29 September 2017
EMA/PRAC/701894/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes for the meeting on 29 August -1 September 2017

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 scope 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, Rev. 1).

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1. Introduction

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

The Chairperson opened the 29 August-1 September 2017 meeting by welcoming all participants.

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

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

The PRAC Chair announced that Marianne Lunzer was to step down after the current PRAC meeting as the alternate for Austria. The PRAC thanked her for her contribution to the work of the Committee.

1.2. Agenda of the meeting on 29 August-1 September 2017

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

1.3. Minutes of the previous meeting on 3-6 July 2017

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

Post-meeting note: the PRAC minutes of the meeting held on 3-6 July 2017 were published on the EMA website on 22 September 2017 (EMA/PRAC/631448/2017).

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

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Daclizumab - ZINBRYTA (CAP) – EMEA/H/A-20/1456

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia; PRAC Co-rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

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

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Zinbryta (daclizumab) indicated for the treatment of relapsing forms of multiple sclerosis (RMS) in order to further investigate the risk of liver injury and assess its impact on the benefit-risk balance of the medicinal product. The review was initiated following cases of serious liver injury, including a fatal case of fulminant liver failure. In July 2017, the PRAC recommended some provisional measures without prejudice to the final conclusions of the ongoing procedure. For further background, see PRAC minutes June 2017 and PRAC minutes July 2017.

Summary of recommendation(s)/conclusions

The PRAC discussed the assessment reports of the Rapporteurs and adopted a list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/366037/2017 Rev. 1). The PRAC also agreed on the need to convene a Scientific Advisory Group (SAG) meeting to take place on 12 October 2017. The PRAC adopted a list of questions (LoQ) to the SAG on Neurology.

3.2.2. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide (NAP) - EMEA/H/A-31/1454

Applicant(s): Sanofi-Aventis, various

PRAC Rapporteur: Sabine Straus; PRAC Co-rapporteur: Jean-Michel Dogné

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for medicinal products containing valproate and related substances indicated for the treatment of bipolar disorder, epilepsy and in some Member States for the treatment of migraine, in order to assess the evidence in support of a contra-indication in the treatment of bipolar disorder during pregnancy and in women of childbearing potential who are not on effective contraception, and to review the effectiveness of the current risk minimisation measures (RMMs) across all indications. For further background, see PRAC minutes March 2017, PRAC minutes June 2017 and PRAC minutes July 2017.

Summary of recommendation(s)/conclusions

The PRAC adopted the list of participants and the agenda for the public hearing on valproate to be held on 26 September 2017 during the October 2017 PRAC meeting.

3.3. Procedures for finalisation

3.3.1. Paracetamol[1] (NAP); paracetamol, tramadol[1] (NAP) - EMEA/H/A-31/1445

Applicant(s): GlaxoSmithKline Consumer Healthcare AB (Alvedon 665 mg modified-release tablet), various

PRAC Rapporteur: Laurence de Fays; PRAC Co-rapporteur: Ulla Wändel Liminga

Scope: Review of the benefit-risk balance of modified release paracetamol-containing products following notification by Sweden of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

A referral procedure under Article 31 of Directive 2001/83/EC is to be concluded for the review of the benefit-risk balance of modified- and prolonged-release (MR) paracetamol-containing medicines, following the recent publication by *Salmonson et al.*[2] of a retrospective pharmacokinetic (PK) and clinical analysis of cases of overdose with modified release paracetamol products. In addition, the procedure includes a review of measures to minimise the risk associated with poisoning with modified- and prolonged-release formulations taking into account the benefit-risk balance for all indications of such modified- and prolonged-release formulations. A final assessment of the data was produced by the

[1] Modified release formulations only
[2] Salmonson H., Sjoberg G., Brogren J., Hansson E. The standard treatment protocol is inadequate following overdose of extended release paracetamol: a pharmacokinetic and clinical analysis of 53 cases. Clinical toxicology. 2016;54:424. Abstract 124, European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) international congress 24-27 May, 2016, Madrid, Spain

Rapporteurs according to the agreed timetable. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes February 2017, PRAC minutes March 2017 and PRAC minutes July 2017.

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs. In addition, the PRAC took into account the views expressed by the ad-hoc expert group meeting and the three oral explanations that took place at the current meeting.

The PRAC noted that the efficacy of MR paracetamol, as a single substance or in combination with tramadol, has been documented in representative acute and chronic pain models, and that the benefits of paracetamol as well as tramadol in general are well established. The PRAC noted the claimed specific benefits of the MR formulations related to a reduction of daily tablet intake; from 4 to 3 times daily dosing for the single ingredient products, and the simplified regimen of 2 from 4 tablets for the combination products.

The PRAC reviewed all the available data submitted with regard to overdose of the paracetamol containing MR products, including intentional and accidental overdose. This included the responses submitted by the MAHs in writing and presented during an oral explanation, as well as the advice from experts in the management of poisoning, published studies and spontaneous reports of overdose. The PRAC also considered risk management of overdoses with paracetamol in general, both in the EU and worldwide. The PRAC considered the highly variable pharmacokinetic (PK)-profile of overdoses with MR paracetamol formulations, and the uncertainties related to the quantity and the formulation of the product that the patient has ingested increase the challenges in effectively minimising the risk for paracetamol toxicity. The PRAC also noted that in addition to the uncertainties on how to minimise the risk for paracetamol toxicity, the safety profile of tramadol was considered to present additional challenges for minimising the risks for toxicity following an overdose with a prolonged release combination product of paracetamol and tramadol.

The PRAC also considered the proposed risk minimisation measures to reduce the risk of overdose e.g. prescription status and reduced pack sizes, and concluded that these measures would not be sufficient to minimise the risk of intentional and accidental overdoses to an acceptable level. Furthermore, the risk minimisation measures intended to reduce the risk for hepatic injury following an overdose with an MR formulation of paracetamol or the combination of paracetamol and tramadol were not considered to be sufficiently effective and reliable.

The Committee concluded, in view of the available data, that the risk for serious hepatic injury following an overdose with MR paracetamol containing products, could not be adequately minimised such as this risk could be outweighed by the benefits of these products in the treatment of pain and fever.

Therefore, the PRAC concluded that the benefit-risk balance of modified release paracetamol-containing products is no longer favourable and recommended that the marketing authorisations of these products should be suspended.

To lift the suspension, the PRAC recommended that the MAHs should provide evidence of proportionate, feasible and effective measures to minimise the risk for hepatic injury following intentional or accidental overdoses with modified release paracetamol containing products.

Summary of recommendation(s)/conclusions

The PRAC adopted a recommendation by majority[3] to be considered by the CMDh to suspend the marketing authorisations of modified release paracetamol-containing products. See EMA Press Release (EMA/562720/2017 Corr 1) entitled 'PRAC recommends modified-release paracetamol be removed from market - Overdose complex and difficult to manage with modified-release products'.

The PRAC also agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

3.4. Re-examination procedures[4]

3.4.1. Human coagulation (plasma-derived) factor VIII: human coagulation factor VIII (antihaemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP)
Recombinant factor VIII: antihaemophilic factor (recombinant) (NAP); efmoroctocog alfa – ELOCTA (CAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY (CAP); turoctocog alfa – NOVOEIGHT (CAP); simoctocog alfa – NUWIQ (CAP); susoctocog alfa – OBIZUR (CAP) - EMEA/H/A-31/1448

Applicant(s): Baxter AG (Advate), Bayer Pharma AG (Helixate Nexgen, Iblias, Kogenate, Kovaltry), CSL Behring GmbH (Voncento), Novo Nordisk A/S (NovoEight), Octapharma AB (Nuwiq), Pfizer Limited (Refacto AF), Swedish Orphan Biovitrum AB (publ) (Elocta), Baxalta Innovations GmbH (Obizur), various

PRAC Rapporteur: Jan Neuhauser; PRAC Co-rapporteur: Ghania Chamouni

Scope: Re-examination procedure under Article 32 of Directive 2001/83/EC of the review of the benefit-risk balance of factor VIII products following notification by Germany of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

Following the PRAC recommendation adopted at the May 2017 PRAC meeting, to vary the terms of the marketing authorisations[5] for human plasma derived factor VIII- and recombinant coagulation factor VIII-containing medicinal products, a MAH concerned by this referral procedure conducted under Article 31 of Directive 2001/83/EC, requested a re-examination of the PRAC recommendation in line with Article 32 of Directive 2001/83/EC. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes January 2017, PRAC minutes February 2017, PRAC minutes March 2017, PRAC minutes May 2017and PRAC minutes June 2017.

Discussion

The PRAC considered the totality of the data submitted with regards to the risk of inhibitor development for the classes of recombinant and plasma derived factor VIII products, in previously untreated patients (PUPs). This included published literature (SIPPET study[6]), data generated in individual clinical trials and a range of observational studies submitted by the

[3] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded
[4] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[5] Update of SmPC sections 4.4, 4.8 and 5.1. The package leaflet is updated accordingly
[6] Peyvandi F, Mannucci PM, Garagiola I, et al. A randomised trial of factor VIII and neutralizing antibodies in hemophilia A. The New England Journal of Medicine 2016, May 26;374(21):2054-64

marketing authorisation holders, including the data generated in large multicentre cohort studies, data submitted by the national competent authorities of the EU Member States as well as responses provided by the authors of the SIPPET study. PRAC also considered the grounds submitted by one concerned MAH as the basis for their request for re-examination of the PRAC recommendation and the views of two expert meetings held on 22 February and 3 August 2017.

The PRAC noted that the SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of factor VIII products in total. Due to the heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies evaluating only class effects to individual products, and in particular to the products that are not included in such studies.

The PRAC also considered that studies conducted to date suffer from a variety of methodological limitations and, on balance, there is no clear and consistent evidence to suggest differences in relative risks of inhibitor development between factor VIII product classes based on available data. Specifically, the findings from the SIPPET study, as well as those from the individual clinical trials and observational studies included in the MAH's responses, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between recombinant factor VIII and plasma derived factor VIII product classes. Given these are heterogeneous products, this does not preclude individual products being associated with an increased risk of inhibitor development in ongoing or future PUP studies.

The PRAC noted that the efficacy and safety of factor VIII products as indicated in the treatment and prophylaxis of bleeding in patients with haemophilia A have been established. Based on the available data, the PRAC considered that product information updates for the factor VIII products are warranted to include a warning on the clinical importance of monitoring patients for factor VIII inhibitor development[7]. With regard to their product information[8], the PRAC noted that several factor VIII products currently include reference to data from study results which do not allow a definite conclusion on the inhibitor risk for individual products. Results of clinical studies which are insufficiently robust (e.g. suffer from methodological limitations) should not be reflected in the product information of factor VIII products. The PRAC accordingly recommended changes to the product information of certain factor VIII products. Besides, as the evidence suggests that all human factor VIII products carry a risk of inhibitor development, within the frequency of 'very common' and 'uncommon', for PUPs and previously treated patients (PTPs) respectively, the PRAC recommended that the product information of these products should be aligned with these frequencies unless justified by product specific data.

Therefore, the PRAC concluded that the benefit-risk balance of the human plasma derived and recombinant coagulation factor VIII containing medicinal products remains favourable and recommended the variations to the terms of the marketing authorisations.

Summary of recommendation(s)/conclusions

Further to the initial assessment and the re-examination procedure, PRAC maintained its conclusion that the benefit-risk balance of the human plasma derived and recombinant coagulation factor VIII-containing medicinal products remains favourable subject to the

[7] SmPC section 4.4
[8] SmPC sections 4.8 and 5.1

agreed changes to the product information[9].

See Press Release (EMA/567277/2017) entitled 'PRAC confirms its previous conclusion on risk of inhibitor development with factor VIII medicines - no clear and consistent evidence exists of a difference in risk between plasma-derived and recombinant factor VIII medicines'.

Post-meeting note: the press release entitled 'Factor VIII medicines: no clear and consistent evidence of difference in risk of inhibitor development between classes - EMA concludes review of human factor VIII medicines authorised in EU' (EMA/603417/2017) representing the opinion adopted by the CHMP was published on the EMA website on 15 September 2017.

3.5. Others

None

4. Signals assessment and prioritisation[10]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Filgrastim - ACCOFIL (CAP), FILGRASTIM HEXAL (CAP), GRASTOFIL (CAP), NIVESTIM (CAP), RATIOGRASTIM (CAP), TEVAGRASTIM (CAP), ZARZIO (CAP), NAP; lenograstim (NAP); lipegfilgrastim – LONQUEX (CAP); pegfilgrastim – NEULASTA (CAP), RISTEMPA (CAP)

Applicant(s): Accord Healthcare Limited (Accofil), Amgen Europe B.V. (Neulasta, Ristempa), Hexal AG (Filgrastim Hexal), Apotex Europe BV (Grastofil), Hospira UK Limited (Nivestim), Ratiopharm GmbH (Ratiograstim), Sicor Biotech UAB (Lonquex), Teva GmbH, Sandoz GmbH (Tevagrastim), various

PRAC Rapporteur: Patrick Batty

Scope: Signal of aortitis

EPITT 18940 – New signal

Lead Member State(s): FI, FR, UK

Filgastrim, lenogastrim, lipegfilgastrim and pegfilgastrim are granulocyte colony stimulating factors (G-CSF) indicated for reduction of the duration of neutropenia under certain conditions (including when occurring following chemotherapy). Through routine literature reviews, EMA identified a case of aortitis with temporal association with pegfilgrastim treatment which led to further review of literature and EudraVigilance data on 31 May 2017. Aortitis is the inflammation of the aorta, and it is representative of a cluster of large-vessel

[9] Update of SmPC sections 4.4, 4.8 and 5.1. The package leaflet is updated accordingly
[10] 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

diseases that have various or unknown aetiologies. While inflammation can occur in response to any injury, including trauma, the most common known causes are infections or connective tissue disorders. Infections can trigger a non-infectious vasculitis by generating immune complexes or by cross-reactivity. A EudraVigilance search revealed four cases of aortitis with pegfilgrastim, and a signal of disproportionality. A signal of disproportionality was also identified for the other substances in class, filgrastim and lenograstim, with similar numbers of case reports, the same pattern and suspected reporter causality.
The cumulative exposure for medicines containing filgrastim is estimated to have been approximately 11,482,325 patients-days worldwide, in the period from first authorisation in 2009 to 2015. The cumulative exposure for medicine containing lenograstim is estimated to have been approximately 5.74 million patient-years worldwide in the period from first authorisation in 1996 to 2016. The cumulative exposure for medicines containing lipegfilgrastim is estimated to have been approximately 4,684,620 patient-days worldwide, in the period from first authorisation in 2013 to 2016. The cumulative exposure for medicines containing pegfilgrastim is estimated to have been approximately 1,720,001 person-years worldwide in the period from first authorisation in 2002 to 2016.

