendation.

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

6.2.4. Toremifene – FARESTON (CAP); NAP - PSUSA/02999/201409

Applicant: Orion Corporation, various

PRAC Rapporteur: Corinne Féchant

Scope of procedure: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fareston, a centrally authorised medicine containing toremifene, 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 Fareston (toremifene) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new warning on liver injury and to include hepatitis as a new undesirable effect with an unknown frequency. In addition the list of CYP 3A inhibitors with which there is a potential for drug interactions is updated in the interaction with other medicinal products and other forms of interaction section. Therefore the current terms of the marketing authorisation(s) should be varied²⁰.
- In the next PSUR, the MAH should include potentially severe liver injury to the summary of important identified risks.

¹⁹ Update of SmPC section 4.3 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁰ Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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.

6.3. PSUR procedures including nationally authorised products (NAPs)

See also Annex I 15.3.

6.3.1. Calcium carbonate, famotidine, magnesium hydroxide (NAP) - PSUSA/00001351/201409

Applicant: various

PRAC lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

Famotidine, a histamine (H)₂-receptor antagonist, reduces acid and pepsin production, as well as the volume of basal, nocturnal and stimulated gastric secretion. Calcium carbonate and magnesium hydroxide have antacid properties via a neutralisation mechanism. In combination, calcium carbonate/famotidine/magnesium hydroxide is indicated in adults and adolescents from 16 years old for short-term symptomatic treatment of heartburn or acid regurgitation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing calcium carbonate/famotidine/magnesium hydroxide, 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 calcium carbonate/famotidine/magnesium hydroxide-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to clarify that the undesirable effects 'pruritus', 'rash' and 'urticaria' with unknown frequencies have been reported with calcium carbonate/famotidine/magnesium hydroxide as a combination and not only with famotidine as a single agent. In addition, 'alopecia' should be added as an undesirable effect reported with famotidine as a single agent. Therefore the current terms of the marketing authorisations should be varied²¹.
- In the next PSUR, the MAH should closely monitor cases of accidental ingestion by children and cases of rhabdomyolysis.

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.

²¹ 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

6.3.2. Corticorelin (NAP) - PSUSA/00000876/201410

Applicant: various

PRAC lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Corticorelin is a human corticotrophin-releasing hormone indicated for diagnostic use in order to test the corticotrophic partial function of the anterior pituitary gland when an organic impairment of this function is suspected.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing corticorelin, 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 corticorelin-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning to ensure that patients known to have a pituitary tumour are observed for signs and symptoms of pituitary haemorrhage (apoplexy) when performing pituitary stimulation test with corticorelin, especially in the case of simultaneous use of other pituitary diagnostic tests. In addition, pituitary apoplexy²² should be added to the product information as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied²³.
- MAHs of corticorelin-containing products that have a RMP in place should include 'use in paediatric patients' as missing information in the framework of the next regulatory procedure affecting the RMP.

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

6.3.3. Famotidine (NAP) - PSUSA/00001350/201409

Applicant: various

PRAC lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Famotidine, a histamine (H)₂-receptor antagonist, is indicated for the treatment of duodenal ulcer, benign gastric ulcer, hypersecretory conditions such as Zollinger-Ellison syndrome,

²² in patient known patients known to have a pituitary tumour

²³ 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

symptomatic relief of gastroesophageal reflux disease, healing of esophageal erosion or ulceration associated with gastroesophageal reflux disease, as well as for the prevention of relapse of duodenal ulceration and relapse of benign gastric ulcer, and the prevention of relapse of symptoms and erosions or ulcerations associated with gastroesophageal reflux disease (GERD). Famotidine-containing products with an over the counter (OTC) status are indicated for acid indigestion, heartburn, sour stomach and symptoms of upset stomach associated with these conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing famotidine, 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 famotidine-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include flatulence and alopecia as undesirable effects with an uncommon and a very rare frequency respectively. Therefore the current terms of the marketing authorisations should be varied²⁴.
- In the next PSUR, the MAHs should provide a detailed review of cases reported under the SOC²⁵ cardiac disorders including a detailed analysis of whether cardiac effects are mostly reported with injectable formulations and whether they occur mainly in renal impaired patients. The MAHs should also provide detailed reviews of cases of QT prolongation, rhabdomyolysis, delirium and tubulointerstitial nephritis. Furthermore, in terms of risk characterisation, the MAHs should add hypersensitivity as an important identified risk, and impaired ability to drive and use machines should be considered as an important identified risk. Finally, the MAHs should discuss efficacy and safety of use of famotidine in patients over 65 years.
- In the next PSUR, the MAHs MSD and Johnson & Johnson should also discuss if a pattern of use could be identified showing evidence of off-label use or drug misuse associated with famotidine. Finally, MSD should keep the signal of psychiatric events in patients under 18 years of age as ongoing and should monitor possible off-label use.

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. Hydroxyzine chloride, hydroxyzine pamoate and all fixed combination; hydroxyzine (NAP) - PSUSA/00001696/201411

Applicant: various

PRAC lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

²⁴ 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

²⁵ MedDRA system organ class

Hydroxyzine is a piperazine derivative indicated for the symptomatic treatment of anxiety, symptomatic treatment of pruritus, preoperative anxiolysis in adults and children and sleep disorders in children only under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing hydroxyzine²⁶, 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 hydroxyzine-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should ensure that QT prolongation and Torsades de Pointes (TdP), cardiac death and sudden death, bullous conditions, hepatic events, cardiac risk in the elderly, depression in the elderly and anticholinergic effects in the elderly should be considered as important identified risks. In addition, thrombocytopenia, respiratory depression, medication errors with the syrup formulation, risk of falls in the elderly, injection site necrosis (injection form only), thrombophlebitis (injection form only) should be considered as important potential risks. Use during breastfeeding, use in children, use in patients with renal impairment, use in patients with hepatic impairment should be considered as important missing information. Moreover, the MAHs should keep the signal of suicidal behaviour open and provide detailed analyses including the indication for use reported in the adverse drug reaction report. The MAHs should also provide detailed safety reviews on the use of hydroxyzine during pregnancy as well as during breastfeeding and based on these data discuss the most relevant recommendation of use in these populations.
- Based on the review provided in the PSUR, the PRAC recommended that the relevant National competent Authorities (NCAs) request the MAHs to submit variations to reflect the risks of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiforme in the product information. The decrease of the total daily dose in patients with hepatic and renal impairment and a precaution for use in these patients should be also mentioned in the product information of all hydroxyzine-containing products. In addition, NCAs should request MAHs of hydroxyzine-containing products with solution for injection formulations to submit variations to update their product information to reflect the risks of thrombosis/thrombophlebitis and skin necrosis/injection site necrosis as necessary.

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

6.3.5. Isoniazid (NAP) - PSUSA/00001789/201411

Applicant: various

PRAC lead: Qun-Ying Yue

²⁶ Including hydroxyzine chloride, hydroxyzine pamoate and fixed combination

Scope: Evaluation of a PSUSA procedure

Background

Isoniazid is an antimicrobial indicated for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing isoniazid, 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 isoniazid-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information²⁷ should be updated to include pancreatitis and vasculitis as undesirable effects with an unknown frequency, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) with a rare frequency, as well as hepatitis with an uncommon frequency. Therefore the current terms of the marketing authorisations should be varied²⁸.

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

6.3.6. Ketotifen (oral formulations) (NAP) - PSUSA/00001813/201410

Applicant: various

PRAC lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Ketotifen (oral formulations) is an anti-allergic substance possessing non-competitive histamine (H1) blocking properties indicated for the preventative treatment of bronchial asthma especially when associated with atopic symptoms, for the prevention and treatment of multisystem allergic disorders (chronic urticaria, atopic dermatitis, allergic rhinitis and conjunctivitis).

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

²⁷ Product information of medicinal products where the undesirable effect is not included yet

²⁸ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should provide findings from a literature search related to the active substance ketotifen and not just to the medicinal product Zaditen. The MAHs should also provide a detailed analysis of cases of overdose/medication errors in the paediatric population and propose measures to mitigate these risks as necessary. In addition, the MAHs should closely monitor events of lack of efficacy in order to ensure that such reports are routinely followed-up and the information is as complete as possible.

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.

6.3.7. Letrozole (NAP) - PSUSA/00001842/201410

Applicant: various

PRAC lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

Letrozole is a non-steroidal aromatase inhibitor indicated as an adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer, as an extended adjuvant treatment of hormone-dependent invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years, as a first-line treatment in postmenopausal women with hormone-dependent advanced breast cancer, also indicated in advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens. Finally, letrozole is indicated for neo-adjuvant treatment of postmenopausal women with hormone receptor positive, human epidermal receptor 2 (HER2) negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing letrozole, 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 letrozole-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide detailed analyses of fatal cases, autoimmune disorders, cognitive disorders, cardiac arrhythmia, hepatitis and peripheral neuropathy. In addition, the MAHs should provide cumulative reviews of cases of palmar-plantar erythrodysesthesia, second primary malignancy, age-related macular degeneration/macular degeneration, blindness/blindness unilateral, glaucoma, visual acuity reduced/visual impairment and lymphoedema.

- In the next PSUR, the MAHs Novartis Pharma and Sandoz should provide detailed analyses of cases of off-label use as well as of lack of efficacy, including the relationship to a potential lack of compliance to the treatment. RMPs should be updated accordingly in the next regulatory procedure affecting the RMP or within 6 months at the latest.
- The MAHs for letrozole-containing products that have an RMP in place should reflect the risk of congenital malformations and co-administration of letrozole with tamoxifen as important identified risks in the RMP in the framework of the next regulatory opportunity affecting the RMP or within 6 months at the latest.
- The MAH Aptil Pharma should add 'angina requiring surgery' as an important identified risk in the RMP in the next regulatory procedure affecting the RMP.