Discussion

The PRAC discussed the information on the signal of aortitis. Having considered the evidence from EudraVigilance and the literature, the PRAC agreed a further cumulative review of all cases of aortitis and related disorders, a review of the literature as well as non-clinical and mechanistic data on the role of G-CSF in the development of aortitis and related disorders, a discussion of biological plausibility and whether the half-life and duration of action of their product is an important factor, were needed. The need for any potential amendment to the product information and/or the RMP should be discussed.

The PRAC appointed Patrick Batty as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for filgrastim-, lenograstim-, lipegfilgrastim- and pegfilgrastim-containing products should submit to EMA, within 60 days, a cumulative review of the signal, including an analysis of all case reports of MedDRA PTs[11] aortitis, aortic dilatation, plus the MedDRA HLT[12] Aortic aneurysms and dissections, and related terms. The MAHs should also include a review of the literature as well as non-clinical and mechanistic data on the role of G-CSF in the development of aortitis and related disorders, a discussion on biological plausibility and whether the half-life and duration of action of their product is an important factor and a proposal for amending the product information and/or RMP as appropriate.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

See also Annex I 14.2.

[11] Medical dictionary for regulatory activities – Preferred terms
[12] Medical dictionary for regulatory activities – High level term

4.2.1. Amlodipine (NAP); rifampicin (NAP)

Applicant(s): various

PRAC Rapporteur: Doris Stenver

Scope: Signal of drug interaction between amlodipine and rifampicin leading to reduced antihypertensive effect of amlodipine

EPITT 18933 – New signal

Lead Member State(s): BG, DK

Background

Amlodipine is a calcium channel blocker indicated for the treatment of essential hypertension in adult patients as well as the prophylaxis of chronic stable angina pectoris. Rifampicin is an antibiotic and first-line antitubercular therapy drug used to treat several types of bacterial infections including tuberculosis, leprosy, and legionnaire's disease but also to prevent haemophilus influenzae type b and meningococcal disease in exposed people.

Rifampicin is a well-known potent inducer of the hepatic cytochrome P450 enzyme system (CYP). In this respect, there is also potential for pharmacokinetic interaction between rifampicin and anti-hypertensives that are CYP substrates: amlodipine and metoprolol. Following the publication by *Agrawal et al.,* 2016[13] a signal of drug interaction between amlodipine and rifampicin leading to reduced antihypertensive effect of amlodipine was identified by a MAH who notified EMA via an emerging safety issue (ESI). In the prospective study performed by *Agrawal et al.,* chronic kidney disease patients on dialysis with tuberculosis and hypertension were followed after rifampicin initiation. There was a decrease in serum amlodipine levels in all 16 patients after initiation of rifampicin. The authors concluded that rifampicin caused a significant decrease in blood levels of commonly used antihypertensives. This decrease in levels correlated with worsening of hypertension. A pharmacokinetic interaction between rifampicin and amlodipine resulting in decreased amlodipine plasma levels was considered plausible, thus a further evaluation was considered warranted to decide on the strength of the potential interaction including in the population of patients with chronic kidney disease (CKD) and on the need to reinforce the existing precautions and warnings in the product information of relevant medicinal products. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information. Having considered the available evidence, including from literature, EudraVigilance and product information of other calcium channel blockers, as well as the current knowledge on the co-administration of amlodipine with inducers or inhibitors of CYP3A4, the PRAC agreed that further evaluation of the co-administration of these products will be carried out in the context of the amlodipine (single ingredient) PSUSA (data lock point (DLP): 7 March 2017).

Summary of recommendation(s)

- Further evaluation of the signal of drug interaction between amlodipine and rifampicin leading to reduced antihypertensive effect of amlodipine will be carried out in the context of the amlodipine (single ingredient) PSUSA.

[13] Agrawal, A., Agarwal, S. K., Kaleekal, T. & Gupta, Y. K. 2016. Rifampicin and anti-hypertensive drugs in chronic kidney disease: Pharmacokinetic interactions and their clinical impact. Indian J Nephrol, 26, 322-328

4.2.2. Azithromycin (NAP)

Applicant(s): various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of increased rate of relapses of haematological malignancies and mortality in hematopoietic stem cell transplantation (HSCT) patients with azithromycin

EPITT 18907 – New signal

Lead Member State(s): FI

Background

Azithromycin is a macrolide indicated for the treatment of various infections when caused by micro-organisms sensitive to azithromycin.

Following the publication in JAMA by *Bergeron et al.*[14], of the French clinical trial ALLOZITHRO[15] which had been prematurely stopped by the sponsor following the detection by the data safety monitoring board (DSMB) of a significant imbalance in both the risk of relapse of the initial haematological disease with a higher rate observed in the azithromycin group, a signal of increased rate of relapses of haematological malignancies and mortality in hematopoietic stem cell transplantation (HSCT) patients with azithromycin was identified by France. Finland confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from the ALLOZITHRO study and in the literature, the PRAC requested a review of all relevant data from all sources with an evaluation of the biological plausibility for a possible association and a discussion of any hypothesis concerning the observed reoccurrences of haematological malignancies in the ALLOZITHRO study. The possibility to extrapolate the risk observed in the study to other patient groups exposed to azithromycin long- or short-term should be analysed. Additionally, the PRAC agreed on a list of questions for the ALLOZITHRO study investigators in order to acquire additional clarification concerning the study outcome.

The PRAC appointed Kimmo Jaakkola as Rapporteur for the signal.

Summary of recommendation(s)

- The originator MAH for azithromycin-containing medicine should submit to EMA, within 60 days, a review of all relevant data from all sources including biochemical-, *in vitro*- and *in vivo*- preclinical studies, clinical trials, post-marketing data and relevant literature and evaluate the biological plausibility for a possible association and discuss any hypothesis concerning the observed reoccurrences of haematological malignancies in the ALLOZITHRO study. The originator MAH should also perform an analysis on whether the risk observed in the ALLOZITHRO study can be extrapolated to other patient groups exposed to azithromycin long- or short-term with the main focus on the long-term treatment data, without excluding any other (including short term) data which might be relevant for the question. Moreover, the originator MAH should discuss the need for any

[14] Bergeron et al. Effect of azithromycin on airflow decline-free survival after allogeneic hematopoietic stem cell transplant. The ALLOZITHRO randomised clinical trial. JAMA.2017;318(6):557-566
[15] Evaluation of the efficacy of azithromycin to prevent bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation - The ALLOZITHRO randomised clinical trial – EudraCT number: 2013-000499

potential amendment to the product information and/or the RMP and make a proposal for the changes accordingly.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.
- Additionally, the ALLOZITHRO study investigators should be asked to submit to EMA within 60 days a response to the list of questions as agreed by the PRAC in order to gain additional clarification with regards to the study outcome.

4.2.3. Doxycycline (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of doxycycline induced Jarisch-Herxheimer reaction

EPITT 18937 – New signal

Lead Member State(s): DE, UK

Background

Doxycycline is a tetracycline indicated for the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria and certain other micro-organisms.

Recently, the German NCA ('Federal Institute for Drugs and Medical Devices' (BfArM)) received the submission of a type II variation for a nationally authorised medicinal product containing doxycycline (Doxycyclin-ratiopharm 100mg) to update the product information by including a new warning on a possible risk of Jarisch-Herxheimer reaction (JHR). Given that none of the publicly available product information for doxycycline-containing products contains such a warning or adverse drug reaction (ADR), supplementary information was requested. A cumulative search of the Teva safety database revealed 7 case reports, of which 6 originated from literature and one from spontaneous sources. Due to the reported temporal link in 5 of the 7 cases a causal relationship with the administration of doxycycline could not be excluded, and a signal of JHR was identified by Germany. In addition to the 7 cases reported by Teva, 34 cases could be found in the EudraVigilance database. From these 41 cases, at least 36 case reports can be assessed as possibly related. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, further supporting the known association of doxycycline with JHR, the PRAC agreed on the need for a variation to amend the product information accordingly.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The originator MAH (Pfizer) for doxycycline-containing medicines should provide comments to EMA, within 10 days, on the proposed amended product information

wording[16] to include a warning on the JHR for patients with spirochete infections shortly after doxycycline treatment as well as to add JHR as an undesirable effect with an unknown frequency.

- A 15-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Azithromycin (NAP); tobramycin[17] – TOBI PODHALER (CAP) - EMEA/H/C/002155/SDA/032, VANTOBRA (CAP) - EMEA/H/C/002633/SDA/002; NAP

Applicant(s): Novartis Europharm Ltd (Tobi Podhaler), Pari Pharma GmbH (Vantobra); various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of possible interaction between tobramycin and azithromycin leading to lower effectiveness of tobramycin

EPITT 18855 – Follow-up to April 2017

Background

The MAHs replied to the request for information on the signal of possible interaction between tobramycin and azithromycin leading to lower effectiveness of tobramycin and the responses were assessed by the Rapporteur. For background information, see PRAC minutes April 2017.

Discussion

Having considered the responses provided by the MAHs for Tobi Podhaler and Vantobra, the PRAC agreed that there was insufficient evidence of an interaction between azithromycin and tobramycin in the light of the current knowledge. As a dedicated, prospective clinical trial (TEACH[18] study) is being performed to test the impact of adding azithromycin to inhaled tobramycin in cystic fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* infection, the PRAC considered that the MAHs should assess the impact of the results of this study on the product information and/or risk management measures for their respective medicinal product.

Summary of recommendation(s)

- The PRAC considered that there was insufficient evidence of an interaction between azithromycin and tobramycin at this stage.
- The MAHs should assess the impact of the results of the ongoing TEACH study on the product information and/or risk management measures for their respective product.

[16] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly
[17] For inhalation use only
[18] Testing the effect of adding chronic azithromycin to inhaled tobramycin. A randomised, placebo-controlled, double-blinded trial of azithromycin 500mg thrice weekly in combination with inhaled tobramycin

4.3.2. Meningococcal group B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/SDA/025

Applicant(s): GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of arthritis and synovitis

EPITT 18764 – Follow-up to April 2017

Background

The MAH of Bexsero (meningococcal group B vaccine) replied to the request for information on the signal of arthritis and synovitis and the responses were assessed by the Rapporteur. For background information, see PRAC minutes April 2017.

Discussion

Having considered the available evidence from the data submitted by the MAH, including data from clinical trials, spontaneous reports and literature, the PRAC agreed that the MAH should further monitor and characterise arthritis cases reported in association with Bexsero (meningococcal group B vaccine) administration and add arthritis/synovitis/reactive arthritis as an important potential risk in the risk management plan at the next regulatory opportunity.

Summary of recommendation(s)

- The MAH should further monitor and characterise arthritis cases following Bexsero (meningococcal group B vaccine) administration and add arthritis/synovitis/reactive arthritis as an important potential risk in the risk management plan at the next regulatory opportunity.
- In addition, in the context of the next PSUR (data lock point (DLP): 13 January 2018), the MAH should monitor and characterise the events of arthritis/synovitis/reactive arthritis in clinical trials, post-marketing data and literature; develop a targeted follow up questionnaire in order to address the incompleteness of information from spontaneous reports; perform an analysis of arthritis/synovitis/reactive arthritis cases to compare the observed frequency of occurrence to the expected background incidence rate in children with relevant ages; evaluate the possibility to monitor arthritis in future clinical trials and propose an update of the product information as appropriate.

4.3.3. Mesalazine (NAP)

Applicant(s): various

PRAC Rapporteur: Patrick Batty

Scope: Signal of risk of photosensitivity reactions

EPITT 18869 – Follow-up to April 2017

Background

The MAH replied to the request for information on the signal of risk of photosensitivity reactions and the responses were assessed by the Rapporteur. For background information, see PRAC minutes April 2017.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the MAHs of mesalazine-containing products should amend the product information to include photosensitivity as an undesirable effect with a rare frequency.

Summary of recommendation(s)

- The MAHs for mesalazine-containing products should submit, within 60 days, a variation to amend the product information[19].

For the full PRAC recommendation, see EMA/PRAC/407007/2017 published on 25/09/2017 on the EMA website.

4.3.4. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP) - EMEA/H/C/003983/SDA/002; NAP

Applicant(s): Nordic Group B.V. (Nordimet); Therakind Limited (Jylamvo); various

PRAC Rapporteur: Martin Huber

Scope: Signal of pulmonary alveolar haemorrhage

EPITT 18850 – Follow-up to April 2017

Background

The MAH replied to the request for information on the signal of pulmonary alveolar haemorrhage and the responses were assessed by the Rapporteur. For background information, see PRAC minutes April 2017.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the PRAC agreed that the originator MAH for methotrexate-containing medicine should submit within 60 days a comprehensive cumulative review of cases of pulmonary alveolar haemorrhage and related terms in oncologic indications, including data from the literature, clinical development and post-marketing.

Summary of recommendation(s)

- The originator MAH for methotrexate-containing medicine should submit to EMA, within 60 days, a cumulative review of cases of pulmonary alveolar haemorrhage and related terms in oncologic indications. Information on background incidence in the oncologic indication should be also provided.
- A 60-day timetable was recommended for the assessment of this cumulative review leading to a further PRAC recommendation.

[19] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

4.3.5. Pramipexole – MIRAPEXIN (CAP) - EMEA/H/C/000134/SDA/040, SIFROL (CAP) - EMEA/H/C/000133/SDA/042, OPRYMEA (CAP) - EMEA/H/C/000941/SDA/017, PRAMIPEXOLE TEVA (CAP) - EMEA/H/C/000940/SDA/010, PRAMIPEXOLE ACCORD (CAP) - EMEA/H/C/002291/SDA/008; NAP

Applicant(s): Boehringer Ingelheim International GmbH (Mirapexin, Sifrol), Krka, d.d., Novo mesto (Oprymea), Teva B.V. (Pramipexole Teva), Accord Healthcare Ltd (Pramipexole Accord); various

PRAC Rapporteur: Doris Stenver

Scope: Signal of dystonia

EPITT 18866 – Follow-up to April 2017

Background

The MAH replied to the request for information on the signal of dystonia and the responses were assessed by the Rapporteur. For background information, see PRAC minutes April 2017.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, and the known association of pramipexole with axial dystonia, the PRAC agreed that the MAHs of pramipexole-containing products should submit a variation to amend the product information to include a warning on dystonia.

Summary of recommendation(s)

- The MAHs for pramipexole-containing products should submit, within 60 days, a variation to amend the product information[20].

For the full PRAC recommendation, see EMA/PRAC/407007/2017 published on 25/09/2017 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

See also Annex I 15.1.

5.1.1. Anagrelide - EMEA/H/C/004585

Scope: Treatment and reduction of elevated platelet counts in patients at essential thrombocythaemia risk

5.1.2. Benralizumab – EMEA/H/C/004433

Scope: Treatment of severe asthma with an eosinophilic phenotype

[20] Update of SmPC section 4.4. The package leaflet is to be updated accordingly

5.1.3. Bevacizumab - EMEA/H/C/004360

Scope: Treatment of breast cancer, non-small cell lung cancer, renal cell cancer, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer

5.1.4. Bevacizumab - EMEA/H/C/004728

Scope: Treatment of metastatic breast cancer, unresectable advanced, metastatic or recurrent non-small cell lung cancer, unresectable advanced metastatic or recurrent non-squamous non-small cell lung cancer, advanced and/or metastatic renal cell cancer, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer

5.1.5. Budesonide - EMEA/H/C/004655, Orphan

Applicant: Dr. Falk Pharma GmbH

Scope: Treatment of eosinophilic esophagitis (EoE)

5.1.6. Ciclosporin - EMEA/H/C/004229

Scope: Treatment of moderate dry eye disease in adults

5.1.7. D-biotin - EMEA/H/C/004153

Scope: Treatment of progressive multiple sclerosis (primary or secondary)

5.1.8. Human fibrinogen, human thrombin - EMEA/H/C/004446

Scope: Treatment of haemostasis

5.1.9. Padeliporfin - EMEA/H/C/004182

Scope: Treatment of prostate cancer

Previous PRAC advice was provided in December 2016 and in July 2017, see PRAC minutes December 2016 and PRAC minutes July 2017.

5.1.10. Plitidepsin - EMEA/H/C/004354, Orphan

Applicant: Pharma Mar, S.A.

Scope: Treatment of multiple myeloma

5.1.11. Rucaparib - EMEA/H/C/004272, Orphan

Applicant: Clovis Oncology UK Ltd

Scope: Treatment of ovarian cancer

5.1.12. Semaglutide - EMEA/H/C/004174

Scope: Treatment to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM) and to prevent cardiovascular events

5.1.13. Shingles herpes zoster vaccine, live - EMEA/H/C/004336

Scope: Treatment and prevention of herpes zoster (HZ) and HZ-related complications

5.1.14. Velmanase alfa - EMEA/H/C/003922, Orphan

Applicant: Chiesi Farmaceutici S.p.A.

Scope: Treatment for long-term enzyme replacement therapy in patients with alpha-mannosidosis

5.1.15. Viable T-cells - EMEA/H/C/002397, Orphan

Applicant: Kiadis Pharma Netherlands B.V., ATMP[21]

Scope: Adjunctive treatment in haematopoietic stem cell transplantation (HSCT) for a malignant disease

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/X/0054

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application (line extension) for a new pharmaceutical form (Exjade 90, 180 and 360 mg granules). The RMP (version 15.0) is updated accordingly

Background

Deferasirox is an orally active chelator selective for iron (III) indicated for the treatment of chronic iron overload in patients with beta thalassaemia major under certain conditions and in adult and paediatric patients with other anaemias aged 2 years and older. In addition,

[21] Advanced therapy medicinal product

deferasirox is indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

The CHMP is evaluating a line extension application for Exjade, a centrally authorised medicine containing deferasirox, assessing the MAH's proposal for a new formulation for oral administration as granules (90, 180 and 360 mg) packaged in sachets. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this line extension. For further background, see PRAC minutes February 2017 and PRAC minutes June 2017.

Summary of advice

- The RMP version 15.2 for Exjade (deferasirox) in the context of the line extension under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC supported the proposed risk minimisation measures to update the existing educational materials for physicians and patients describing the new formulation. In addition, the PRAC supported the addition of the ongoing study CICL670F2202[22] to evaluate the compliance and safety of the granules formulation to the pharmacovigilance plan as a category 3 study.

5.3.2. Febuxostat - ADENURIC (CAP) - EMEA/H/C/000777/II/0047

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to reflect the results of preclinical study MRPO-2015-PKM-005: 'a pharmacokinetic study of azathioprine in the rat after one-week daily oral treatment at three different dosages and with the concomitant oral administration of febuxostat or allopurinol' and clinical study REP-POPPK-MRP-2015-PKM-005: 'a population pharmacokinetic analysis from study titled pharmacokinetics of azathioprine in the rat after one-week daily oral treatment at three different dosages and with the concomitant oral administration of febuxostat or allopurinol', investigating the drug-drug interaction with azathioprine when co-administered with febuxostat. The RMP (version 6.0) is updated accordingly. In addition, the MAH took the opportunity to correct typing errors and to bring the Product Information in line with the latest QRD template (version 10)

Background

Febuxostat is a 2-arylthiazole derivative indicated in adults for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis) as well as for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of tumour lysis syndrome (TLS).

The CHMP is evaluating a type II variation for Adenuric, a centrally authorised medicine containing febuxostat, assessing the MAH's proposal to reflect in the product information the

[22] A randomised, open-label, multicentre, two arm, phase 2 study allowing to evaluate the safety of deferasirox granules in paediatric patients with iron overload

results of preclinical study MRPO-2015-PKM-005 on 'pharmacokinetics of azathioprine in the rat after one-week daily oral treatment at three different dosages and with the concomitant oral administration of febuxostat or allopurinol' and clinical study REP-POPPK-MRP-2015-PKM-005 on 'population pharmacokinetic analysis from study entitled pharmacokinetic of azathioprine in the rat after one-week daily oral treatment at three different dosages and with the concomitant oral administration of febuxostat or allopurinol' investigating the drug-drug interaction with azathioprine when co-administered with febuxostat. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 6.0 for Adenuric (febuxostat) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The MAH should classify the FAST study: 'febuxostat versus allopurinol streamlined trial', aiming at comparing the cardiovascular safety profile of febuxostat versus allopurinol when taken for an average of 3 years in patients aged 60 years or older with chronic hyperuricaemia in conditions where urate deposition has already occurred, as a category 3 study in the RMP pharmacovigilance plan. In addition, the MAH should propose a PASS (as a category 3 study in the RMP) including patients who are treated with febuxostat and dose adjusted for azathioprine (AZA)/6-mercaptopurine (6-MP) in order to confirm the results of the pharmacokinetics (PK) modelling study.

5.3.3. Idarucizumab - PRAXBIND (CAP) - EMEA/H/C/003986/II/0007

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to reflect the final results from study 1321.3, the RE-VERSE-AD study (reversal effects of idarucizumab on active dabigatran): a phase 3 case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0 g idarucizumab (BI 655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures - RMP category 3 study (MEA 001)). The RMP (version 3.0) is updated accordingly. In addition, the MAH took the opportunity to update the immunogenicity section in 5.1 of SmPC and to bring the product information (PI) in line with the latest QRD template (version 10)

Background

Idarucizumab is a humanised monoclonal antibody fragment (Fab) indicated as a specific reversal agent for dabigatran and is indicated in adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding.

The CHMP is evaluating a type II variation for Praxbind, a centrally authorised medicine containing idarucizumab, assessing the MAH's proposal to update the product information with the final results of study 1321.3 (RE-VERSE-AD): a phase 3, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0 g idarucizumab in patients treated with dabigatran etexilate who have uncontrolled bleeding or

require emergency surgery or procedures. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes July 2017.

Summary of advice

- The RMP version 3.0 for Praxbind (idarucizumab) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- With regard to the two safety concerns 'immunogenicity' and 'hypersensitivity', the PRAC considered that the impact of these safety concerns (frequency, seriousness and relatedness) should be kept in the safety specification of the RMP as important risks and should be further monitored in PSURs. As for the safety concern of 'thrombotic events', the PRAC considered that data on idarucizumab-treated patients is to date insufficient to fully characterise this potential important risk. Therefore, 'thrombotic events' should remain as an important potential risk in the RMP safety specification.

5.3.4. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0093/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Grouped variation consisting of: 1) addition of a new device: the on-body injector (Onpro kit) to be used with Neulasta, 6mg solution for injection, pre-filled syringe; 2) change the fill volume for Neulasta, 6 mg, solution for injection pre-filled syringe co-packed with the on-body injector (Onpro kit). In addition, the MAH took the opportunity to introduce editorial changes to module 3.2.P.2.4 on the container closure system. As a consequence, sections 3, 4.2, 5.1, 6.4, 6.5, 6.6 and 8 of the SmPC are updated. The Labelling, Package Leaflet and the RMP (version 4.2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to include some editorial changes and correct some typos throughout the product information. Finally, the MAH brought the product information in line with the latest QRD template (version 10)

Background

Pegfilgrastim is a covalent conjugate of recombinant human granulocyte colony stimulating factor (G-CSF) (r-metHuG-CSF) indicated for reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

The CHMP is evaluating a grouped variation for Neulasta, a centrally authorised medicine containing pegfilgrastim, assessing the MAH's proposal to introduce a new presentation consisting of a pre-filled syringe (PFS), with a higher fill volume than currently authorised, co-packed with an administration device termed the 'on-body injector' (OBI) (together known as the Onpro Kit). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this grouped variation. For further background, see PRAC minutes June 2017.

Summary of advice

- The RMP version 4.3 for Neulasta (pegfilgrastim) in the context of the grouped variation under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The MAH should add 'glomerulonephritis' as an important identified risk in the safety specification. The MAH should also ensure that the identified risk of 'medication errors, including underdose via the OBI resulting in lack of efficacy' is accurately reflected in the pharmacovigilance plan. In addition, the applicant should further justify that the proposed risk minimisation measures (e.g. patient alert card (PAC)) are sufficiently effective in preventing errors and educating patients prior to receiving the OBI device, and the strategy should ensure patients are well equipped to recognise device failures and associated risks. The proposed PAC should be revised to ensure it provides additional value beyond the proposed patient leaflet. Furthermore, the MAH should also explore ways to make the PAC more widely accessible to HCPs. The PRAC considered that it would be advisable to amend the proposed product information to make HCPs and patients aware of the availability of the PAC. Moreover, the MAH should submit a draft protocol for the study to measure the effectiveness of the PAC in the post-marketing settings.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Abatacept - ORENCIA (CAP) - PSUSA/00000013/201612

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Abatacept is a selective co-stimulation modulator indicated in combination with methotrexate for the treatment of moderate to severe rheumatoid arthritis (RA) in adult patients, and for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older under certain conditions. In addition, alone or in combination with methotrexate, abatacept is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Orencia, a centrally authorised medicine containing abatacept, 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 Orencia (abatacept) in the approved indications remains unchanged.

- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a cumulative review on pneumocystis jirovecii infections.
- In the next PSUR, the MAH should provide a safety review of venous embolic and thrombotic events, and a review of all the cases of nephritis and glomerulonephritis, as rheumatoid arthritis may itself be associated with mesangial glomerulonephritis.

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

6.1.2. Adalimumab - HUMIRA (CAP) - PSUSA/00000057/201612

Applicant: AbbVie Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Adalimumab is a tumour necrosis factor alpha (TNF-α) inhibitor indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, enthesitis-related arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease in adults and children, uveitis, and ulcerative colitis under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Humira, a centrally authorised medicine containing adalimumab, 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 Humira (adalimumab) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a clarifying statement that allergic reactions with this medicinal product can in rare cases be life-threatening. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should address several safety concerns including a cumulative review of all cases of myelitis and a review of diarrhoea events, in order to assess if an update to the product information is required.

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.

[23] Update of the package leaflet section 2. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.3. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/201701

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor indicated in combination with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Kyprolis, a centrally authorised medicine containing carfilzomib, 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 Kyprolis (carfilzomib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include tinnitus as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide detailed analyses of cases of chronic kidney disease (CKD) and cases of pancreatitis. Finally, the MAH should provide further follow-up on cases of herpes zoster reactivation in order to obtain information about the use of prophylaxis, to be able to assess whether the measures implemented are effective.

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. Dasabuvir - EXVIERA (CAP) - PSUSA/00010363/201701

Applicant: AbbVie Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Dasabuvir is a non-nucleoside inhibitor of the hepatitis C virus (HCV) ribonucleic acid (RNA)-dependent RNA polymerase part of the class of direct-acting antivirals (DAAV) 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 Exviera, a centrally authorised medicine containing dasabuvir, and issued a recommendation on its marketing authorisation(s).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Exviera (dasabuvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on depression, suicidal ideation and suicide attempt in order to ensure that caution is used in patients with a pre-existing history of depression or psychiatric illness and to request patients and caregivers to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- The MAH should submit to EMA, within 30 days, a comprehensive safety review evaluating the potential risk of anaphylactic reaction associated with dasabuvir and propose to update the product information as appropriate.
- The MAH should submit an updated RMP at the next regulatory opportunity.
- In the next PSUR, the MAH should provide detailed reviews of cases of anaemia, of acute pancreatitis and of hepatorenal syndrome. In addition, the MAH should include a review of cases of major acute cardiovascular events (MACE) including a further analysis of cases of ischaemic cardiac/cerebral reactions where raised cholesterol has been reported, in light of recent publications about dyslipidaemia observed after DAAV treatment. The MAH should also provide a detailed analysis of cases of neoplasms with an evaluation of the potential relationship of these neoplasms with DAAV treatment. Moreover, the MAH should include a review of hepatotoxicity amongst non-users of ethinylestradiol containing medications, and a review of psoriasis/psoriatic arthropathy including cases of exacerbation.