The frequency of PSUR submission should be revised from three-yearly to yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.8. Miconazole; miconazole nitrate, hydrocortisone; miconazole nitrate, zinc oxide (NAP) - PSUSA/00002052/201410

Applicant: various

PRAC lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Miconazole is a synthetic 1-phenethyl-imidazole derivative indicated alone or in combination for the treatment of candidiasis of the oropharynx and gastrointestinal tract and treatment of digestive tract mycoses, for the local treatment of vulvovaginal candidiasis (VVC) and superinfections due to gram positive bacteria as well as for the treatment of mycotic infections of skin or skin appendages.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing miconazole, miconazole nitrate/hydrocortisone, miconazole nitrate/zinc oxide 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 miconazole, miconazole nitrate/hydrocortisone, miconazole nitrate/zinc oxide-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to extend the contraindication on hypersensitivity to all imidazole derivatives for all miconazole formulations and to include a new warning for miconazole gynaecological formulations to mention that concurrent use of latex condoms or diaphragms with vaginal anti-infective preparations may decrease the effectiveness of latex contraceptive products. In addition, a warning should be added for all miconazole dermatological (including combination products), oral, gynaecological and intravenous formulations on severe hypersensitivity reactions and ensure that in case of occurrence of hypersensitivity or irritation reactions, the

treatment should be withdrawn immediately. Moreover, 'acute generalised exanthematous pustulosis' (AGEP) (oral formulations), 'acute generalised exanthematous pustulosis', 'Stevens-Johnson syndrome' (SJS) and 'toxic epidermal necrolysis' (TEN) (intravenous formulations) should be added to the product information as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied²⁹.

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

6.3.9. Pramiracetam (NAP) - PSUSA/00002492/201409

Applicant: various

PRAC lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Pramiracetam belongs to the nootropic therapeutic drug class and is indicated for the treatment of degenerative or vascular pathology-related concentration and memory disorders in elderly patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing pramiracetam, 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 pramiracetam-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to update the section on 'posology and method of administration' in order to include the need for regular evaluation of the creatinine clearance in long-term treatment and to delete posology recommendations for adult patients which are not included in the approved indication. Therefore the current terms of the marketing authorisations should be varied³⁰.

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

6.3.10. Prulifloxacin (NAP) - PSUSA/00002569/201410

Applicant: various

PRAC lead: Carmela Macchiarulo

²⁹ Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³⁰ Update of SmPC section 4.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Scope: Evaluation of a PSUSA procedure

Background

Prulifloxacin is a fluoroquinolone indicated for the treatment of acute uncomplicated lower urinary tract infections (simple cystitis), acute exacerbation of chronic bronchitis as well as for acute bacterial rhinosinusitis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing prulifloxacin, 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 prulifloxacin-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new warning on Clostridium difficile-associated disease and to include lip oedema, face oedema, angioedema, dyspnoea, paraesthesia, tremor, tachycardia and pseudomembranous colitis as new undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied³¹.
- In the next PSUR, the MAHs should closely monitor cases of renal disorders. In addition, the MAHs should clarify applied criteria for off-label use.

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

6.3.11. Tetrabenazine (NAP) - PSUSA/00002911/201410

Applicant: various

PRAC lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Tetrabenazine is a reversible inhibitor of human vesicular monoamine transporter type 2 (VMAT2) and is indicated for the treatment of Huntington's chorea. Other authorised indications in the EU include hyperkinesia, hemiballismus, senile chorea and moderate to severe tardive dyskinesia.

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

³¹ 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

- Nevertheless, the product information should be updated to strengthen the existing warning on dose titration and to provide further information to the prescriber regarding the potential influence of CYP2D6 metaboliser status and concomitant strong CYP2D6 inhibitors on dose and dose related adverse effects. Therefore the current terms of the marketing authorisations should be varied³².
- In the next PSUR, the MAHs should discuss possible reasons for the increase in the number of reported adverse events. The MAHs should also provide detailed reviews of cases of convulsions, hallucinations, tardive dyskinesia, blindness and vision impairment as well as thromboembolic events, and update the product information as warranted. In addition, in line with the product information warning on QT prolongation, the MAHs should consider updating the section on undesirable effects accordingly and discuss the addition of electrocardiogram monitoring before starting and during treatment with tetrabenazine as necessary as well as the concomitant use with other drugs with an effect on QT prolongation. Moreover, the MAHs should provide an assessment of the effectiveness of routine risk minimisation measures relevant to depression/suicidality within the EU. The MAHs should also discuss if the current available evidence supports further strengthening the warning on parkinsonism and evaluate whether the product information section on pregnancy should be further revised in view of the available reports of exposure to tetrabenazine during pregnancy. Furthermore, the MAHs should provide a detailed analysis of data available regarding the safety profile of tetrabenazine in poor and intermediate CYP2D6 metabolisers versus extensive metabolisers and propose an update of the product information as warranted. The MAHs should also present a further detailed analysis of drug interactions involving CYP2D6. Finally, MAHs should closely monitor cases of death, overdose, off label use and paediatric use.

The frequency of PSUR submission should be revised from three-yearly to yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.4. Follow-up to PSUR procedures

See Annex I 15.4. 15.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)³³

See also Annex I 16.1.

7.1.1. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSP/0025

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

³² 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

³³ In accordance with Article 107n of Directive 2001/83/EC

Scope: Evaluation of a protocol for a pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany, Netherlands, UK and Sweden

Background

Rivaroxaban is a highly selective direct factor Xa inhibitor indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) under certain conditions, for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in adult patients under certain conditions and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

With the approval of the line extension procedure [EMA/H/C/000944/X/017](#) for Xarelto, the obligation to conduct a non-interventional PASS was imposed as a condition to the marketing authorisation. A draft protocol for this PASS (XAMACS) was submitted to PRAC in June 2013. In the second round of assessment, the PRAC raised some objections against this protocol, in particular with regard to the feasibility of the study. The MAH consequently submitted a type II variation to amend the condition to the marketing authorisation regarding the requested PASS and proposed a new post-authorisation study program including the draft PASS protocols. This post-authorisation study programme is to address the safety of rivaroxaban in the secondary prevention of ACS outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all populations and particularly in patients at increased risk of bleeding. This variation procedure (EMA/H/C/000944/II/0034) was finalised, following a PRAC recommendation, with a positive opinion on 26 February 2015.

A revised protocol for a pharmacoepidemiological study on the use of rivaroxaban and potential adverse outcomes in routine clinical practice in Germany, the Netherlands, the UK and Sweden was submitted to the PRAC by the MAH in accordance with the condition to the marketing authorisations.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 5.2 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for the above listed medicinal product.

7.1.2. Rivaroxaban – XARELTO (CAP) - EMA/H/C/PSP/0026

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a protocol for an observational post-authorisation Safety Specialist Cohort Event Monitoring study (SCEM) to monitor the safety and utilisation of rivaroxaban initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales.

Background

Rivaroxaban is a highly selective direct factor Xa inhibitor indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) under certain conditions, for the prevention of venous thromboembolism in adult patients

undergoing elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in adult patients under certain conditions and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

With the approval of the line extension procedure [EMEA/H/C/000944/X/017](#) for Xarelto, the obligation to conduct a non-interventional PASS was imposed as a condition to the marketing authorisation. A draft protocol for this PASS (XAMACS) was submitted to PRAC in June 2013. In the second round of assessment, the PRAC raised some objections against this protocol, in particular with regards to the feasibility of the study. The MAH consequently submitted a type II variation to amend the condition to the marketing authorisation regarding the requested PASS and proposed a new post-authorisation study program including the draft PASS protocols. This post-authorisation study program is to address the safety of rivaroxaban in the secondary prevention of ACS outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all populations and particularly in patients at increased risk of bleeding. This variation procedure (EMEA/H/C/000944/II/0034) was finalised, following a PRAC recommendation, with a positive opinion on 26 February 2015.

A revised protocol for an observational post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of rivaroxaban (Xarelto) initiated in secondary care for the prevention of atherothrombotic events in patients who have had ACS in England and Wales was submitted to the PRAC by the MAH in accordance with the condition to the marketing authorisations.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 4.0 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for the above listed medicinal product.

7.1.3. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSP/0027

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a revised protocol for an observational post-authorization Modified Prescription-Event Monitoring safety study (M-PEM) to monitor the safety and utilization of rivaroxaban (XARELTO) for the prevention of stroke in patients with atrial fibrillation (AF), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England – including an extension to the Rivaroxaban M-PEM Study to include Acute Coronary Syndrome Patients.

Background

Rivaroxaban is a highly selective direct factor Xa inhibitor indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) under certain conditions, for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in adult patients under certain conditions and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

With the approval of the line extension procedure [EMA/H/C/000944/X/017](#) for Xarelto, the obligation to conduct a non-interventional PASS was imposed as a condition to the marketing authorisation. A draft protocol for this PASS (XAMACS) was submitted to PRAC in June 2013. In the second round of assessment, the PRAC raised some objections against this protocol, in particular with regards to the feasibility of the study. The MAH consequently submitted a type II variation to amend the condition to the marketing authorisation regarding the requested PASS and proposed a new post-authorisation study program including the draft PASS protocols. This post-authorisation study program is to address the safety of rivaroxaban in the secondary prevention of ACS outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all populations and particularly in patients at increased risk of bleeding. This variation procedure (EMA/H/C/000944/II/0034) was finalised, following a PRAC recommendation, with a positive opinion on 26 February 2015.