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. Dexamethasone[26] - OZURDEX (CAP) - PSUSA/00000985/201701 (with RMP)

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Dexamethasone is a corticosteroid indicated, as Ozurdex, for the treatment of adult patients with visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy, and adult patients with macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), and adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

[25] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[26] Uveitis and macular oedema indication only

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ozurdex, a centrally authorised medicine containing dexamethasone, 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 Ozurdex (dexamethasone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the current safety experience to include information related to repeat administrations beyond two implants in posterior segment non-infectious uveitis and retinal vein occlusion. Therefore the current terms of the marketing authorisation(s) should be varied[27].
- The MAH should submit an updated RMP at the next regulatory opportunity.
- In the next PSUR, the MAH should provide reviews of cases of device dislocation and cases of vitreous detachment/haemorrhage. In addition, the MAH should provide reviews of cases of blurred vision and cases of central serous chorioretinopathy, and should propose to update the product information as appropriate.

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

6.1.6. Eluxadoline - TRUBERZI (CAP) - PSUSA/00010528/201703

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Eluxadoline is a locally acting, mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist as well as a kappa opioid receptor (κOR) agonist. It is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-D).

The PRAC is currently reviewing the benefit-risk balance of Truberzi (eluxadoline), a centrally authorised medicine, in the framework of the assessment of a PSUR single assessment (PSUSA) procedure due for PRAC recommendation at the October 2017 PRAC meeting.

Summary of conclusions

The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUSA procedure, which is due to complete at the following PRAC meeting, identifying some risks that potentially impact on the overall benefit-risk balance of the medicinal product. To this effect, the PRAC adopted a list of questions (LoQ) to the MAH. Further discussion and adoption of a recommendation is planned at the October 2017 PRAC meeting.

[27] Update of SmPC sections 4.2 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.7. Florbetaben (^{18}F) - NEURACEQ (CAP) - PSUSA/00010094/201702

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Neuraceq, a centrally authorised medicine containing florbetaben (^{18}F), and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Neuraceq (florbetaben (^{18}F)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to change the frequency of the undesirable effect 'injection site irritation' from common to uncommon. In addition, the number of administrations/subjects on which the safety profile of Neuraceq is based should be updated accordingly. Therefore the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should report on the strategy and effectiveness of the measures taken to address the low recruitment rate by healthcare professionals (HCP) for PASS-2 (FBB-01_03_13) study: a non-interventional prospective observational multicentre, multinational registry to observe usage pattern, safety and tolerability of the diagnostic agent Neuraceq in clinical practice.

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

6.1.8. Gimeracil, oteracil monopotassium, tegafur - TEYSUNO (CAP) - PSUSA/00002875/201701

Applicant: Nordic Group B.V.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor, oteracil potassium, an orotate phosphoribosyltransferase (OPRT) inhibitor and tegafur, a 5-fluorouracil (5-FU) prodrug are

[28] 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

indicated in combination in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Teysuno, a centrally authorised medicine containing gimeracil/oteracil monopotassium/tegafur, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Teysuno (gimeracil/oteracil monopotassium/tegafur) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hepatitis B reactivation as a warning, and advise that patients should be tested for hepatitis B virus (HBV) infection before initiating treatment. In addition, hepatitis B reactivation should be added as an undesirable effect with a rare/very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[29].

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

6.1.9. Idelalisib - ZYDELIG (CAP) - PSUSA/00010303/201701

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Idelalisib is an adenosine-5'-triphosphate (ATP) selective inhibitor indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies. Idelalisib is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zydelig, a centrally authorised medicine containing idelalisib, 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 Zydelig (idelalisib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on transaminase elevation to a warning on hepatotoxicity, to ensure that in the event of grade 3 or 4 elevation of aspartate transaminase (AST) or alanine transaminase (ALT)

[29] Update of SmPC section 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

treatment with idelalisib is withheld and liver function is monitored. Treatment may be resumed at a lower dose once values have returned to grade 1 or lower (ALT/AST < 3 times upper limit of normal (ULN)). If grade 2 or higher elevations of ALT and/or AST are observed, the patient's ALT, AST and total bilirubin must be monitored weekly until the values return to grade 1 or below. Moreover, hepatocellular injury should be added as an undesirable effect with a common frequency. Lymphocytosis should be added as an undesirable effect with a very common frequency for any grade and with a common frequency for grade 3 and over, and detailed information included in the section on pharmacodynamic properties. Therefore the current terms of the marketing authorisation(s) should be varied[30].

- In the next PSUR, the MAH should provide a detailed analysis of cases of progressive multifocal leukoencephalopathy (PML).

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

6.1.10. Lixisenatide - LYXUMIA (CAP) - PSUSA/00010017/201701

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Lixisenatide is a selective glucagon-like peptide-1 (GLP-1) receptor agonist indicated for the treatment of adults with type 2 diabetes mellitus (T2DM) to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lyxumia, a centrally authorised medicine containing lixisenatide, 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 Lyxumia (lixisenatide) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a cumulative review including a causality assessment of all cases of 'biliary disorders' identified in clinical trials and in the post-marketing setting. Based on the outcome of the review, the MAH should discuss the need to update the product information and RMP as appropriate.

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

[30] Update of SmPC sections 4.4, 4.8 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.11. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - PSUSA/00010367/201701

Applicant: AbbVie Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Ombitasvir is a hepatitis C virus (HCV) non-structural protein 5A (NS5A) inhibitor, paritaprevir a HCV non-structural proteins 3/4A (NS3/4A) protease inhibitor and ritonavir is a CYP3A[31] inhibitor; they are all direct-acting antivirals (DAAV). Their combination is indicated 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 Viekirax, a centrally authorised medicine containing ombitasvir/paritaprevir/ritonavir, 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 Viekirax (ombitasvir/paritaprevir/ritonavir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on depression, suicidal ideation and suicide attempt in order to ensure that caution is used in patients with a pre-existing history of depression or psychiatric illness and to request patients and caregivers to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation. Therefore the current terms of the marketing authorisation(s) should be varied[32].
- The MAH should submit to EMA, within 30 days, a comprehensive safety review evaluating the potential risk of anaphylactic reaction associated with dasabuvir and propose to update the product information as appropriate.
- The MAH should also submit to EMA, within 30 days, a detailed analysis of the possible drug-drug interaction between ombitasvir/paritaprevir/ritonavir and disopyramide due to the inhibition of CYP3A4 by ritonavir that can lead to increased plasma concentrations of disopyramide. The MAH should propose to update the product information as appropriate.
- The MAH should submit an updated RMP at the next regulatory opportunity.
- In the next PSUR, the MAH should provide detailed reviews of cases of anaemia, of acute pancreatitis and of hepatorenal syndrome. In addition, the MAH should include a review of cases of major acute cardiovascular events (MACE) including a further analysis of cases of ischaemic cardiac/cerebral reactions where raised cholesterol has been reported in light of recent publications about dyslipidaemia observed after DAAV

[31] Cytochrome P450, family 3, subfamily A
[32] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

treatments. The MAH should also provide a detailed analysis of cases of neoplasms with an evaluation of the potential relationship of these neoplasms with DAAV treatment. Moreover, the MAH should include a review of hepatotoxicity amongst non-users of ethinylestradiol containing medications, and a review of psoriasis/psoriatic arthropathy including cases of exacerbation. Finally, the MAH should include an analysis of the possible drug-drug interaction between ombitasvir/paritaprevir/ritonavir and fentanyl and propose to update the product information as appropriate.

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

6.1.12. Peginterferon beta-1a - PLEGRIDY (CAP) - PSUSA/00010275/201701

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Plegridy, a centrally authorised medicine containing peginterferon beta-1a, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Plegridy (peginterferon beta-1a) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include alopecia as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH should detail the number of medication errors including premature locking of the needle shield (PLNS) events.

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

6.1.13. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) - PREVENAR 13 (CAP) - PSUSA/00009263/201701

Applicant: Pfizer Limited

[33] 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

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) is indicated for the active immunisation against disease caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (including sepsis, meningitis, pneumonia, bacteraemia and acute otitis media) in infants and children from 2 months up to 5 years of age.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prevenar 13, a centrally authorised vaccine containing pneumococcal polysaccharide conjugate vaccine (13-valent, 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 Prevenar 13 (pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should clarify the location of vaccination site granulomas and vaccination site hypertrichosis and should discuss the significance of this observation. The MAH should propose to update the product information as applicable. In addition, the exposure to Prevenar 13 increased in the last years and the effectiveness and the impact of the vaccine have been further studied globally and for specific populations. The MAH should summarise the available information and discuss how the missing information on the effectiveness of the vaccine should be adapted and rephrased in the RMP.

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.

6.1.14. Sorafenib - NEXAVAR (CAP) - PSUSA/00002773/201612

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Sorafenib is a multikinase inhibitor indicated for the treatment of hepatocellular carcinoma, for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alfa or interleukin-2 (IL-2) based therapy or are considered unsuitable for such therapy as well as for the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nexavar, a centrally authorised medicine containing sorafenib, 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 Nexavar (sorafenib) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should submit a cumulative review on cerebral ischaemia and propose to update on the product information as applicable.
- The MAH should submit to EMA, within 60 days, an updated cumulative review on hypoglycaemia and propose to update the product information if deemed 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.

6.1.15. Tipranavir - APTIVUS (CAP) - PSUSA/00002973/201612

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Tipranavir is a protease inhibitor (PI) indicated in combination with a low dose of ritonavir for combination antiretroviral treatment of human immunodeficiency virus 1 (HIV-1) infection in highly pre-treated patients with virus resistant to multiple protease inhibitors.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aptivus, a centrally authorised medicine containing tipranavir, 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 Aptivus (tipranavir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to reflect a contraindication for the concomitant use of tipranavir with lurasidone as it leads to an increase of lurasidone concentration that can induce potentially serious and/or life-threatening events including coma. Therefore the current terms of the marketing authorisation(s) should be varied[34].

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.

[34] Update of SmPC sections 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

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

See also Annex I 16.2.

6.2.1. Alitretinoin - PANRETIN (CAP); NAP - PSUSA/00000090/201701

Applicants: Eisai Ltd (Panretin), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Alitretinoin is a retinoid compound and a vitamin A derivative. Panretin (alitretinoin) is indicated for the topical treatment of cutaneous lesions in patients with acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma (KS) under certain conditions. Alitretinoin is also indicated nationally for the treatment of severe chronic hand eczema in adults under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Panretin, a centrally authorised medicine containing alitretinoin together with nationally authorised medicines containing alitretinoin, 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 alitretinoin-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained. This recommendation is without prejudice to the final conclusions of the ongoing referral procedure under Article 31 of Directive 2001/83/EC for retinoid-containing medicinal products (EMEA/H/A-31/1446).
- The PRAC noted the accumulating data with regards to the risk of cardiovascular disorders with alitretinoin oral formulations. Taking into account the limited information, the likely confounding by underlying comorbidities in the reported cases and the existing risk minimisation measures (RMM) it was considered that the available data were not supportive of a causal association. However, the PRAC agreed that this is an area that should be kept under close review in future PSURs.

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. Docetaxel - DOCETAXEL WINTHROP (CAP); TAXOTERE (CAP); NAP - PSUSA/00001152/201611

Applicants: Aventis Pharma S.A. (Docetaxel Winthrop, Taxotere), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Docetaxel is an antineoplastic agent indicated for the treatment of breast cancer, non-small lung cancer, prostate cancer, gastric adenocarcinoma as well as head and neck cancer under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Docetaxel Winthrop and Taxotere, centrally authorised medicines containing docetaxel, and nationally authorised medicines containing docetaxel, 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 docetaxel-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of docetaxel at a different site)' as an undesirable effect with an unknown frequency. In addition, a warning on hypersensitivity reactions to docetaxel should be included in order to inform healthcare professionals that patients who have had previous hypersensitivity reactions to paclitaxel should be closely monitored during docetaxel therapy initiation. Hypersensitivity reaction should be also added as an undesirable effect with an unknown frequency. Finally, the information related to the risk of potential effects of alcohol and interactions with other medicinal products is amended as per relevant guidance documents[35]. Therefore the current terms of the marketing authorisation(s) should be varied[36].
- In the next PSUR, the MAHs should submit cumulative reviews of cases of optic nerve disorders and tumour lysis syndrome, and prepare a synthesis of cumulative pregnancy cases reported with docetaxel including treated females, female partners of treated males, and pregnancy outcomes. In addition, MAHs should provide a discussion on cross resistance between docetaxel and abiraterone. Finally, the MAH Sanofi should submit an updated review of cases of second primary malignancies (SPM).

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

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

See also Annex I 16.3.

6.3.1. Allopurinol (NAP) - PSUSA/00000095/201612

Applicant(s): various

[35] Excipients in the label and package leaflet of medicinal products for human use, European Commission, Notice to applicants, volume 3B; Quality review of documents (QRD) template
[36] Update of SmPC section 4.4, 4.5, 4.7 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Allopurinol is a xanthine-oxidase inhibitor indicated for the treatment of gout, primary and secondary hyperuricaemia.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing allopurinol, 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 allopurinol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, following a review of recently published literature the product information should be updated to include a recommendation to consider conducting HLA[37]-B*5801 genotype screening before initiating therapy with allopurinol in population subgroups with Asian descent (Han Chinese, Thai, Korean) to minimise the risk of allopurinol-induced serious severe cutaneous adverse reactions (SCARs). In addition, information on increased thyroid stimulating hormone (TSH) levels on long term treatment with allopurinol should be included, as well as updating the information with regards to the concomitant administration of allopurinol and cytostatic agents and also concomitant allopurinol and aluminium hydroxide. Furthermore, information on breastfeeding should be included. Finally, agranulocytosis, thrombocytopenia and aplastic anaemia should be included as undesirable effects with a very rare frequency and blood increased TSH with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[38].
- In the next PSUR, the MAHs should discuss the association of the use of allopurinol with renal impairment and bladder cancer as well as the cross-reaction between allopurinol and febuxostat. In addition, the MAHs should discuss the possibility of vaccination triggering hypersensitivity reactions in patients treated with allopurinol. Finally, the MAH Teofarma should provide and discuss information on their signal of haemolytic anaemia.

The frequency of PSUR submission should be revised from yearly to three-yearly. This new frequency will take effect after the next data lock point. The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.2. Antithrombin III (NAP) - PSUSA/00003159/201612

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

[37] Human leukocyte antigen
[38] Update of SmPC section 4.4, 4.5, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Background

Antithrombin III is an endogenous inhibitor of blood coagulation indicated for the prophylaxis and treatment of thromboembolic complications in acquired and hereditary antithrombin deficiency.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing antithrombin III, 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 antithrombin III-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should submit a detailed review of cases of cardiac arrest and provide a discussion on the need to update the product information as applicable. In addition, MAHs of antithrombin III-containing products indicated in the treatment of disseminated intravascular coagulation (DIC) should provide a critical and detailed discussion on the benefit-risk balance in this indication, and how it may be impacted by recent data.

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

6.3.3. Bacillus clausii multi-antibioresistant spores (NAP) - PSUSA/00000284/201611

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Bacillus clausii multi-antibioresistant spores belong to the class of antidiarrhoeal microorganisms, indicated for the treatment and prophylaxis of intestinal dysmicrobism and subsequent endogenous dysvitaminosis, for aiding the recovery of the intestinal microbial flora, for the treatment of acute and chronic gastrointestinal disorders in breastfeeding infants, as well as for the treatment of diarrhoea and vitamin deficiency.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing *bacillus clausii* multi-antibioresistant spores, 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 *bacillus clausii* multi-antibioresistant spores-containing medicinal products in the approved indications remains unchanged.

- Nevertheless, the product information should be updated to include bacteraemia (in immunocompromised patients) as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[39].

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. Bendamustine hydrochloride (NAP) - PSUSA/00003162/201701

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Bendamustine hydrochloride is an alkylating antitumour agent with an anti-neoplastic and cytocidal effect indicated for the first-line treatment of chronic lymphocytic leukaemia (CLL; Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate, for the treatment of indolent and/or low grade non-Hodgkin's lymphomas (NHL) as monotherapy in patients, who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen, and as a first line treatment of multiple myeloma (MM; Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation (AutoSCT) and who have clinical neuropathy at the time of diagnosis, precluding the use of thalidomide or bortezomib containing treatment.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing bendamustine hydrochloride, 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 bendamustine hydrochloride-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on infections, in order to raise awareness that in case of low CD4[40]-positive T-cell counts, Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered. In addition, a warning on skin reactions, specifically on drug reaction with eosinophilia and systemic symptoms (DRESS) should be added to advise patients to seek medical advice if they experience signs and symptoms of severe cutaneous reactions. Finally, DRESS, urticaria, pneumonitis, and pulmonary alveolar haemorrhage should be added as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[41].

[39] 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
[40] Cluster of differentiation 4
[41] Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- In the next PSUR, the MAH(s) should provide a discussion on cases of interstitial lung disease and associated events.

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

6.3.5. Chlormadinone (NAP) - PSUSA/00000677/201611

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Chlormadinone is a synthetic progesterone derivative indicated for hormone replacement therapy in addition to an oestrogen, secondary amenorrhoea, dysfunctional haemorrhage, irregular cycles, mastalgia and for diagnostic purposes (gestagen test).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing chlormadinone, 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 chlormadinone-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include depression and anxiety, as a warning in order to advise patients to seek medical advice in case of appearance or aggravation of symptoms for depression and anxiety; and to include a warning about the risk of thromboembolic events to advise doctors to consider a medical history of thromboembolic events when prescribing. In addition, depression, anxiety and thromboembolic events should be included as adverse events with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[42].
- In the next PSUR, the MAHs should provide a detailed review on the risk of development of breast cancer with progestogens. In addition, MAHs should closely monitor thromboembolic events.

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

6.3.6. Chlormadinone acetate, ethinylestradiol (NAP) - PSUSA/00000679/201611

Applicant(s): various

[42] 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

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Chlormadinone is a progestogen and ethinyestradiol is an estrogen. The combination of chlormadinone acetate and ethinylestradiol is indicated for contraception and for the treatment of some dermatological diseases.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing ethinylestradiol/chlormadinone acetate, 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 ethinylestradiol/chlormadinone acetate-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- MAHs that have a RMP in place should include drug-drug interaction between combined hormonal contraceptives (CHC)-containing ethinylestradiol and antiviral medication(s) indicated for the treatment of hepatitis C virus (HCV) as an important identified risk.

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

6.3.7. Dexlansoprazole (NAP), lansoprazole (NAP) - PSUSA/00001827/201612

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Dexlansoprazole and lansoprazole are proton pump inhibitors (PPI). Lansoprazole is indicated for the treatment of peptic ulcers, symptomatic gastroesophageal reflux disease, prophylaxis and treatment of reflux oesophagitis, Zollinger-Ellison syndrome, treatment of *Helicobacter pylori*, prophylaxis and treatment of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric and duodenal ulcers, acute gastric mucosal lesion and gastric and duodenal ulcer in patients under certain conditions. Dexlansoprazole is indicated for the treatment of symptomatic non-erosive gastroesophageal reflux disease, healing of all grades of erosive oesophagitis and maintenance treatment of healed erosive oesophagitis, and relief of heartburn.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing dexlansoprazole and containing lansoprazole, 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 dexlansoprazole- and lansoprazole-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include visual hallucinations as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisations should be varied[43].
- In the next PSUR, MAHs of dexlansoprazole-containing products should further review and discuss the cases of pancreatitis, colitis and rhabdomyolysis, and propose to update the product information as applicable. Furthermore, a cumulative review of cases of drug ineffective and related terms should be presented. In addition, the MAHs of lansoprazole- and dexlansoprazole-containing products should review and further discuss the possible causal relationship between the drugs and gastrointestinal candidiasis. Finally, the MAHs should also provide a cumulative review of cases of galactorrhoea and hyperprolactinaemia and update the product information as applicable.

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

6.3.8. Diacerein (NAP) - PSUSA/00001026/201612

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Diacerein is an anthraquinone derivative indicated for the symptomatic treatment in patients with osteoarthritis of the hip or knee, with delayed onset of action.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing diacerein, 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 diacerein-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include chromaturia as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[44].

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

[43] 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
[44] 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

Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.9. Flurbiprofen (NAP) - PSUSA/00001450/201611

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Flurbiprofen is a propionic acid derivative indicated for the treatment of rheumatoid disease, osteoarthritis, ankylosing spondylitis, musculoskeletal disorders, trauma, and relief of mild to moderate pain in certain conditions. In addition, ophthalmic formulations are indicated for the treatment of inflammation of the anterior segment of the eye after cataract surgery and laser trabeculoplasty, as well as for the inhibition of intraoperative miosis, and as an analgesic in relieving ocular pain associated with surgery.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing flurbiprofen, 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 flurbiprofen-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAH should provide cumulative reviews on myocardial infarction, cerebrovascular accident, and on hepatobiliary adverse events.

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

6.3.10. Furosemide, spironolactone (NAP) - PSUSA/00001493/201612

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Furosemide is a loop diuretic and spironolactone is an aldosterone antagonist. In combination, furosemide and spironolactone are indicated for the treatment of hypertension, ascites in patients with liver diseases, oedema and congestion of the lungs due to cardiac insufficiency and oedema in patients with nephrotic syndrome under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing furosemide/spironolactone, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of furosemide/spironolactone-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should provide a detailed review on renal impairment/renal dysfunction in relation to furosemide/spironolactone treatment and propose to update the product information as applicable. MAHs should also provide a cumulative review of cases of secondary hyperparathyroidism and discuss its impact on bone mineral density. Furthermore, the MAHs should provide a cumulative review of decreased bone mineral density and osteoporosis and discuss the need for an update to the product information.

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. Iron[45] (NAP) - PSUSA/00010236/201701

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Iron complexes include iron sucrose, iron carboxymaltose, iron (III) isomaltoside and sodium ferric gluconate for parenteral preparations are indicated for the treatment of intravenous (IV) iron supplementation to correct iron deficiency and to replenish iron stores.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing iron sucrose, iron (III) isomaltoside, iron carboxymaltose and sodium ferric gluconate complex in parenteral indications, 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 iron sucrose-, iron (III) isomaltoside-, iron carboxymaltose- and sodium ferric gluconate complex-containing medicinal products in the approved parenteral indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- Nevertheless, taking into account the risk minimisation measures previously implemented, the PRAC expressed concerns with regard to the recently reported cases of serious hypersensitivity reactions reported with the iron isomaltoside-containing product after the data lock point (DLP) of the current PSUSA procedure. In view of the uncertainties regarding the risk of serious hypersensitivity and anaphylactic reactions, the PRAC concluded that this issue should be further investigated and spontaneous data

[45] Parenteral preparations only

should be complemented as soon as possible by the results of the PASS[46], and the annual updates requested from MAHs for all IV iron-containing products further to the conclusions of the procedure on iron containing IV medicinal products under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1322) finalised in 2013. The requested data should be presented in the context of the therapeutic indication of these medicinal products and the effectiveness of risk minimisation measures.

- In the next PSUR, the MAHs should provide the PASS interim results further characterising the safety concerns of hypersensitivity reactions, together with annual cumulative reviews of cases of hypersensitivity, fatal cases, pregnancy cases including usage data. A critical discussion on cases of serious hypersensitivity reactions, and cases with fatal outcome should be provided in light of the benefit-risk of the indication(s) in relation to the safety profile of the products and the effectiveness of risk minimisation measures. The consortium of the MAHs for IV iron-containing products is encouraged to agree on a single methodology of classification and causality assessment of cases and a single statistically comparable way of data presentation in the annual reviews to ensure comparability as required in the EC decision (EMEA/H/A-31/1322). In addition, the MAHs should provide a cumulative comprehensive safety review of cases of cardiac rhythm disorders (supraventricular and ventricular) and propose to update the product information as appropriate. Moreover, the MAHs should investigate the risk of iron overload, particularly in chronic kidney disease (CKD) patients and in patients with inflammatory bowel disease (IBD) and provide a cumulative review of all cases of iron overload reported with iron-containing products. The MAHs should discuss the need to update the product information accordingly and develop appropriate communications to remind prescribers of the measures to minimise this risk. Furthermore, the MAHs should provide a comprehensive safety review of cases of disseminated intravascular coagulation (DIC) in pregnant women including a proposal for updating the product information as applicable. The MAHs should provide detailed reviews of cases of thrombosis and venous disorders and of cases of livedo reticularis.
- In the next PSUR, MAHs (except for iron isomaltoside-containing products) should provide a cumulative review of cases of delayed adverse reactions and propose to update the product information as applicable. MAHs for iron sucrose- and sodium ferric gluconate complex-containing products should provide a cumulative review of cases of influenza-like illness and related symptoms/complex of symptoms, and propose to update the product information as applicable.

The frequency of PSUR submission should be revised from thirteen-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.

The PRAC also considered that PSURs for medicinal products containing iron dextran for parenteral use should be assessed within the same PSUSA procedures. Therefore, the EURD list should be updated accordingly.

[46] Study evaluating the risk of severe hypersensitivity reactions and assessing the risk of anaphylactic or severe immediate hypersensitivity reactions on the day of or the day after first IV iron use (procedure: EMEA/H/N/PSP/J/0053)

6.3.12. Levobunolol[47] (NAP) - PSUSA/00010109/201701

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Levobunolol is a non-cardioselective beta-adrenoceptor blocking agent indicated for the reduction of intraocular pressure in chronic open-angle glaucoma and ocular hypertension as well as for the reduction of the incidence and severity of ocular hypertension associated with ocular surgery.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of medicines containing levobunolol nationally authorised in ophthalmic indications, 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 levobunolol-containing medicinal products in the approved ophthalmic indications remains unchanged.
- Nevertheless, the product information should be updated to include alopecia, foreign body sensation in the eye, hypersensitivity reaction including symptoms or signs of eye allergy and skin allergy as adverse events with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[48].

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

6.3.13. Octenidine dihydrochloride, phenoxyethanol (NAP) - PSUSA/00002199/201701

Applicant(s): various

PRAC Lead: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

Background

Octenidine dihydrochloride and phenoxyethanol are antiseptics and are indicated in combination for antiseptic treatment of wounds, mucous membrane and adjacent skin disinfection, in interdigital mycoses, and also for antiseptic treatment of local bacterial and fungal infections in the vaginal area.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing octenidine dihydrochloride/phenoxyethanol, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the risk-benefit balance of octenidine dihydrochloride/phenoxyethanol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include warnings on the use of octenidine dihydrochloride/phenoxyethanol in low weight preterm neonates and on the need to avoid use in the eye. Therefore the current terms of the marketing authorisation(s) should be varied[49].
- In the next PSUR, the MAH(s) should provide a detailed assessment of all reports of adverse events in neonates.

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.

6.3.14. Quinine (NAP) - PSUSA/00002598/201611

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Quinine is a cinchona alkaloid indicated for the therapy and prophylaxis of nocturnal leg cramps in adults under certain conditions and for the treatment of uncomplicated chloroquine-resistant malaria.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing quinine, 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 quinine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include warnings on dose-dependent QT prolonging effects, and to recommend caution when using quinine in patients with conditions which predispose to QT-prolongation and in patients with atrioventricular block. In addition, a warning on concomitant use of quinine with phenobarbital and carbamazepine should be included in order to ensure that these patients are monitored closely. Therefore the current terms of the marketing authorisations should be varied[50].