A revised protocol for an extension to the observational post-authorisation modified prescription-event monitoring (M-PEM) safety study to monitor the safety and utilisation of rivaroxaban (Xarelto) for the prevention of stroke in patients with AF, treatment of DVT and PE, and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England to include ACS patients was submitted to the PRAC by the MAH in accordance with the condition to the marketing authorisations.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 5.2 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for the above listed medicinal product.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)³⁴

See also Annex I 16.2.

7.2.1. Canakinumab – ILARIS (CAP) - EMA/H/C/001109/MEA 037.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a MAH's responses to a request for supplementary information for MEA 037.1 [non-interventional study collecting safety and efficacy data from systemic juvenile idiopathic arthritis (SJIA) patients enrolled in Pharmachild JIA registry, protocol, Study no. CACZ885G2401] adopted in September 2014

Background

Ilaris is a centrally authorised medicine containing canakinumab, a fully human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody used in the treatment of cryopyrin-associated periodic syndromes, systemic juvenile idiopathic arthritis (SJIA) and gouty arthritis under certain conditions.

As part of the RMP for Ilaris, a centrally authorised medicine containing canakinumab, the MAH was required to conduct a PASS i.e. participate to the Pharmachild Registry

³⁴ 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

(Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic agents and/or methotrexate, study CACZ885G2401) conducted by PRINTO (Paediatric Rheumatology International Trials Organization) and PRES (Paediatric Rheumatology European Society). The aim was to collect prospective safety, tolerability, efficacy, and treatment adherence information on juvenile idiopathic arthritis (JIA) subjects exposed to any biologic agents and methotrexate, according to local standard practice. A first draft protocol was submitted for review in December 2013. Since then, there have been several rounds of assessments. The MAH submitted a new study protocol concerning the non-interventional study collecting safety data from SJIA patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) disease registry (US and Canada) who initiate treatment with canakinumab or comparator (intended to replace the former Pharmachild registry study) which has been assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC noted that some safety concerns addressed in the previous study protocol of the Pharmachild registry would not be addressed with this new PASS proposed by the MAH. Assessing the protocol for the new PASS CACZ885G2403, new questions arose concerning milestones, setting, data sources, study size and power, data analysis, management and reporting of adverse events/adverse reactions. In addition no statistical analysis plan was provided. The proposed new design of study CACZ885G2403 was not considered consistent with the RMP or to address the points outlined in the pharmacovigilance plan.
- The study protocol for study CACZ885G2403 could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA within 30 days.

7.3. Results of PASS imposed in the marketing authorisation(s)³⁵

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)³⁶

See also Annex I 16.4.

7.4.1. Rotavirus vaccine, live – ROTARIX (CAP) - EMEA/H/C/000639/II/0062 (with RMP)

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report of genetic stability study EPI-ROTA-014 VS BE – 112560 that addresses the Post-Approval Measure ME2 005.2 in which the MAH commits to monitor for the potential occurrence of genetic drifts and shifts in the vaccine strain in post-marketing settings.

Background

³⁵ In accordance with Article 107p-q of Directive 2001/83/EC

³⁶ 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

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

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

A first interim report with a preliminary analysis of the data from Phase I of the study was submitted in February 2012. A second interim report including a preliminary analysis of the data from Phase II of the study was submitted at the end of February 2013. The MAH submitted the final report of study EPI-ROTA-014 VS BE and thus presented the final analysis of the study data. See [PRAC minutes March 2015](#).

Summary of advice

- The PRAC discussed the Vaccines Working Party (VWP) responses to the CHMP's and the PRAC's questions adopted in March 2015. The PRAC supported the VWP's position and agreed that the PRAC Rapporteur should update the third request for supplementary information (RSI) removing the request for the MAH to conduct an additional PASS and circulate the report for comments. The updated RSI will be adopted during the July 2015 PRAC meeting.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation³⁷

See Annex I 16.5.

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

See Annex I 17.2.

8.3. Renewals of the marketing authorisation

8.3.1. Telmisartan, amlodipine – TWYNSTA (CAP) - EMEA/H/C/001224/R/0026 (without RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Valerie Strassmann

Scope: 5-year renewal of the marketing authorisation

³⁷ In line with the revised variations regulation for any submission before 4 August 2013

Background

Telmisartan is an angiotensin II receptor antagonist and amlodipine is a calcium channel blocker, indicated in combination for the treatment of essential hypertension in adults as add-on therapy in patients whose blood pressure is not adequately controlled on amlodipine alone.

Twynsta, a centrally authorised medicine containing telmisartan/amlodipine, was authorised in 2010.

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

Summary of advice

- Based on the review of the available pharmacovigilance data for Twynsta (telmisartan/amlodipine) and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal of the marketing authorisation could be granted with unlimited validity. Based on the recent review of the risk of interstitial lung disease (ILD) for telmisartan-containing medicinal products (see [PRAC minutes March 2015](#), LEG 012) and further evidence suggesting a causal relationship between telmisartan and ILD, the PRAC supported the addition of ILD to the product information.

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 of centrally authorised products for human use

The PRAC agreed the list of planned pharmacovigilance inspections 2015-2018, first revision, reviewed according to a risk based approach. This list is subsequently due for agreement 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.

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. Naltrexone, bupropion – MYSIMBA (CAP) – EMEA/H/C/003687/ANX 001

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: PRAC consultation on a PASS protocol for a multicentre, randomised, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone extended release (ER) /bupropion ER on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects

Background

Naltrexone is an opioid antagonist and bupropion an aminoketone derivative. Their combination is indicated as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients with an initial body mass index (BMI) of ≥ 30 kg/m² (obese), or ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of one or more weight-related co-morbidities.

In line with the CHMP opinion dated December 2014 and the marketing authorisation granted by the European Commission in March 2015, including an obligation for the MAH to conduct a cardiovascular outcome trial (CVOT), the MAH submitted a PASS protocol for a multicentre, randomised, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone/bupropion extended release on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects. The CHMP requested advice from the PRAC on the assessment of this PASS protocol.

Summary of advice

- Based on the review of the available information, the PRAC considered that the study fulfils the intention to proof whether there is an excess of MACE, provided consideration is given to several issues. Indeed, it was noted that the CVOT-2 study, to be conducted in the US, will not mandate cessation of treatment in non-responders at 16 weeks, which is required in the EU product information, as this cessation rule was thought to introduce a methodological limitation in the CVOT-1 clinical trial. The PRAC also noted that the study was included in the RMP to address other non-cardiovascular safety concerns. Nevertheless, these safety concerns are not adequately addressed in the protocol, therefore the PRAC suggested that such additional endpoints should be monitored appropriately. In addition, the PRAC advised that in case of early termination due to an excess CV risk being ruled out, the MAH should be requested to submit a summary of the data likely to be available on other key aspects of the safety profile to assess whether they meet the requirements included in the RMP. Overall, the PRAC agreed with the CHMP Rapporteur's position that there is a need for further clarification on the study protocol before a final approval could be granted. The PRAC provided input in the draft CHMP's list of questions to the MAH.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Ciprofloxacin for systemic use (NAP) – NO/H/PSUR/0010/002

Applicant: Bayer Health Care

PRAC lead: Ingebjørg Buajordet

Scope: PRAC consultation on a PSUR work-sharing procedure relating to signal of rhabdomyolysis and the need to request an interaction study with agomelatine

Background

Ciprofloxacin is a fluoroquinolone antibiotic indicated for uncomplicated and complicated infections caused by ciprofloxacin susceptible pathogens.

During the current PSUR work-sharing procedure for ciprofloxacin for systemic use, some potential signals had arisen. Norway, as the P-RMS, requested the advice of the PRAC on aspects concerning the assessment of these signals in the context of this ongoing procedure, following a first advice adopted in December 2014. For further background, see [PRAC minutes December 2014](#).

Summary of advice

- With regard to rhabdomyolysis, the PRAC considered that the available evidence was not supportive of raising a new signal. Routine pharmacovigilance activities were considered sufficient to monitor the concern.
- With regard to the potential drug-drug interaction with agomelatine, the PRAC considered that routine pharmacovigilance activities were also sufficient to monitor the concern and that the MAH should not be required to conduct interaction studies. In addition, the PRAC agreed with the proposed MAH's changes to the product information³⁸.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. Mandate of Chair and Vice-Chair

As the first three year mandate of the PRAC Chair and Vice-Chair will expire in September 2015, the EMA Secretariat explained to the Committee the next steps in line with Article 3³⁹

³⁸ SmPC section 4.4 and 4.5, as well as package leaflet

³⁹ The Chair and Vice-Chair of the PRAC shall be elected by and from amongst its members for a term of three years, which may be prolonged once

of the Rules of Procedure of the PRAC ([EMA/PRAC/567515/2012 Rev.1](#)) and voting process. Subject to confirmation of the current Chair's and Vice-Chair's interest in prolonging their mandate, the EMA Secretariat will organise a vote on the prolongation by secret ballot at the July 2015 PRAC meeting.

12.1.2. ORGAM: introduction of a topic request form

The EMA Secretariat presented to the PRAC a proposal to introduce an ORGAM topic request form to streamline the ORGAM topics coming to the PRAC. The draft template was presented to the PRAC. This initiative was welcomed by the Committee.

12.2. Coordination with EMA Scientific Committees or CMDh-v

12.2.1. CHMP guidelines concerning tools for early access to medicines (accelerated assessment and conditional marketing authorisations): revision

The EMA Secretariat presented to the PRAC a summary of the proposed changes to the draft revised CHMP guidelines on tools for early access to medicines, on accelerated assessment⁴⁰ and on conditional marketing authorisation⁴¹ respectively, together with the expectations of their impact. With regard to the draft revised guideline on accelerated assessment, currently under review by the CHMP, PRAC and CAT, the EMA secretariat invited PRAC delegates to provide comments by 30 June 2015. As for the draft revised guideline on conditional marketing authorisation, currently under review by the CHMP, CAT, PRAC and PDCO, PRAC delegates were invited to provide comments by 22 June 2015. Following the consolidation of both draft guidelines, they will be released for public consultation on the EMA website.

12.2.2. PRAC lead variations: appointment of CHMP liaison persons

At the organisational matters teleconference on 25 June 2015, the EMA Secretariat provided some background information on the new role of the CHMP/PRAC liaison. The reimbursement of PRAC Rapporteurs as set out in [Regulation \(EU\) No 658/2014](#) (Pharmacovigilance fee regulation) is not foreseen for type II variations and therefore under the current process, for variations for which PRAC is in the lead for the assessment the so called PRAC-led variations (certain C.I.11 or C.I.13 type II variations), the fees can only be paid to the national competent authority to which the CHMP rapporteur belongs. The new role of the CHMP/PRAC liaison role has been created to allow that the payment of the fees for PRAC led variations is made to the delegation of the PRAC Rapporteur (in charge of the assessment) when it is not the same as the delegation of the CHMP Rapporteur. The CHMP/PRAC liaison will be the CHMP member or alternate from the same delegation as the PRAC Rapporteur. The responsibilities and appointment of the CHMP/PRAC liaison were also presented to the PRAC.

⁴⁰ Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004

⁴¹ Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004

12.3. Coordination with EMA working parties/working groups/drafting groups

12.3.1. Scientific Advice Working Party (SAWP): call for PRAC members

The EMA Secretariat presented to the PRAC some clarifications on the call for expression of interests for joint SAWP/PRAC membership that went out on 17 May 2015. To support the non-imposed non-interventional PASS protocols pilot through the SAWP, two positions for joint SAWP/PRAC membership are open for PRAC members. One defined alternate from their respective organisations who are not PRAC members may be named by each appointed joint member. The decision on appointment to the SAWP will be made collectively by the CHMP, PRAC and SAWP based on relevant experience and expertise. A short outline of the timetable for the launch of the PASS pilot was also presented to PRAC. It was agreed to extend the deadline for nominations to 9 July 2015.

12.4. Cooperation within the EU regulatory network

12.4.1. EuroMediCAT: safety of medication use in pregnancy (7th Framework project) - conclusion

The topic was deferred to July 2015 PRAC meeting.

12.4.2. Strategy for EU medicines network to 2020

At the organisational matters teleconference on 25 June 2015, the EMA Secretariat presented an outline of the strategy for EU medicines network to 2020. Following endorsement by the EMA management board in March 2015, this strategy document was released for public consultation on 31 March 2015 with 30 June 2015 as the deadline for comments. The PRAC was invited to submit comments by the deadline. In terms of next steps, all the comments received from the public consultation will be carefully reviewed and the need to amend the draft strategy document will be considered. The strategy document is planned to be finalised by the end of 2015.

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

12.6.1. World Medical Association declaration on ethical considerations regarding health databases and biobanks

At the organisational matters teleconference on 25 June 2015, the EMA Secretariat presented to PRAC the draft EMA comments to the World Medical Association (WMA) on the WMA declaration on ethical considerations regarding health databases and biobanks released for public consultation. The PRAC supported the comments suggested by EMA.

12.7. PRAC work plan

12.7.1. PRAC work plan 2015

The EMA Secretariat presented the draft 2015 PRAC work plan for final adoption before publication. The EMA Secretariat took this opportunity to provide a short update on progress made with the different topics and activities included in the draft 2015 PRAC work plan. The PRAC was given the opportunity to provide some final comments in advance of the organisational matters teleconference on 25 June 2015. The 2015 PRAC work plan was formally adopted by the PRAC on 25 June 2015.

Post-meeting note: the 2015 PRAC work plan was published on the EMA website on 07/07/2015, see: [EMA/PRAC/794108/2013](http://ema.europa.eu/PRAC/794108/2013)

12.7.2. PRAC work plan 2016: process and template

At the organisational matters teleconference on 25 June 2015, the EMA Secretariat presented the process for developing the 2016 PRAC work plan. The process for developing the work plan and the template have been harmonised across all EMA scientific Committees to facilitate the coordination. All the activities of all the Committees have been mapped and a tracking tool for all the work plans has been developed with a traffic light system to see clearly the progress made with each topic. The detailed process for developing the 2016 Committees work plan was then presented. The 2016 PRAC work plan should be built on the 2015 work plan foundations in alignment with the EMA work programme objectives.

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. PSURs repository: update on the pilot and audit

The EMA Secretariat presented to the PRAC an update on the pilot activity between February and May 2015, including feedback from NCAs, MAHs and EMA on the functionalities as well as the outcome of the first pilot phase. The second pilot phase will continue by increasing or modulating the capacity in terms of PSURs and volume of involved stakeholders. As part of the following steps, the timing of the switch-on of the PSUR repository will need to be agreed by the EU network before being switched-on. EMA will provide support to NCAs, especially at key milestones of the procedure to facilitate the use of the repository, e.g. guiding on upload, search and retrieve functionality. Regular bulletins and training sessions are being provided to ensure a smooth transition to the switch-on of the PSUR repository.

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

The PRAC endorsed the draft revised EURD list version June 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 June 2015, the updated EURD list was adopted by the CHMP and CMDh at their June 2015 meeting and published on the EMA website on 01/07/2015, 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. Electronic reaction monitoring reports (eRMR) pilot phase: specific consideration in signal detection

The EMA Secretariat presented to PRAC a status update on the electronic reaction monitoring reports (eRMR) pilot phase and related considerations in signal detection. The eRMR pilot phase aims at improving efficiency, allows for early detection of signals, simplify the screening of eRMR while decreasing the workload for all stakeholders. Currently some changes are under testing, this includes the implementation of PROTECT⁴² results, revised designated medical events (DME), inclusion of special populations (e.g. paediatrics, geriatrics), enhanced visualisation of cases occurring in the context of abuse, misuse, overdose, medication error and occupational exposure as well as monitoring the trends in reporting product quality defects. As next steps, the EMA Secretariat will assess the impact of the pilot in practice, present the results to the PRAC and reflect the findings in guidelines that are currently under development within SMART 2/3.

⁴² Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

12.11.2. Guideline on screening for adverse drug reactions in EudraVigilance

The PRAC was further updated on the development of the statistical guideline and the screening of adverse drug reactions in EudraVigilance following discussion in May 2015 (see [PRAC minutes May 2015](#)). The paper aims at providing methods to screen drug-event combinations (DEC) efficiently and to provide an opportunity for reviewing and improving current methods used to highlight cases for review and look for alternatives to the current methodology; in particular to investigate whether the additional methods used in the eRMR are appropriate and whether any changes should be implemented.

See also 12.11.1.

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

The PRAC was updated on the outcome of the June 2015 SMART Working Group (SMART WG) meeting. As a follow-up to previous discussion (see [PRAC minutes May 2015](#)), the SMART discussed a draft process for the handling of MAHs' validated signals from EudraVigilance. The work is ongoing and a refined proposal will be discussed in future SMART meetings and once the proposal is mature, it will also be brought for discussion at PRAC for a plenary discussion. In addition, the SMART discussed the possibility to revise the frequency of EudraVigilance eRMR monitoring for mature products based on a set of criteria. Follow-up discussion will take place in future meetings.

See also 12.11.1.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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 24/06/2015 on the EMA website (see: [Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#))

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality: road map

At the organisational matters teleconference on 25 June 2015, the EMA Secretariat presented a short update on the development of the revised EudraVigilance functionalities and the new system implementation timelines. At present EudraVigilance is in the development phase (until mid-2016). When the new EudraVigilance web (EVWEB) application will go live (planned for June-July 2017), it will only support the creation of E2B(R3) messages. It will be able to review and load E2B(R2) messages, however any individual case safety reports (ICSRs) created will be in E2B(R3) format. To plan for this, all organisations using EVWEB will need to be trained in advance and all national competent authorities receiving ICSRs from EVWEB users and the medical literature monitoring service will need to support E2B(R3).

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 - non-imposed PASS protocols: revised process

See under **Error! Reference source not found.**

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

12.17.1. Five year-renewal procedure: revised assessment process

The EMA Secretariat presented to the PRAC the key principles of the revised assessment process for 5 year renewals and a proposal for revised criteria for PRAC plenary discussion. The PRAC was invited to provide comments on the draft joint assessment report template. It was agreed to organise some training sessions on the new process and that the new process will be implemented as of September 2015.

12.18. Risk communication and transparency

12.18.1. Good pharmacovigilance practice GVP Module XV - communication and DHPC

The EMA Secretariat presented an update on the revision of the good pharmacovigilance practice (GVP) module XV on safety communication and highlighted the main proposed changes: revision of the DHPC template and the communication plan template, introduction of a concept of core EU DHPC and a process for DHPC preparation and dissemination. The PRAC was invited to provide comments by 24 June 2015. The draft revised GVP module is planned to go for 2 months' public consultation.

12.18.2. Public participation in pharmacovigilance

None

12.18.3. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

13. Any other business

13.1. Pharmacovigilance programme and revised implementation

At the organisational matters teleconference on 25 June 2015, the EMA Secretariat provided to the PRAC an update on the following pharmacovigilance projects: Article 57 database, EudraVigilance auditable requirements, medical literature monitoring, pharmacovigilance fees and the PSUR repository.

13.2. Strategy on impact of pharmacovigilance

The EMA Secretariat presented to PRAC a draft paper on a strategy on impact of the pharmacovigilance system, including the objectives and the structured approach to be followed. The strategy on impact of pharmacovigilance has been developed as a health-focused and science-based approach that would enable the continuous monitoring of key outputs and activities. PRAC delegates were invited to provide comments on the draft strategic paper by 30 June 2015. Follow-up discussion is planned in July 2015.