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.

[49] 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
[50] Update of SmPC section 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.15. Roxithromycin (NAP) - PSUSA/00002669/201612

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of roxithromycin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include visual impairment and blurred vision as undesirable effects with an unknown frequency, and the corresponding warning regarding ability to drive or operate machinery should be updated. Therefore the current terms of the marketing authorisations should be varied[51].
- In the next PSUR, the MAHs should provide cumulative reviews of haematuria and renal failure as well as of drug reaction with eosinophilia and systemic symptoms (DRESS) and exfoliative dermatitis, and discuss the need for an update of the product information.

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

6.3.16. Topiramate (NAP) - PSUSA/00002996/201701

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Topiramate is a sulfamate-substituted monosaccharide indicated for the treatment of epilepsy under certain conditions, and indicated as adjunctive therapy for patients with seizures under certain conditions. Finally, topiramate is indicated for migraine prophylaxis in adults.

[51] Update of SmPC section 4.7 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing topiramate, 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 topiramate-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated in order to strengthen the precautionary warnings for teratogenicity, and to better reflect the risks related to the dose-dependent increase of malformations as well as the risk of malformations in subsequent pregnancies. In addition, the breastfeeding information should also be updated to include information on the effects that have been observed in breastfed newborns/infants of treated mothers. Therefore the current terms of the marketing authorisation(s) should be varied[52].
- In the next PSUR, if further cases of anorexia nervosa occur the MAH should discuss whether the available evidence justifies the inclusion of a warning in the product information regarding teenagers vulnerable to anorexia or with a previous diagnosis of anorexia nervosa.

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.

Considering that data from PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC did not raise any safety concerns, the PRAC agreed that no further PSURs are required for those products. This will be reflected in the EURD list.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/LEG 034.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to LEG 034 [cumulative review of data from all sources on the risk of rebound multiple sclerosis (MS) with fingolimod, as requested in the conclusions of EMEA/H/C/PSUSA/00001393/201602 adopted by PRAC in October 2016] as adopted in March 2017 further to the submission of a cumulative review of data from all per the request for supplementary information (RSI) adopted in March 2017

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated as single disease modifying therapy (DMT) in highly active relapsing remitting multiple sclerosis (MS) for adult

[52] Update of SmPC section 4.4, 4.6 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

patients with highly active disease despite a full and adequate course of treatment with at least one DMT, as well as for adult patients with rapidly evolving severe relapsing remitting MS defined by two or more disabling relapses in one year, and with one or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load.as compared to a previous recent MRI.

Following the evaluation of the most recently submitted PSURs for the above-mentioned medicine(s), the PRAC requested the MAH to submit further data. For background, see PRAC minutes October 2016 and PRAC minutes March 2017. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit a variation to EMA, within 60 days, to reflect in the product information that cases of severe exacerbation of disease have been observed in patients stopping fingolimod therapy. Therefore, caution should be exercised when stopping fingolimod therapy due to the risk of a rebound effect. If discontinuation of Gilenya is deemed necessary, patients should be monitored during this time for relevant signs of a possible rebound effect.
- The MAH should update the RMP at the next regulatory opportunity in order to improve risk minimisation via the careful management of withdrawal from fingolimod therapy in patients who wish to become pregnant. Additional risk communication should be considered in the RMP as well as in the product information as applicable.

6.4.2. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/LEG 084.1

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to LEG 084 [cumulative review on the teratogenic risk and the risk of neurodevelopmental disorders associated with the use of levetiracetam during pregnancy, based on data from all available sources as requested in the conclusions of EMEA/H/C/PSUSA/00001846/201511 adopted by PRAC in September 2016] as per the request for supplementary information (RSI) adopted in March 2017

Background

Levetiracetam is a pyrrolidone derivative indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. Levetiracetam is also indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy; in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy and in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

Following the evaluation of the most recently submitted PSURs for the above-mentioned medicine(s), the PRAC requested the MAH to submit further data. For background, see PRAC minutes September 2016 and PRAC minutes March 2017. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 60 days, a variation to update the section on pregnancy and lactation of the product information in order to advise avoiding sudden discontinuation of treatment with levetiracetam as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. In addition, in light of evidence from post-marketing data on pregnant women and epidemiological studies that do not suggest a substantial increase in the risk for major congenital malformations and, the product information should be updated to state that levetiracetam can be used during pregnancy if after careful assessment it is considered clinically needed. In such cases, the lowest effective dose is recommended.
- The MAH should update the RMP to extend the missing information 'long-term effects in children on learning, intelligence, growth, endocrine function, puberty, and childbearing potential', currently restricted to the population of patients 'aged 1 month to less than 4 years' to the population 'aged 4 years and older'. In addition, the missing information 'use during pregnancy (including deterioration of seizure control during pregnancy) for the population 'aged 4 years and older' should be removed from the RMP as these concerns are to be addressed in the product information.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[53]

See also Annex I 17.1.

7.1.1. Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Daclatasvir – DAKLINZA (CAP); dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir – ZEPATIER (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, peritepreviir, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatasvir – EPCLUSA (CAP) - EMEA/H/N/PSP/J/0056

Applicant(s): AbbVie Limited (Exviera, Viekirax), Bristol-Myers Squibb Pharma EEIG (Daklinza), Gilead Sciences International Ltd (Epclusa, Harvoni, Sovaldi), Janssen-Cilag International NV (Olysio), Merck Sharp & Dohme Limited (Zepatier)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Joint PASS protocol for a prospective, non-interventional study evaluating the risk of early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAAV) therapy compared to HCV-infected patients without previous DAAV therapy during routine clinical care with previous successfully treated HCC, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

Background

A review of direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free) (daclatasvir (Daklinza), dasabuvir (Exviera), ombitasvir/paritaprevir/ritonavir (Viekirax), simeprevir (Olysio), sofosbuvir (Sovaldi),

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

sofosbuvir/ledipasvir (Harvoni)) was carried out by the PRAC in a referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1438) to assess the risk of hepatitis B virus (HBV) reactivation as well as the risk of unexpected early hepatocellular carcinoma (HCC) recurrence in patients treated with a DAAV and to establish whether any measures are necessary to minimise these risks. The benefit-risk balance of Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax was considered to remain favourable subject to amendments to the product information and to conditions. As a condition, in order to evaluate the risk of early recurrence of hepatocellular carcinoma associated with DAAV, the MAHs shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. For further background, see PRAC minutes December 2016.

The joint PASS protocol for a prospective, non-interventional study evaluating the risk of early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after DAAV therapy compared to HCV-infected patients without previous DAAV therapy during routine clinical care with previous successfully treated HCC, was presented for review by the PRAC.

Endorsement/Refusal of the protocol

- The PRAC, having considered the joint final draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that the design of the study did not fulfil the study objective given that the MAHs proposed to base the analysis of the DAAV-PASS on the comparison of two internal cohorts from TARGET-HCC study, utilising a design that estimates the risk of HCC recurrence as a time-varying function of all DAAV exposure.
- The PRAC therefore recommended that a comparison with a suitable historical reference cohort of patients with previous HCC never treated with DAAV who have been followed for an appropriate length of time after HCC remission with periodic and adequate monitoring should be set up. Moreover, individual level data from this historical cohort would also allow adjusting for confounding factors based on patient characteristics and statistical adjustment of hazard ratios.
- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 60 days-assessment timetable will be applied.

7.1.2. Parathyroid hormone – NATPAR (CAP) - EMEA/H/C/PSP/S/0058

Applicant: Shire Pharmaceuticals Ireland

PRAC Rapporteur: Almath Spooner

Scope: PASS protocol for a registry for subjects with chronic hypoparathyroidism (PARADIGHM: physicians advancing disease knowledge in hypoparathyroidism)

Background

Natpar is a centrally authorised medicine containing parathyroid hormone that was granted a conditional marketing authorisation in April 2017 as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone. The authorisation is subject to a number of conditions which include conduct of a non-

interventional PASS in order to collect long-term data on the clinical efficacy and safety of Natpar based on data derived from a registry of patients with hypoparathyroidism.

The protocol (PAR-R13-001 amendment 2, 30 June 2017) for the PARADIGHM (a long-term, observational, prospective registry of patients with chronic hypoparathyroidism which will include patients being treated with Natpar and/or standard therapy) registry study was presented for review by the PRAC.

Endorsement/Refusal of the protocol

- The PRAC, having considered the protocol version PAR-R13-001 amendment 2, in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that the design of the study did not fulfil the study objective. A number of issues requiring further clarification (rationale, research question, methods, milestones, and plans for communicating the study results) should be addressed upon submission of a revised protocol.
- In particular, the PRAC recommended that additional details should be given with regard to planned comparative evaluations between Natpar (parathyroid hormone) treated/untreated cohorts and that the factors that will be considered in guiding plans around secondary analysis, including analytical plans to address confounding, should be provided.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[54]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[55]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[56]

See also Annex I 17.4.

7.4.1. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0204

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final registry report from C0168T71 study: a review and analysis of birth outcomes from Swedish, Danish and Finish medical birth registers and an evaluation of pregnancy data from multiple sources. As a consequence, section 4.6 of the SmPC is

[54] 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
[55] In accordance with Article 107p-q of Directive 2001/83/EC
[56] 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

updated. The Package Leaflet and the RMP (version 13.2) are updated accordingly. In addition, the MAH took the opportunity to bring the product in line with the latest QRD template and update the local representative section of the Package Leaflet

Background

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

The MAH for Remicade (infliximab) conducted a non-imposed PASS, a pregnancy registry study (C0168T71) to gather birth outcome data for infants born to mothers exposed to infliximab, including follow-up of infants up to 1 year after birth. The Rapporteur assessed the MAH's final C0168T71 study report for the review and analysis of birth outcomes from Swedish, Danish and Finish medical birth registers.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC considered that product information amendments[57] were warranted based on the current knowledge on the use of infliximab in pregnancy.

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

See Annex I 17.5.

7.6. Others

See also Annex I 17.6.

7.6.1. Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/MEA 019

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

Background

A review of direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free) (daclatasvir (Daklinza), dasabuvir (Exviera), ombitasvir/paritaprevir/ritonavir (Viekirax), simeprevir (Olysio), sofosbuvir (Sovaldi), sofosbuvir/ledipasvir (Harvoni)) was carried out in 2016 by the PRAC in a referral procedure

[57] Update of SmPC section 4.6. The package leaflet is not to be updated accordingly

under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1438) to assess the risk of hepatitis B virus (HBV) reactivation as well as the risk of unexpected early hepatocellular carcinoma (HCC) recurrence in patients treated with a DAAV and to establish whether any measures are necessary to minimise these risks. The benefit-risk balance of Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax was considered to remain favourable subject to amendments to the product information and to conditions. As a consequence, the RMP was amended including the addition of a category 3 prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without a history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV). For further background, see PRAC minutes December 2016.

The feasibility assessment for the category 3 cohort study was presented for review by the PRAC.

Discussion

The PRAC considered that none of the recently published studies provide meaningful evidence of a reduction of HCC incidence in DAAV treated patients compared to untreated patients or demonstrate a similar incidence compared to interferon (IFN)-containing regimens. In light of the submitted information, there is also no evidence that any of the 13 secondary data sources surveyed by the MAHs is a feasible data source to perform a retrospective study including DAAV-IFN-free treated patients. The data presented by the MAHs show that it is not possible to have a data source with all the relevant exposure cohorts (DAAV, IFN-containing and untreated) while with one of the data sources (CirVir[58]) historical reference cohorts of IFN-containing and untreated patients can be built. Although the feasibility assessment performed by the MAHs is incomplete, the PRAC considered that the NAVIGATORE[59] registry should be further analysed as this registry cannot be disregarded as a feasible data source for the study. In the current therapeutic scenario, the feasibility of the implementation of a new prospective study with recruitment of untreated cirrhotic patients as a comparator might be highly challenging, and impossible with recruitment of patients exposed to IFN-based regimens. Therefore, the use of appropriate historical cohorts is necessary. The PRAC emphasized that the CirVir cohort results are likely to be very valuable data source for this purpose.

Summary of advice

- The PRAC agreed that a prospective study would be preferable in this situation but considered it important that the feasibility and timelines for such study should be further explored. In relation to this, the PRAC supported establishing contact with the relevant French and Italian cohorts (HEPATHER[60] and NAVIGATORE) as well as CirVir in order to obtain additional data to be collected from the perspective of retrospective and prospective data collection.
- The MAHs should commit to explore other possibilities to address the question.

[58] ANRS CO12 CIRVIR - Prospective cohort involving patients with viral cirrhosis B and C, aiming at describing the natural history of hepatitis B virus (HBV) and/or hepatitis C virus (HCV) compensated cirrhosis
[59] NAVIGATORE web-platform: efficacy and safety of direct-acting antivirals (DAAV)-based oral therapy in a large cohort of hepatitis C virus (HCV) patients treated in clinical practice and monitored in Italy aiming at describing virological and clinical outcomes collected prospectively in all patients with chronic HCV treated with DAAVs in the Veneto region
[60] HEPATHER: therapeutic option for hepatitis B and C, a French cohort consisting of: 1) measuring the effectiveness of hepatitis C virus (HCV) or hepatitis B virus (HBV) treatments: virological response, seroconversion, loss of HBsAg (HBV surface antigen), liver fibrosis or clinical response (including quality of life), safety; 2) measuring prognostic factors of HCV or HBV infection: liver fibrosis, cirrhosis, clinical or biological event; 3) conducting biomarker studies: virological response, seroconversion, loss of HBsAg, liver fibrosis, clinical or biological event, safety; 4) conducting cost-effectiveness studies: cost per year of life saved (YLS), cost per quality-adjusted-life-year (QALY)

7.6.2. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 007

Applicant: AbbVie Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

See under 7.6.1.

7.6.3. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/MEA 004

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

See under 7.6.1.

7.6.4. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 017

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

See under 7.6.1.

7.6.5. Simeprevir - OLYSIO (CAP) - EMEA/H/C/002777/MEA 013

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No

726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

See under 7.6.1.

7.6.6. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 007

Applicant: AbbVie Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

See under 7.6.1.

7.6.7. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/MEA 024

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

See under 7.6.1.

7.6.8. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/MEA 008

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

See under 7.6.1.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 0

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

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 minutes.

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Darbepoetin alfa – ARANESP (CAP) - EMEA/H/C/000332/II/0143

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: PRAC consultation on a type II variation to update section 4.8 the SmPC in order to add a warning on injection site bruise and haemorrhage with frequency unknown and to provide additional instructions on the use of the device in the Package Leaflet following signal procedure EMEA/H/C000332/SDA/090 on cases of incorrect device use/ device malfunction

Background

Darbepoetin alfa is a recombinant glycoprotein hormone regulating erythropoiesis indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adults and paediatric patients and for the treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy. In January 2017, further to the assessment of a signal of incorrect device use associated with adverse reactions including underdose, drug dose omission, accidental exposure to product and injection site reactions (EMEA/H/C000332/SDA/090), the PRAC recommended the amendment of the product information of Aranesp (darbepoetin alfa) to reflect 'injection site bruising' and 'injection site haemorrhage' as undesirable effects as well as the revision of the user manual part of the package leaflet after further consideration of user testing results.

A type II variation proposing to update the product information of Aranesp (darbepoetin alfa) accordingly is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation. For further background, see PRAC minutes January 2017.

Summary of advice

- Based on the review of the available information, the PRAC endorsed the proposed changes to the product information[61] relating to inclusion of 'injection site bruising' and 'injection site haemorrhage' as undesirable effects with frequency unknown as well as the revision of the user manual part of the package leaflet as recommended within signal procedure EMEA/H/C000332/SDA/090.
- With regards to the need for additional risk minimisation activities, the PRAC was of the view that pen dummies are important to minimise the risk of handling failures and also emphasised the importance of adequate training of healthcare providers alongside dissemination of pen-dummies. PRAC also considered the possible need for national adaption regarding educational material and recommended that the key principles of educational material should be included in the RMP.

[61] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

- The key elements of any proposed educational material would need to be submitted for assessment in a revised RMP, which should also include clear description of the dissemination of the educational material. This could be done in the context of a separate variation procedure.

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

None

10.3. Other requests

None

10.4. Scientific advice

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

See also under Annex I 19.4.

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Moxifloxacin (NAP) - DE/H/xxxx/WS/387; DE/H/xxxx/WS/388

Applicant(s): Bayer AG (Avelox, Avalox)

PRAC Lead: Martin Huber

Scope: PRAC consultation on variation (DE/H/xxxx/WS/387) on uveitis and bilateral acute iris transillumination and on a variation (DE/H/xxxx/WS/388) on increased intracranial pressure (including benign intracranial hypertension) submitted at national level following conclusions of procedure PSUSA/00009231/201605 adopted in January 2017

Background

Moxifloxacin is a fluoroquinolone antibiotic indicated for the treatment of bacterial infections in adults susceptible to moxifloxacin (systemic use) as a second line treatment option. In January 2017, as an outcome of the PSUSA procedure for moxifloxacin-containing medicinal products for systemic use (PSUSA/00009231/201605), the PRAC recommended the product information update[62] to modify the warnings on hypersensitivity reactions to specify that moxifloxacin (systemic use) should be discontinued in case of clinical manifestations of severe hypersensitivity reactions and that patients under treatment with moxifloxacin should

[62] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation were transmitted to the CMDh for adoption of a position

be advised to inform their doctor prior to continuing treatment if they experience symptoms of neuropathy, in order to prevent the development of an irreversible condition; as well as to include vasculitis as an undesirable effect with a very rare frequency. Following the PSUSA procedure outcome, the MAH was requested to submit a cumulative review of all cases of uveitis and bilateral acute iris transillumination (BAIT) and associated terms associated with moxifloxacin (systemic use), as well as a cumulative review of increased intracranial pressure (including benign intracranial hypertension) in two stand-alone work-sharing variations within 90 days after the finalisation of the PSUSA procedure. For further background, see PRAC minutes January 2017 and CMDh minutes January 2017.

In the context of the evaluation of the two corresponding work-sharing type II variation procedures regarding the issues of uveitis and BAIT and increased intracranial pressure (including benign intracranial hypertension), Germany requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC expressed support for the scientific assessment of the data submitted and for the two lists of questions proposed by Germany to be answered by the MAH in the context of the two ongoing work-sharing variations.

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Brexit ancillary working group

PRAC lead: Almath Spooner

At the organisational matters teleconference on 14 September 2017, the chair of the PRAC ancillary working group on Brexit preparedness reported to PRAC from the third group meeting that took place on 21 July 2017 as well from the second cross-Committee EMA 'Working Group on Committees' operational preparedness for human medicines' meeting held on 4 September 2017.

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Advanced therapy medicinal products (ATMP) - Revision of procedural advice on the evaluation of ATMP in accordance with Article 8 of Regulation (EC) No 1394/2007

The procedural advice for advanced therapy medicinal products (ATMP) was originally adopted by CAT and CHMP for public consultation in March 2009 and has been in draft status since then. The document describes the procedure for evaluation of ATMPs for initial

marketing authorisation (principles to be applied also for post-authorisation procedures); it details the respective roles and responsibilities, and the interactions, of the committees involved in the assessment of ATMPs. The document originated prior to the creation of the PRAC and is currently being revised to better reflect the role of PRAC in the assessment of ATMPs, to take account of experience of marketing authorisation applications (MAAs) and to streamline the procedural aspects. The proposed updates were presented and discussed at the organisational matters teleconference held on 14 September 2017. After presentation to all committees, comments will be considered and a revised version will be presented for discussion and adoption by Committees in Q4 2017.

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. EMA reflection paper on extrapolation across age groups

PRAC lead: Jolanta Gulbinovič

As a follow-up to previous discussions on the EMA 'reflection paper on extrapolation of efficacy and safety in paediatric medicine development' (EMA/199678/2016) (see PRAC minutes March 2016 and PRAC minutes November 2016) and its public consultation, the EMA Secretariat reported to PRAC at the organisational matters teleconference held on 14 September 2017 on the updated reflection paper further to the comments received and the outcome of the 'Workshop on extrapolation of efficacy and safety in medicine development across age group' held on 17-18 May 2016 (EMA/478467/2016). The reflection paper will be adopted at the October 2017 PRAC meeting (scheduled on 25-29 September 2017) and published afterwards for public consultation.

12.4.2. Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) - update

At the organisational matters teleconference held on 14 September 2017, the PRAC was further updated on the SCOPE Joint Action project initiated by the European Commission (EC) following the implementation of the revised EU pharmacovigilance legislation in 2012 to support medicines regulators to collaboratively operate pharmacovigilance systems in accordance with the EU legislative requirements (see also PRAC minutes July 2016 and PRAC minutes November 2016). The SCOPE sustainability plan foresees maximising the impact of SCOPE by ensuring continuous access to the SCOPE deliverables by hosting and maintaining the training materials with the European Network Training Centre (EU-NTC) learning platform and via the Pharmacovigilance training curriculum. The PRAC welcomed the updates on the progress of SCOPE including the availability of the e-learning package about adverse drug reaction (ADR) reporting which was developed to support healthcare professionals and which received accreditation from the European Union of medical

specialists. The PRAC also noted the recent publication on risk communications[63], assessing current NCA safety communication practices and investigating European general practitioners (GP)'s awareness and preferences for safety communications on medicines. Any questions can be sent to the MHRA as coordinator of the project: scope@mhra.gsi.gov.uk.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan for 2017 - update

PRAC lead: June Raine

At the organisational matters teleconference held on 14 September 2017, the EMA Secretariat presented to PRAC a mid-year status update on the activities described in the PRAC work plan 2017.The PRAC will now initiate its work plan for 2018 taking into account the activities completed, progress made as well as priorities identified at the level of the Committee, EMA, HMA and EU network.

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

[63] de Vries, S.T., van der Sar, M.J.M., Cupelli, A. et al., On behalf of SCOPE Work Package 6. communication on safety of medicines in Europe: current practices and general practitioners' awareness and preferences. Drug Saf (2017) 40: 729. https://doi.org/10.1007/s40264-017-0535-0

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

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

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version September 2017 reflecting the PRAC's 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 of September 2017, the updated EURD list was adopted by the CHMP and CMDh at their September 2017 meetings and published on the EMA website on 25/09/2017, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 14 September 2017, the PRAC was updated on the outcome of the 29 August 2017 SMART Working Group (SMART WG) work stream WS1. Practical considerations regarding the electronic reaction monitoring report (eRMR) were discussed. Moreover, the SMART WG WS1 discussed the feedback from July

2017 PRAC meeting and the updated GVP module IX will be presented to PRAC for adoption at the October 2017 PRAC meeting (scheduled on 25-29 September 2017).

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 27/09/2017 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 - EudraVigilance auditable requirement project – update on going live

As agreed in June 2017 (see PRAC minutes June 2017) and July 2017 (see PRAC minutes July 2017), the EMA Secretariat provided PRAC at the organisational matters teleconference held on 14 September 2017 with further updates on the EudraVigilance auditable requirement project. In particular, the EMA Secretariat presented the EudraVigilance go-live strategy, which was endorsed by the PRAC. As part of the go-live strategy, a detailed go-live plan involving all national Competent Authorities in the EEA has been elaborated to deal with a planned downtime of 10 business days from 8 to 21 November 2017 and focusing on alternative arrangements for the reporting of suspected adverse reactions related to pharmacovigilance and clinical trials during this downtime. The plan has been prepared with involvement of the applicable expert groups and the IT Directors to allow for a smooth transition from the current to the new and enhanced EudraVigilance system. Failback procedures are already in place for urgent reporting and these are being reinforced and communicated to all involved parties over the coming weeks leading up to 22 November 2017.

Post-meeting note: the EudraVigilance go-live plan was also endorsed by the 'Heads of medicines agencies – Clinical trial facilitation group' (HMA CTFG) on 5 September 2017.

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 – Results[64] of PASS imposed in the marketing authorisation(s) for nationally approved products – proposal for PRAC involvement in assessing MAH(s)' request for submission delays

At the organisational matters teleconference held on 14 September 2017, the EMA Secretariat presented to PRAC a proposal to involve the Committee together with CMDh in assessing MAH(s)' requests to extend deadline(s) for submission of final results for non-interventional imposed PASS involving nationally approved products (NAPs) and performed in more than one Member State. The PRAC agreed that requests for submission deadline extension of imposed PASS results should be handled under Article 107(o) of Directive 2001/83/EC. Follow-up discussion will be scheduled in due course.

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

12.17.1. Renewals, conditional renewals, annual re-assessments and type II variations - update of assessment report templates

At the organisational matters teleconference held on 14 September 2017, the PRAC endorsed the updates to type II variation, 5-year renewal assessment report template, annual renewal assessment report template and annual re-assessment assessment report template that have also been updated/published on the EMA website along with the template for PRAC advice. Of

[64] In accordance with Article 107p of Directive 2001/83/EC

note, some changes have been introduced such as sub-templates, available on the EMA website, for risk management plan (RMP) assessment report sub-template for type II variations and periodic safety update reports (PSURs) and non-imposed post-authorisation safety study (PASS) final results assessment report sub-template for type II variations.

12.18. Risk communication and transparency

12.18.1. Good pharmacovigilance practice (GVP) Module XV on 'safety communication' – revision 1

PRAC lead: Amelia Cupelli, Sabine Straus

The PRAC Secretariat presented to PRAC revision 1 of GVP module XV on 'safety communication' following comments received during the public consultation as well as input from SCOPE work package 2 on communication and dissemination. Main changes were highlighted, in particular the updated section on 'communication materials from competent authorities targeted at healthcare professionals'. The document will be presented to PRAC for adoption at the October 2017 PRAC meeting (scheduled on 25-29 September 2017).

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

12.20.1. Good Pharmacovigilance Practices (GVP) - revised PRAC process for GVP modules in 2017 - update on GVP status overview

The PRAC was provided with an overview of the GVP module status, including an update on the ongoing or planned work on new or revised GVP modules together with their scope, proposed timelines for PRAC discussion and adoption.

12.20.2. Initial marketing authorisation(s) - update to CHMP rapporteur assessment report – due date in the first phase of initial marketing authorisation application (MAA)

At the organisational matters teleconference held on 14 September 2017, the PRAC was consulted on the potential need to change the timing of initial Rapporteur assessment

reports (ARs) in the first phase of initial MAAs. A further written procedure was organised and the PRAC was in favour of extending the due date of the PRAC Rapporteur's AR by three days in line with a similar change to the due of the CHMP Rapporteur's and co-Rapporteur's assessment reports (ARs).

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[65]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria under evaluation for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[66].