13.3. Type II variations: revised procedural timetables

As agreed at its April 2015 PRAC, the PRAC further discussed the proposed type II variations timetables. The EMA Secretariat presented a revised proposal which was endorsed by the PRAC. The revised timetables will be implemented for procedures starting

in July 2015 and will also apply to procedures started since March 2015 that will go for a request for supplementary information as of July 2015. The revised procedural timetables will be published on the EMA website. See:

Post-meeting note: The revised procedural timetables were published on 02/07/2015 on the EMA website (see: [Home>Human regulatory>Pre-authorisation>Submission dates>Timetables](#)).

14. Annex I – Risk Management Plans

14.1. Medicines in the pre-authorisation phase

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

14.1.1. Amikacin - EMEA/H/C/003936, Orphan

Applicant: Insméd Limited

Scope: Treatment of nontuberculous mycobacterial (NTM) lung infections in adult patients and management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older

14.1.2. Amlodipine, valsartan – EMEA/H/C/004037, Generic

Scope: Treatment of essential hypertension

14.1.3. Aripiprazole - EMEA/H/C/004008, Generic

Scope: Treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder

14.1.4. Asfotase alfa - EMEA/H/C/003794

Scope: Treatment of paediatric-onset hypophosphatasia

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

Applicant: Amgen Europe B.V.

Scope: Treatment of multiple myeloma

14.1.6. Cobimetinib - EMEA/H/C/003960

Scope: Treatment of metastatic melanoma

14.1.7. Duloxetine - EMEA/H/C/003935, Generic

Scope: Treatment of depressive disorder, diabetic neuropathic pain, anxiety disorder

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

Applicant: Horizon Therapeutics Limited

Scope: Treatment of patients with urea cycle disorders

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

Scope: Treatment of sialorrhoea

14.1.10. Guanfacine - EMEA/H/C/003759

Scope: Treatment of attention deficit hyperactivity disorder (ADHD)

14.1.11. Insulin human - EMEA/H/C/003858, Biosimilar

Scope: Treatment of diabetes

14.1.12. Idebenone - EMEA/H/C/003834, Hybrid

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

14.1.13. Pancreas powder - EMEA/H/C/002070

Scope: Treatment in exocrine pancreatic insufficiency

14.1.14. Pemetrexed - EMEA/H/C/004109, Hybrid

Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer

14.1.15. Pemetrexed - EMEA/H/C/004011, Generic

Scope: In combination with cisplatin is indicated for the treatment malignant pleural mesothelioma and non-small cell lung cancer

14.1.16. Sirolimus - EMEA/H/C/003978, Orphan

Applicant: Santen Oy

Scope: Treatment of chronic non-infectious uveitis

14.1.17. Talimogene laherparepvec - EMEA/H/C/002771, ATMP

Scope: Treatment of adults with melanoma regionally or distantly metastatic

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

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

14.2.1. Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/II/0026

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Following low number of eltrombopag users in registry, the MAH is proposing to terminate study WEUSKOP7134 and remove the post-approval measure MEA 026 from the RMP. An updated RMP version 30 has been provided accordingly

14.2.2. Filgrastim – ACCOFIL (CAP) - EMEA/H/C/003956II/0002

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP following a product information update with regard to routine risk minimisation measures of for several safety concerns

14.2.3. Lapatinib – TYVERB (CAP) - EMEA/H/C/000795/II/0041/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a revised RMP in order to include general updates in the RMP regarding posology update, addition of some new studies to pharmacovigilance activities and addition of details on three newly available study reports. Timelines have been also changed for study EGF114299 and study EGF117165. The RMP and Annex II have been updated accordingly

14.2.4. Liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/WS0746/0001; VICTOZA (CAP) - EMEA/H/C/001026/WS0746/0031

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP for Victoza and Saxenda in order to change the due date for the pharmacovigilance activity relating to submission of a final report of the cardiovascular outcome study EX2211-3748 LEADER to November 2016

14.2.5. Rivastigmine – EXELON (CAP) - EMEA/H/C/000169/WS0743/0106; PROMETAX (CAP) - EMEA/H/C/000255/WS0743/0106

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Update of the RMP (version 8.1) including a proposal to remove the important potential risk 'acute renal failure' and the important identified risk 'dehydration', and to add the potential complications of gastro-intestinal symptoms as dehydration and renal failure. An updated protocol for CENA713D2409 is also proposed

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

14.3.1. Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/II/0137

Applicant: AbbVie Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas. Consequential changes are proposed for sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet

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

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: Extension of indication to the treatment in adults of visual impairment due to myopic choroidal neovascularisation (myopic CNV). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 are updated. The package leaflet is updated in accordance

14.3.3. Ambrisentan – VOLIBRIS (CAP) - EMEA/H/C/000839/II/0039, Orphan

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

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

14.3.4. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0005/G

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of non-clinical study 100011749 (study of Ataluren (PTC124) and M4 metabolite in the β 3 binding assay) and non-clinical study 100012124 (study of ataluren (PTC124) and M4 (PTC-0256858-04) functional activity in a beta-3 adrenergic cellular assay) in fulfilment of MEA 006. The results of these studies have no impact on the Translarna product information

14.3.5. Bosentan – STAYVEER (CAP) - EMEA/H/C/002644/II/0011

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Isabelle Robine

Scope: Update of SmPC sections 4.2, 4.5, 4.6, 4.8, 5.1, 5.2 and 5.3 to reflect non-clinical and clinical data generated in studies conducted according to the agreed Paediatric Investigation Plan for bosentan (EMEA-000425-PIP02-10-M04) in line with the recently approved variation II/66 for Tracleer (bosentan). The Annex II and the package leaflet have been updated accordingly. Furthermore, the MAH took the opportunity to make editorial changes in the SmPC and to update the contact details of the local representatives in the package leaflet. In addition, taking into account the new data in the paediatric population, an updated version of the RMP (version 7) aligned with RMP version 7 for Tracleer was provided

14.3.6. Brentuximab – ADCETRIS (CAP) - EMEA/H/C/002455/II/0025

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include a new indication for Adcetris for the treatment of adult patients at increased risk of relapse or progression following autologous stem cell transplant. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance

14.3.7. Cabozantinib – COMETRIQ (CAP) - EMEA/H/C/002640/II/0015

Applicant: TMC Pharma Services Ltd

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.8 and 5.1 of the SmPC following the results of study XL184-301. The RMP and the package leaflet are updated accordingly

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

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

14.3.9. Conestat alfa – RUCONEST (CAP) - EMEA/H/C/001223/R/0023

Applicant: Pharming Group N.V

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of the RMP in the context of a 5-year renewal of the marketing authorisation

14.3.10. Darbapoetin alfa – ARANESP (CAP) - EMEA/H/C/000332/II/0130

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

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

14.3.11. Denosumab – XGEVA (CAP) - EMEA/H/C/002173/II/0038

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC in order to update the safety information regarding the risk of osteonecrosis of the jaw (ONJ). In addition, the MAH took the opportunity to bring the SmPC in line with the package leaflet regarding typographical errors in section 4.2 of the SmPC

14.3.12. Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/II/0019

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 4.8 of the SmPC to include the adverse drug reaction 'thrombotic microangiopathy (TMA) with acute renal failure'. The package leaflet has been updated accordingly. In addition, the MAH took the opportunity to make a minor change to section 4.8 of the SmPC clarifying that the safety data included are derived both from studies and from post-marketing reports

14.3.13. Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/II/0020

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication: Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to add a new indication for the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy. The package leaflet is updated accordingly. In addition, the MAH has corrected the acronym used for full blood counts (FBC) in the SmPC, Annex II and package leaflet

14.3.14. Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/X/0022/G

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication for paediatric (age 1 year and above) chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who had an insufficient response to other treatments (e.g. corticosteroids, immunoglobulins). Grouping with line extension for one new tablet strength (12.5mg) and a new powder for oral suspension formulation (25mg)

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

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.6 of the SmPC in order to update the information on the effects of etanercept on pregnancy and lactation. The package leaflet and the RMP are updated accordingly

14.3.16. Human normal immunoglobulin – HYQVIA (CAP) - EMEA/H/C/002491/II/0013

Applicant: Baxter Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.4, 4.6 and 5.3 of the SmPC in order to update the safety information regarding pregnancy, fertility and lactation following new additional preclinical data. The package leaflet is updated accordingly. Furthermore, Annex II has been revised to remove educational material based on the availability of additional new data. An updated RMP (version 7.0) has been submitted accordingly

14.3.17. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - EMEA/H/C/000721/II/0067

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to update the RMP (version 11.0) including the new indication

14.3.18. Ingenol mebutate – PICATO (CAP) - EMEA/H/C/002275/II/0012

Applicant: Leo Pharma A/S

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC to provide new efficacy and safety data supporting a labelling update that introduces repeat treatment of Picato gel (150 mcg/g and 500 mcg/g), based on study LP0041-22. The package leaflet is updated accordingly

14.3.19. Interferon alfa-2b – INTRONA (CAP) - EMEA/H/C/000281/WS0611/0099 peginterferon alfa-2B – PEGINTRON (CAP) - EMEA/H/C/000280/WS0611/0119; VIRAFERONPEG (CAP) - EMEA/H/C/000329/WS0611/0112

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.4 of the SmPC to include updated information on homicidal ideation and for patients with decompensated liver disease, and update of section 4.8 of the SmPC to add pulmonary fibrosis as a post-marketing adverse drug reaction. The package leaflet have been revised accordingly

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

Applicant: Vertex Pharmaceuticals (U.K.) Ltd

PRAC Rapporteur: Miguel-Angel Macia

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

14.3.21. Levetiracetam – KEPBRA (CAP) - EMEA/H/C/000277/R/0154

Applicant: UCB Pharma SA

PRAC Rapporteur: Veerle Verlinden

Scope: Evaluation of the RMP in the context of a 5-year renewal of the marketing authorisation

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

Applicant: Actelion Registration Ltd

PRAC Rapporteur: Dolores Montero Corominas

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

14.3.23. Natalizumab – TYSABRI (CAP) - EMEA/H/C/000603/II/0077

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adults with highly active relapsing remitting multiple sclerosis with high disease activity despite treatment with at least one modifying therapy (DMT). As a consequence, sections 4.1 and 4.4 of the SmPC are updated in order to provide physicians with more options for treating relapsing remitting multiple sclerosis (RRMS) patients with high disease activity who fail an initial disease modifying therapy (DMT). Consequential changes to SmPC sections 4.2, 4.3, 5.1 and package leaflet sections 2 and 3 are submitted accordingly

14.3.24. Nilotinib – TASIGNA (CAP) - EMEA/H/C/000798/II/0075

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Update of section 5.3 of the SmPC in order to update the safety information based on the results from a 26-week oral gavage carcinogenicity study in 001178 T

14.3.25. Nonacog alfa – BENEFIX (CAP) - EMEA/H/C/000139/II/0133

Applicant: Pfizer Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.8 of the SmPC in order to revise adverse event frequencies based on all-causality data set. In addition, the MAH took the opportunity to update SmPC sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8 and 4.9 in line with the latest revision of the Core SmPC for factor IX Products. The package leaflet and RMP are updated accordingly

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

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include a new indication for Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance

14.3.27. Regorafenib – STIVARGA (CAP) - EMEA/H/C/002573/II/0011

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Submission of study results from retrospective biomarker analyses from the pivotal GRID trial (study 14874) in order to fulfil ANX 003.2

14.3.28. Rilpivirine – EDURANT (CAP) - EMEA/H/C/002264/II/0017/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of antiretroviral treatment-naïve paediatric patients aged 12 to <18 years of age based on the results of the 48-week data of study TMC278-TiDP38-C213 (PAINT), undertaken to evaluate the pharmacokinetics, safety/tolerability, and efficacy of rilpivirine 25 mg qd in combination with an investigator-selected background regimen containing 2 nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs) in this adolescent population. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated and the package leaflet has been updated accordingly. A revised RMP (version 6.0) is submitted accordingly

14.3.29. Ritonavir – NORVIR (CAP) - EMEA/H/C000127/X/0127

Applicant: AbbVie Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Line extension of a new oral powder formulation of Norvir (ritonavir) as a replacement for the currently marketed Norvir oral solution for a more suitable ritonavir formulation for the paediatric population

14.3.30. Secukinumab – COSENTYX (CAP) - EMEA/H/C/003729/II/0001/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include a new indication for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate as monotherapy or in combination with methotrexate (MTX). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated in order to update the safety and efficacy information. The package leaflet is updated in accordance

14.3.31. Secukinumab – COSENTYX (CAP) - EMEA/H/C/003729/II/0002

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to the treatment of severe active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. Consequently SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 have been revised to include new efficacy and safety information. The package leaflet and RMP have been updated accordingly

14.3.32. Sodium oxybate – XYREM (CAP) - EMEA/H/C/000593/R/0054

Applicant: UCB Pharma Ltd

PRAC Rapporteur: Magda Pedro

Scope: Evaluation of the RMP in the context of a 5-year renewal of the marketing authorisation

14.3.33. Telaprevir - INCIVO (CAP) - EMEA/H/C/002313/II/0035

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of SmPC section 4.2 to provide posology information for the special population of liver transplant patients without cirrhosis and of SmPC section 4.4 to add a warning for organ transplant patients, as part of the RMP commitments to address the missing information in the liver post-transplant population and based on the submission of the study report for phase 3b study HPC3006. SmPC section 4.5, 4.8 and 5.1 and the package leaflet are updated accordingly

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

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.5 and 5.2 of the SmPC in order to update the safety information based on new preclinical data provided to fulfil 4 nonclinical Post-authorisation measures (REC 001, MEA 004, MEA 005 and MEA 006). Moreover, an updated RMP (version 10) has been submitted

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

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

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

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

Applicant: Roche Registration Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to reflect the safety information of Herceptin 600 mg solution for injection (EU/1/00/145/002 and EU/1/00/145/003) in line with the interim report of study MO28048 (SafeHER). The RMP is updated accordingly

14.3.37. Umeclidinium bromide – INCRUSE (CAP) - EMEA/H/C/002809/ WS0723/0004/G umeclidinium bromide, vilanterol – ANORO (CAP) - EMEA/H/C/002751/WS0723/0004/G; LAVENTAIR (CAP) - EMEA/H/C/003754/WS0723/0004/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Submission of two non-clinical studies (2014N214514 and 2014N214870) regarding in-vitro investigations to determine the potential for drug-drug interactions in fulfilment of MEA 003 for Anoro and Laventair and MEA 002 for Incruse. The RMP is updated accordingly. In addition the MAH take the occasion to include minor routine updates in the RMP and to include in the MA for Anoro and Laventair report 2012N156532 on results of physiologically based PK modelling and simulation already assessed during the initial marketing authorisation application procedure

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

Applicant: Roche Registration Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.5 of the SmPC in order to update the drug-drug interaction information following finalisation of study GO28394 (phase I, open-label, multicentre, 3-period, fixed sequence study to investigate the effect of vemurafenib on the pharmacokinetics of a single dose of digoxin in patients with BRAFV600 mutation-positive metastatic malignancy – MEA 013). The MAH took the opportunity to introduce editorial changes to improve clarity and consistency in the SmPC and package leaflet

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 procedure(s).

15.1. PSUR procedures including centrally authorised products only

15.1.1. Afibercept – EYLEA (CAP) - PSUSA/10020/201411

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope of procedure: Evaluation of a PSUSA procedure

15.1.2. Boceprevir – VICTRELIS (CAP) - PSUSA/09081/201411

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Isabelle Robine

Scope of procedure: Evaluation of a PSUSA procedure

15.1.3. Darbepoetin alfa – ARANESP (CAP) - PSUSA/00932/201410

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

Scope of procedure: Evaluation of a PSUSA procedure

15.1.4. Ethinylestradiol, norelgestromin – EVRA (CAP) - PSUSA/01311/201411

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

15.1.5. Erlotinib – TARCEVA (CAP) - PSUSA/01255/201411

Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope of procedure: Evaluation of a PSUSA procedure

15.1.6. Fidaxomicin – DIFICLIR (CAP) - PSUSA/01390/201411

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.7. Flutemetamol (¹⁸F) – VIZAMYL (CAP) - PSUSA/10293/201410

Applicant: GE Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

15.1.8. Fluticasone furoate, vilanterol – RELVAR ELLIPTA (CAP); REVINTY ELLIPTA (CAP) - PSUSA/10099/201411

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

15.1.9. Fondaparinux – ARIXTRA (CAP) - PSUSA/01467/201412

Applicant: Aspen Pharma Trading Limited

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.10. Fosamprenavir – TELZIR (CAP) - PSUSA/01470/201410

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Isabelle Robine

Scope of procedure: Evaluation of a PSUSA procedure

15.1.11. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - PSUSA/09175/201411

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope of procedure: Evaluation of a PSUSA procedure

15.1.12. Insulin detemir – LEVEMIR (CAP) - PSUSA/01750/201410

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope of procedure: Evaluation of a PSUSA procedure

15.1.13. Lidocaine, prilocaine – FORTACIN (CAP) - PSUSA/10110/201411

Applicant: Plethora Solutions Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

15.1.14. Nelarabine – ATRIANCE (CAP) - PSUSA/02132/201410

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope of procedure: Evaluation of a PSUSA procedure

15.1.15. Pandemic influenza vaccine (H1N1) (whole virion, inactivated, prepared in cell culture) – CELVAPAN (CAP) - PSUSA/02280/201410

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

15.1.16. Pixantrone dimaleate – PIXUVRI (CAP) - PSUSA/09261/201411

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.17. Pneumococcal polysaccharide conjugate vaccine, 10 valent adsorbed – SYNFLORIX (CAP) - PSUSA/09262/201412

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

15.1.18. Radium-223 – XOFIGO (CAP) - PSUSA/10132/201411

Applicant: Bayer Pharma AG

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.19. Rilpivirine – EDURANT (CAP) - PSUSA/09282/201411

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Sabine Straus

Scope of procedure: Evaluation of a PSUSA procedure

15.1.20. Rituximab – MABTHERA (CAP) - PSUSA/02652/201411

Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope of procedure: Evaluation of a PSUSA procedure

15.1.21. Rotavirus vaccine (live, oral) – ROTATEQ (CAP) - PSUSA/02666/201411

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

15.1.22. Sapropterin – KUVAN (CAP) - PSUSA/02683/201412

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Almath Spooner

Scope of procedure: Evaluation of a PSUSA procedure

15.1.23. Saquinavir – INVIRASE (CAP) - PSUSA/02684/201412

Applicant: Roche Registration Ltd

PRAC Rapporteur: Marianne Lunzer

Scope of procedure: Evaluation of a PSUSA procedure

15.1.24. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP) - PSUSA/09289/201411

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

15.1.25. Stiripentol – DIACOMIT (CAP) - PSUSA/02789/201411

Applicant: Biocodex

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

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

15.2.1. Insulin human, isophane insulin – ACTRAPHANE (CAP); ACTRAPID (CAP); INSULATARD (CAP); INSULIN HUMAN WINTHROP (CAP); INSUMAN (CAP); MIXTARD (CAP); PROTAPHANE (CAP); NAP - PSUSA/01753/201410

Applicant: Novo Nordisk A/S, various

PRAC Rapporteur: Doris Stenver

Scope of procedure: Evaluation of a PSUSA procedure

15.2.2. Sevelamer – RENAGEL (CAP), RENVELA (CAP); NAP - PSUSA/02697/201410

Applicant: Genzyme Europe BV, various

PRAC Rapporteur: Veerle Verlinden

Scope of procedure: Evaluation of a PSUSA procedure

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

15.3.1. Betamethasone, tetrazyline (NAP) - PSUSA/00010072/201409

Applicant: various

PRAC lead: Viola Macolić Šarinić

Scope: Evaluation of a PSUSA procedure

15.3.2. Cefuroxime sodium (for intracameral use) (NAP) - PSUSA/00010206/201411

Applicant: various

PRAC lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

15.3.3. Desflurane (NAP) - PSUSA/00000958/201409

Applicant: various

PRAC lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.4. Etifoxine (NAP) - PSUSA/00001321/201410

Applicant: various

PRAC lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

15.3.5. Fluticasone, salmeterol (NAP) - PSUSA/00001455/201410

Applicant: various

PRAC lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.3.6. Human von Willebrand factor (NAP) - PSUSA/00001642/201409

Applicant: various

PRAC lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.3.7. Idebenone (NAP) - PSUSA/00001721/201409

Applicant: various

PRAC lead: Amy Tanti

Scope: Evaluation of a PSUSA procedure

15.3.8. Insulin porcine (NAP) - PSUSA/00001756/201410

Applicant: various

PRAC lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.9. Sumatriptan (NAP) - PSUSA/00002832/201409

Applicant: various

PRAC lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.3.10. Tapentadol (NAP) - PSUSA/00002849/201411

Applicant: various

PRAC lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

15.3.11. Vigabatrin (NAP) - PSUSA/00003112/201409

Applicant: various

PRAC lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

15.4. Follow-up to PSUR procedures

15.4.1. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/LEG 007

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to PSUV/0023

15.4.2. Methoxypolyethylene glycol-epoetin beta – MIRCERA (CAP) - EMEA/H/C/000739/LEG 037

Applicant: Roche Registration Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to PSUSA/00002017/201407 - PSUR#9

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

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

16.1. Protocols of PASS imposed in the marketing authorisation(s)⁴³

16.1.1. Cholic acid– KOLBAM (CAP) - EMEA/H/C/PSP/0017

Applicant: ASK Pharmaceuticals GmbH

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PASS protocol for a patient registry to monitor the long term safety and efficacy in patients treated with cholic acid FGK

16.1.2. Ivabradine – CORLENTOR (CAP), PROCOLORAN (CAP) - EMEA/H/C/PSP/0019.1

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a revised DUS protocol for a multinational, retrospective, observational study to assess effectiveness of risk-minimisation measures

16.1.3. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSP/0020

Applicant: Celgene Europe Limited

PRAC Rapporteur: Corinne Féchant

⁴³ In accordance with Article 107n of Directive 2001/83/EC

Scope: Evaluation of a PASS protocol for study CC-5013-MM-034, a lenalidomide product registry of previously untreated adult multiple myeloma patients who are not eligible for transplant

16.1.4. Teicoplanin (NAP) - EMEA/H/N/PSP/0011.3

Applicant: Sanofi

PRAC Rapporteur: Valerie Strassmann

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

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁴

16.2.1. Alglucosidase alfa – MYOZYME (CAP) - EMEA/H/C/000636/MEA 053

Applicant: Genzyme Europe BV

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PASS protocol for an epidemiology study ALGMYC07390: Prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions

16.2.2. Delamanid – DELTYBA (CAP) - EMEA/H/C/002552/MEA 002.2

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a MAH's responses to a request for supplementary information for MEA 002.1 [PASS study 242-120402] as adopted in February 2015

16.2.3. Elvitegravir – VITEKTA (CAP) - EMEA/H/C/002577/MEA 007.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a MAH's responses to a request for supplementary information for MEA 007 [Feasibility Study / Drug Utilisation Study (DUS) GS-EU-183-1335] as adopted in February 2014

16.2.4. Exenatide – BYDUREON (CAP) - EMEA/H/C/002020/MEA 011.4

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of MAH's responses to a request for supplementary information for MEA 011.3 [annual report of study B017] as adopted in January 2015

⁴⁴ 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

16.2.5. Human normal immunoglobulin – HYQVIA (CAP) - EMEA/H/C/002491/MEA 004.1

Applicant: Baxter Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Revised pregnancy registry PASS protocol [study 161301]

16.2.6. Insulin lispro – HUMALOG (CAP) - EMEA/H/C/000088/MEA 025.1, LIPROLOG (CAP) - EMEA/H/C/000393/MEA 108.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of MAH's responses to a request for supplementary information for MEA 025 [Protocol synopsis for PASS study examining the effectiveness of risk minimisation on 200 units strength] as adopted in January 2015

16.2.7. Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/MEA 011

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Synopsis protocol for a study to collect and/or retrieve prospective data from sizeable patient cohorts with ovarian cancer, representing real world evidence from relevant countries

16.2.8. Ramucirumab – CYRAMZA (CAP) - EMEA/H/C/002829/MEA 001.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Revised PASS protocol for a prospective observational registry of safety and effectiveness of ramucirumab in patients with advanced gastric cancer in the European Union and North America (I4T-MC-JVDD)

16.2.9. Secukinumab – COSENTYX (CAP) - EMEA/H/C/003729/MEA 002

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: 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

16.2.10. Telavancin – VIBATIV (CAP) - EMEA/H/C/001240/ANX 007.3

Applicant: Clinigen Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of the MAH's responses to a request for supplementary information for ANX 007.2 (Pregnancy Exposure Registry study 9809-CL-1409) adopted in October 2014

16.3. Results of PASS imposed in the marketing authorisation(s)⁴⁵

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁶

16.4.1. Dabigatran – PRADAXA (CAP) - EMEA/H/C/000829/II/0079/G (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final clinical study report (CSR) for study 1160.84: observational cohort study undertaken to evaluate the safety and efficacy of Pradaxa in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) undergoing elective total hip replacement surgery or total knee replacement surgery. The provision of the CSR addresses the post-authorisation measure MEA 010.1. The application includes an updated RMP version 31.0, which includes changes pertaining to the study report of study 1160.84, the update of due dates in the RMP for the provision of 14 study reports, and the inclusion of the outcome of 2 phase I studies (studies 1160.141 and 1160.142) following the CHMP assessment of variations II/46 and II/61

16.4.2. Epoetin theta – BIOPOIN (CAP) - EMEA/H/C/001036/II/0023 (without RMP)

Applicant: Teva GmbH

PRAC Rapporteur: Isabelle Robine

Scope: Submission of a PASS final report relating to epoetin theta in patients with chronic kidney disease to assess the incidence and severity of predefined cardiovascular events including ischaemic stroke, and to detect and describe any adverse drug reaction including pure red cell aplasia (PASS XM01-30)

16.4.3. Epoetin theta – EPORATIO (CAP) - EMEA/H/C/001033/II/0022 (without RMP)

Applicant: Ratiopharm GmbH

PRAC Rapporteur: Isabelle Robine

Scope: Submission of a PASS final report relating to epoetin theta in patients with chronic kidney disease to assess the incidence and severity of predefined cardiovascular events including ischaemic stroke, and to detect and describe any adverse drug reaction including pure red cell aplasia (PASS XM01-30)

16.4.4. Ribavirin – REBETOL (CAP) - EMEA/H/C/000246/II/0076 (with RMP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Isabelle Robine

Scope: Submission of a final study report for study MK-8908-060 assessing the utilisation of ribavirin in paediatric patients with hepatitis C virus. A revised RMP has been submitted with this procedure

⁴⁵ In accordance with Article 107p-q of Directive 2001/83/EC

⁴⁶ 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

16.4.5. [Rotigotine – LEGANTO \(CAP\) - EMEA/H/C/002380/WS0751/0018/G \(with RMP\);](#)
[NEUPRO \(CAP\) - EMEA/H/C/000626/WS0751/0068/G \(with RMP\)](#)

Applicant: UCB Manufacturing Ireland Ltd

PRAC Rapporteur: Magda Pedro

Scope: Submission of two final study reports for PASS studies which investigated the potential risk of cardiovalvular fibrosis in Parkinson's disease patients treated with rotigotine and other anti-Parkinson's drugs. The RMP is updated accordingly

16.4.6. [Sofosbuvir – SOVALDI \(CAP\) - EMEA/H/C/002798/II/0015 \(with RMP\)](#)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report to investigate the safety and efficacy of GS-7977 and ribavirin for 24 weeks in subjects with recurrent chronic HCV post liver transplant (GS-US-334-0126). This submission fulfils MEA 005. An updated RMP (version 3.0) is proposed accordingly

16.4.7. [Tolvaptan – SAMSCA \(CAP\) - EMEA/H/C/000980/II/0020 \(without RMP\)](#)

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report for Samsca Post-Authorisation Safety Study (FUM 004)

16.4.8. [Tenofovir disoproxil – VIREAD \(CAP\) - EMEA/H/C/000419/WS0731/0147 \(with RMP\)](#)

[tenofovir disoproxil, emtricitabine – EVIPLERA \(CAP\) - EMEA/H/C/002312/WS0731/0056 \(with RMP\);](#)
[TRUVADA \(CAP\) - EMEA/H/C/000594/WS0731/0113 \(with RMP\)](#)

[tenofovir disoproxil, emtricitabine, efavirenz – ATRIPLA \(CAP\) - EMEA/H/C/000797/WS0731/0101 \(with RMP\)](#)

[tenofovir disoproxil, emtricitabine, elvitegravir, cobicistat – STRIBILD \(CAP\) - EMEA/H/C/002574/WS0731/0044 \(with RMP\)](#)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Submission of the final clinical study report for Viread study GS-US-104-0423 'phase 4 cross-sectional study of bone mineral density in HIV-1 infected subjects' in fulfilment of a post-authorisation measure (PAM) for Viread, Truvada, Eviplera, Stribild and Atripla (category 3 additional pharmacovigilance activity for Viread, Truvada, Eviplera and Stribild, and category 4 for Atripla). An updated RMP for each product is proposed accordingly

16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation⁴⁷

16.5.1. Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/MEA 066.4

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of safety data from the clinical use of adalimumab from the national registry activities that are ongoing in Germany, Sweden and the UK

16.5.2. Crizotinib – XALKORI (CAP) - EMEA/H/C/002489/MEA 011.2

Applicant: Pfizer Limited

PRAC Rapporteur: Corinne Féchant

Scope: Report for PASS study A8081038 to estimate the incidence rate and incidence proportion over a 3-year period of observation for hepatotoxicity, pneumonitis/interstitial lung disease (ILD), QTc prolongation related events, bradycardia, and visual disorder among lung cancer patients receiving crizotinib prescriptions

16.5.3. Eliglustat – CERDELGA (CAP) - EMEA/H/C/003724/MEA 005

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Pilot study report for a drug utilisation study of eliglustat in Europe using electronic healthcare records

16.5.4. Entecavir – BARACLUDE (CAP) - EMEA/H/C/000626/MEA 026.7

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Qun-Ying Yue

Scope: Eighth annual report on a large prospective, observational study including 12,500 patients with chronic hepatitis B virus (HBV) infection randomised to either entecavir (ETV) or to another standard-of-care nucleos(t)ide analogue, including cancer surveillance

16.5.5. Exenatide – BYDUREON (CAP) - EMEA/H/C/002020/MEA 010.3

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of MAH's responses to a request for supplementary information for MEA 010.2 (modified prescription event monitoring (PEM) study H8O-MC-B016) as adopted in January 2015

16.5.6. Infliximab – REMICADE (CAP) - EMEA/H/C/000240/MEA 099.9

Applicant: Janssen Biologics B.V.

⁴⁷ In line with the revised variations regulation for any submission before 4 August 2013

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Sixth interval report for a pregnancy registry study to gather birth outcome data for infants born to mothers exposed to infliximab, including follow-up of infants up to 1 year after birth

16.5.7. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.2

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of MAH's responses to a request for supplementary information for MEA 004.1 [PASS study D2560C00008, first summary safety report] as adopted in February 2015

16.5.8. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 006.1

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of MAH's responses to a request for supplementary information for MEA 006 [first annual report for an observational prospective cohort study MI-MA194] RSI as adopted in January 2015

16.5.9. Influenza vaccine (split virion, inactivated) – IDFLU (CAP) - EMEA/H/C/000966/MEA 032.1; INTANZA (CAP) – EMEA/H/C/000957/MEA 032.1

Applicant: Sanofi Pasteur

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a MAH's responses to a request for supplementary information for MEA 032 (from WS/638, enhanced safety surveillance for NH 2014-2015 campaign / intermediate results interventional studies / GID47 final report) as adopted in February 2015

16.5.10. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP) - EMEA/H/C/000758/LEG 050.1

Applicant: Novartis Influenza Vaccines Marburg GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to a request for supplementary information for LEG 050 [study No. V58_400B surveillance report] as adopted in February 2015

16.5.11. Insulin lispro – HUMALOG (CAP) - EMEA/H/C/000088/MEA 028; LIPROLOG (CAP) - EMEA/H/C/000393/MEA 021

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Summary report on the analysis of the effectiveness of the US surveillance programme and how any limitations in the methodology will be addressed in the European programme

16.5.12. Ketoconazole – KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/MEA 004

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Viola Macolic Sarinic

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

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. Antithrombin alfa – ATRYN (CAP) - EMEA/H/C/000587/S/0021 (without RMP)

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Isabelle Robine

Scope: Annual reassessment of the marketing authorisation

17.1.2. Idursulfase – ELAPRASE (CAP) - EMEA/H/C/000700/S/0055 (without RMP)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation

17.2. Conditional renewals of the marketing authorisation

17.2.1. Brentuximab – ADCETRIS (CAP) - EMEA/H/C/002455/R/0026 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

17.3. Renewals of the marketing authorisation

None

18. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 8-11 June 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 |
| Maria Popova-Kiradjieva | Member | Bulgaria | No interests declared | Full involvement |
| Viola Macolić Šarinić | Member | Croatia | No interests declared | Full involvement |
| Nectaroula Cooper | Member | Cyprus | No interests declared | Full involvement |
| Jana Mladá | Member | Czech Republic | No interests declared | Full involvement |
| Doris Stenver | Member | Denmark | No interests declared | Full involvement |
| Torbjörn Callreus | Alternate | Denmark | No interests declared | Full involvement |
| Maia Uusküla | Member | Estonia | No interests declared | Full involvement |
| Kirsti Villikka | Member | Finland | No interests declared | Full involvement |
| Isabelle Robine | Member | France | No interests declared | Full involvement |
| Corinne Fechant | Alternate | France | No restrictions applicable to this meeting | Full involvement |
| Martin Huber | Member | Germany | No interests declared | Full involvement |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---------------------------------|---------------------------|-----------------------------|---|---|
| Valerie Strassmann | Alternate | Germany | No interests declared | Full involvement |
| Julia Pallos | Member | Hungary | No interests declared | Full involvement |
| Guðrún Kristín Steingrimsdóttir | Member | Iceland | No interests declared | Full involvement |
| Almath Spooner | Member (Vice-Chair) | Ireland | No interests declared | Full involvement |
| Ruchika Sharma | Alternate | Ireland | No restrictions applicable to this meeting | Full involvement |
| Carmela Macchiarulo | Member | Italy | No interests declared | Full involvement |
| Amelia Cupelli | Alternate | Italy | No interests declared | Full involvement |
| Zane Neikena | Alternate | Latvia | No interests declared | Full involvement |
| Jolanta Gulbinovic | Member | Lithuania | No interests declared | Full involvement |
| Nadine Petitpain | Alternate | Luxembourg | No restrictions applicable to this meeting | Full involvement |
| John Joseph Borg | Alternate | Malta | No interests declared | Full involvement |
| Sabine Straus | Member | Netherlands | No interests declared | Full involvement |
| Menno van der Elst | Alternate | Netherlands | No interests declared | Full involvement |
| Ingebjørg Buajordet | Member | Norway | No interests declared | Full involvement |
| Adam Przybylkowski | Member - via telephone | Poland | No interests declared | Full involvement |
| Magdalena Budny | Alternate | Poland | No interests declared | Full involvement |
| Margarida Guimarães | Member | Portugal | No interests declared | Full involvement |
| Magda Pedro | Alternate - via telephone | Portugal | No interests declared | Full involvement |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---------------------------------|----------------------|--|---|---|
| Roxana Stefania Stroe | Member | Romania | No interests declared | Full involvement |
| Miroslava Matíková | Alternate | Slovakia | No restrictions applicable to this meeting | Full involvement |
| Milena Radoha-Bergoč | Member | Slovenia | No restrictions applicable to this meeting | Full involvement |
| Dolores Montero Corominas | Member | Spain | No interests declared | Full involvement |
| Miguel-Angel Maciá | Alternate | Spain | No interests declared | Full involvement |
| Qun-Ying Yue | Member | Sweden | No interests declared | Full involvement |
| Ulla Wändel Liminga | Alternate | Sweden | No interests declared | Full involvement |
| Julie Williams | Member | United Kingdom | No interests declared | Full involvement |
| Rafe Suvarna | Alternate | United Kingdom | No interests declared | Full involvement |
| Jane Ahlqvist Rastad | Member | Independent scientific expert | No interests declared | Full involvement |
| Marie Louise (Marieke) De Bruin | Member | Independent scientific expert | No interests declared | Full involvement |
| Brigitte Keller-Stanislawski | Member via telephone | 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 | No restrictions | Full involvement |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|--|-------------------------|-----------------------------|---|---|
| | | Representative | applicable to this meeting | |
| Tessy Bensabat | Expert - via telephone* | France | No interests declared | Full involvement |
| Vincent Gazin | Expert - via telephone* | France | No interests declared | Full involvement |
| Mélanie Leplay | Expert - via telephone* | France | No interests declared | Full involvement |
| Fanny Raguideau | Expert - via telephone* | France | No restrictions applicable to this meeting | Full involvement |
| Thomas Grüger | Expert - via telephone* | Germany | No interests declared | Full involvement |
| Vahid Taravati | Expert - via telephone* | Germany | No interests declared | Full involvement |
| Zane Stade | Expert - in person* | Latvia | No interests declared | Full involvement |
| Stéphany Suoth | Expert - in person* | Netherlands | No restrictions applicable to this meeting | Full involvement |
| Annika Ekbon Schnell | Expert - via telephone* | Sweden | No restrictions applicable to this meeting | Full involvement |
| Karl-Mikael Kälkner | Expert - via telephone* | Sweden | No interests declared | Full involvement |
| Miriam Taekema | Expert - via telephone* | Sweden | No restrictions applicable to this meeting | Full involvement |
| Jennifer Matthissen | Expert - in person* | United Kingdom | No interests declared | Full involvement |
| A representative from the European Commission attended the meeting | | | | |
| Meeting run with support from relevant EMA staff | | | | |

* Experts were only evaluated against the product(s) they have been invited to talk about.

Explanatory notes

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

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