14.1.1. Cefalexin[67] (NAP)

Applicant(s): various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

EPITT 18911 – New signal

Lead Member State(s): ES

14.1.2. Dexmedetomidine – DEXDOR (CAP)

Applicant(s): Orion Corporation

PRAC Rapporteur: Julie Williams

Scope: Signal of polyuria

EPITT 18926 – New signal

Lead Member State(s): UK

14.1.3. Dulaglutide – TRULICITY (CAP)

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

[65] 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

[66] Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

[67] First-generation cephalosporin

PRAC Rapporteur: Carmela Macchiarulo

Scope: Signal of gastrointestinal stenosis and obstruction

EPITT 18931– New signal

Lead Member State(s): IT

14.1.4. Hydroxycarbamide – SIKLOS (CAP), NAP

Applicant(s): Addmedica, various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of cutaneous lupus erythematosus

EPITT 18939 – New signal

Lead Member State(s): BE

14.1.5. Ipilimumab – YERVOY (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Signal of histiocytosis haematophagic

EPITT 18929 – New signal

Lead Member State(s): NL

14.1.6. Pemetrexed – ALIMTA (CAP)

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

PRAC Rapporteur: Ghania Chamouni

Scope: Signal of nephrogenic diabetes insipidus

EPITT 18930 – New signal

Lead Member State(s): FR

14.1.7. Rivaroxaban – XARELTO (CAP); Azithromycin (NAP); clarithromycin (NAP); dirithromycin (NAP); erythromycin (NAP); flurithromycin (NAP); josamycin (NAP); midecamycin (NAP); miocamycin (NAP); oleandomycin (NAP); rokitamycin (NAP); roxithromycin (NAP); solithromycin (NAP); spiramycin (NAP); telithromycin – KETEK (CAP); troleandomycin (NAP)

Applicant(s): Aventis Pharma S.A. (Ketek), Bayer AG (Xarelto), various

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of increased risk of bleeding following drug interaction between rivaroxaban and macrolide antibiotics

EPITT 18934 – New signal

Lead Member State(s): FI, HU, IE, IT, SE

14.2. New signals detected from other sources

14.2.1. Megestrol (NAP); Vitamin K antagonists: acenocoumarol (NAP); fluindione (NAP); phenindione (NAP); phenprocoumon (NAP); warfarin (NAP)

Applicant(s): various

PRAC Rapporteur: Almath Spooner

Scope: Signal of drug interaction leading to elevated international normalised ratio (INR)/haemorrhage with megestrol and vitamin K antagonists

EPITT 18910 – New signal

Lead Member State(s): BG, IE

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Darunavir - EMEA/H/C/004273

Scope: Treatment of human immunodeficiency virus type 1 (HIV-1) infection

15.1.2. Fulvestrant - EMEA/H/C/004649

Scope: Treatment of breast cancer

15.1.3. Imatinib - EMEA/H/C/004748

Scope: Treatment of newly diagnosed and chronic Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML), gastrointestinal stromal tumours (GIST), unresectable dermatofibrosarcoma protuberans (DFSP) and recurrent and/or metastatic DFSP

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

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

15.2.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0030

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Update of the RMP (version 7.0) in order to reflect changes requested in the conclusion of the PSUSA procedure (PSUSA/00010077/201603) finalised in November 2016 and LEG reviewing cases of pancreatitis as well as the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442). In addition, the RMP is updated to reflect labelling changes resulting from a variation procedure to add information on fatal diabetic ketoacidosis (DKA) cases to the existing DKA warning and following the referral procedure under Article 31 of Directive 2001/83/EC reviewing metformin-containing medicines completed in October 2016 (EMEA/H/A-31/1432)

15.2.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0031

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 7.0) in order to reflect changes requested in the outcome of the PSUSA procedure (PSUSA/00010077/201603) finalised in November 2016 and LEG reviewing cases of pancreatitis as well as the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442). In addition, the RMP is updated to reflect labelling changes resulting from a variation procedure to add information on fatal diabetic ketoacidosis (DKA) cases to the existing DKA warning and following the referral procedure under Article 31 of Directive 2001/83/EC reviewing metformin-containing medicines completed in October 2016 (EMEA/H/A-31/1432)

15.2.3. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0054

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 25) in order to reflect that cataract is no longer considered as a potential risk associated with denosumab therapy, following the recent completion of study 20080560 (a phase 3, randomised, double-blind, placebo-controlled study to evaluate new or worsening lens opacifications in subjects with non-metastatic prostate cancer receiving denosumab for bone loss due to androgen deprivation therapy) where results showed no difference between the risk of developing cataracts in the denosumab and placebo groups

15.2.4. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/II/0024, Orphan

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMP (version 3.1) in order to submit protocol amendments of SHP617-400 (EU-AIR) study: a European multicentre, multi-country, post-authorisation, observation study (registry) of patients with chronic adrenal insufficiency (category 3). In addition, the MAH took the opportunity to implement a change agreed by the PRAC/CHMP as part of the assessment of MEA 005.3 dated July 2016 to remove from the RMP reference to study SHP617-404 (SWE-DUS): a category 3 study to monitor off-label use of Plenadren to evaluate physician prescribing patterns

15.2.5. Insulin human - ACTRAPHANE (CAP) - EMEA/H/C/000427/WS1197/0072; ACTRAPID (CAP) - EMEA/H/C/000424/WS1197/0066; INSULATARD (CAP) - EMEA/H/C/000441/WS1197/0069; MIXTARD (CAP) - EMEA/H/C/000428/WS1197/0073; PROTAPHANE (CAP) - EMEA/H/C/000442/WS1197/0068

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 2.1) in line with the Guidance on format of the RMP in the EU (revision 2). Moreover, significant changes to the safety specification are proposed with this RMP update as some risks are now considered fully characterised and appropriately managed: 1) removal of the following important identified risks: hypoglycaemia, anaphylactic reactions, peripheral neuropathy, refraction disorders, lipodystrophy, urticaria, rash, oedema and diabetic retinopathy; 2) removal of the following important potential risks: immunogenicity, allergic reactions and lack of efficacy related to the new NN729 manufacturing process; and 3) Removal of the following missing information: special patient groups

15.2.6. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0049

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Update of the RMP (version 17) in order to amend the study objectives and milestones for two studies: 1) study CA184332 (a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab (Yervoy) as first line therapy in a community setting, a category 3 study in the RMP (MEA 029): to submit the final study report with 2-years of follow-up); 2) study CA184338 (a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab (Yervoy) as first line therapy, a category 3 study in the RMP (MEA 030): to submit the final study report with 4-years of follow-up)

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

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

15.3.1. Albiglutide - EPERZAN (CAP) - EMEA/H/C/002735/II/0033

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

Scope: Update of the Package Leaflet in order to amend the layout and content of the instructions for use (IFU) for Eperzan (albiglutide). In addition, the RMP (version 8) is updated to implement additional pharmacovigilance and risk minimisation activities addressing the safety concern of 'medication errors/device issue potentially leading to lack of efficacy or inadequate diabetes control'.

15.3.2. Aliskiren - RASILEZ (CAP) - EMEA/H/C/000780/WS1026/0110; aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/WS1026/0080

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of section 5.1 of the SmPC in order to reflect the results of study SPP100F2301 (ATMOSPHERE): a multicentre, randomised, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of both aliskiren monotherapy and aliskiren/enalapril combination therapy compared to enalapril monotherapy, on morbidity and mortality in patients with chronic heart failure (New York Heart Association (NYHA) Class II-IV). The RMP (version 13) is updated accordingly

15.3.3. Atazanavir, atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/II/0111

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: Update of sections 4.4 and 4.8 of the SmPC to add a warning on chronic kidney disease (CKD) observed in human immunodeficiency virus (HIV) infected patients during treatment with atazanavir (with or without ritonavir). This update is based on a review of the MAH safety database, a cohort study of patients with laboratory values from a large US administrative claims database and a review of published scientific literature. The Package Leaflet and the RMP (version 12.0) are updated accordingly

15.3.4. Avanafil - SPEDRA (CAP) - EMEA/H/C/002581/II/0027/G

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variation consisting of: 1) update of section 4.4 to reflect the results of clinical study TA-402: a double-blind, randomised, placebo-controlled, single-dose, parallel study to assess the effects of avanafil on multiple parameters of vision, including, but not limited to visual acuity, intraocular pressure, pupillometry, and colour vision discrimination, in healthy male subjects; 2) update of section 4.6 of the SmPC in order to reflect the results of clinical study TA-401: a randomised, double-blind, placebo-controlled, parallel group, multicentre clinical trial of the effect of avanafil on spermatogenesis in healthy adult males and adult males with mild erectile dysfunction. The Package Leaflet and the RMP (version

5.1) are updated accordingly. In addition, the MAH took the opportunity to make an editorial correction on the approved SmPC by adding the missing adverse reaction epistaxis from the tabulated list of adverse reactions reported in section 4.8. Additionally, the MAH took the opportunity to align the information of Package Leaflet section 3 to SmPC section 4.2

15.3.5. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0002

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.5 and 5.2 of the SmPC, based on the final study report of an in vitro study investigating the inhibitory effect of baricitinib on the organic anion transporter 2 (OAT2) in fulfilment of MEA 001. The RMP (version 3.0) is updated accordingly

15.3.6. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0045

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information on the risk of venous thrombosis of the renal allograft when anti-thymocyte globulin (ATG) and belatacept are coadministered (at the same or nearly the same time) in patients with other predisposing risk factors for thrombosis. The update is based on a review of the potential increased risk for allograft thrombosis with belatacept given in close temporal relation to anti-thymocyte globulin (rabbit), as requested in the conclusion of the last PSUSA procedure (PSUSA/00000311/201606) finalised in January 2017. In addition, the MAH took the opportunity to update section 6 of the SmPC and the 'information for healthcare professionals (HCPs)' in the Package Leaflet (PL) with additional safety instructions for the co-administration of belatacept with anti-thymocyte globulin (rabbit). This variation fulfils LEG 021. The RMP (version 14) is updated accordingly

15.3.7. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/X/0046/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) line extension to introduce a new pharmaceutical form (solution for injection), a new strength (200 mg) and a new route of administration (subcutaneous use); 2) update of sections 4.2, 4.8, 5.1 and 5.2 for the authorised presentations (Benlysta powder for concentrate for solution for infusion) as a consequence of the data package submitted to support the new proposed solution for injection subcutaneous. The RMP (version 21) is updated accordingly

15.3.8. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0049, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with data from study C25002: a phase 1/2, non-randomised single arm study of brentuximab vedotin (SGN-35) in paediatric patients with relapsed or refractory systemic anaplastic large cell lymphoma or Hodgkin lymphoma (listed in the agreed paediatric investigation plan (PIP) covering the conditions of Hodgkin lymphoma and anaplastic large cell lymphoma for Adcetris (EMEA-000980-PIP01-10-M04)). The RMP (version 11.0) is updated accordingly

15.3.9. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0002/G

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.1 of the SmPC to reflect the final study results from clinical study XL184-308: a phase 3, randomised, controlled study of cabozantinib (XL184) *vs* everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior vascular endothelial growth factor (VEGFR) tyrosine kinase inhibitor therapy, to fulfil the condition to the marketing authorisation listed as a post-authorisation efficacy study (PAES) in Annex II. The RMP (version 2.0) is updated accordingly

15.3.10. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0060

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to update the information on pregnancy and lactation based on two pharmacokinetic (PK) studies evaluating the transfer of Cimzia into breastmilk (UP0016 study: a multicentre, post-marketing study to evaluate the concentration of certolizumab pegol in the breast milk of mothers receiving treatment with Cimzia phase 1B (clinical pharmacology) study) and via the placenta (UP0017 study: a multicentre post-marketing study to evaluate the placental transfer of certolizumab pegol in pregnant women receiving treatment with Cimzia). The Package Leaflet and the RMP (version 12) are updated accordingly

15.3.11. Daptomycin - CUBICIN (CAP) - EMEA/H/C/000637/II/0061

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to extend the *S. aureus* bacteraemia indication to include paediatric patients 1 to 17 years of age. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet, Labelling and the RMP (version 10.0) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10) and to combine the SmPCs for both strengths (350 and 500 mg)

15.3.12. Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/X/0056/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Grouped application consisting of: 1) extension application (line extension) to introduce a new pharmaceutical form (powder for oral suspension) associated with a new strength (10 mg/ml); 2) extension of indication to include the treatment of children and adolescents aged 1 year to 18 years with Ph+ chronic phase in chronic myeloid leukaemia (CML). 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 add the new indication and its relevant posology, to add a warning on effects on growth and development in the paediatric population and to update the safety information. The Package Leaflet and the RMP (version 15.0) are updated accordingly

15.3.13. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0069

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 as cataract is no longer considered as a potential risk and/or adverse reaction associated with denosumab therapy following the completion of study 20080560: a phase 3, multicentre, randomised, double-blind, placebo-controlled study in men to evaluate new or worsening lens opacifications in subjects with non-metastatic prostate cancer receiving denosumab for bone loss due to androgen deprivation therapy and progression study using a slit-lamp-based evaluation system (lens opacities classification system III (LOCS III)). The Package Leaflet is updated accordingly. In addition, the RMP (version 20.0) is updated to remove the important potential risk of 'cataract in men with prostate cancer receiving androgen deprivation therapy'

15.3.14. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0098, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.6 and 5.3 of the SmPC in order to update the safety information related to pregnancy, lactation and fertility following the review of data in PSUR#13 and PSUR#14. Annex II, the Package Leaflet and the RMP (version 17) are updated accordingly

15.3.15. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/II/0013, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 4.8 of the SmPC in order to amend the safety information based on the analysis of adverse events from the following clinical trials: GZGD00304 (a phase 2, open-Label, multicentre study evaluating the efficacy, safety and pharmacokinetics of eliglustat (Genz-112638) in Gaucher type 1 patients), GZGD02507 (a phase 3, randomised, double-blind, placebo-controlled, multicentre study confirming the efficacy and safety of Genz-112638 in patients with Gaucher disease type 1 (ENGAGE)), GZGD02607 (a phase 3, randomised, multicentre, multinational, open-label, active comparator study to evaluate the efficacy and safety of Genz-112638 in patients with Gaucher disease type 1 who have

reached therapeutic goals with enzyme replacement therapy (ENCORE)) and GZGD03109 (a phase 3, randomised, multicentre, multinational, double-blind study to evaluate the efficacy, safety and pharmacokinetics of once daily versus twice daily dosing of Genz-112638 in patients with Gaucher disease type 1 who have demonstrated clinical stability on a twice daily dose of Genz-112638 (EDGE)) to address post-authorisation MEA 011.1 included in the current approved RMP. The Labelling is updated in order to reflect the instructions for use for the sleeve of the intermediate packaging of the single blister. The RMP (version 4.0) is updated accordingly

15.3.16. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/II/0079

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include the treatment of human immunodeficiency virus type 1 (HIV-1) infected adolescents, with nucleoside reverse transcriptase inhibitors (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years and weighing ≥ 35 kg. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on results from study GS-US-236-0112 (a phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity through 48 weeks of treatment with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naive adolescents). The Package Leaflet and the RMP (version 12) are updated accordingly. In addition, the MAH took the opportunity to introduce minor linguistic amendments to the Product Information

15.3.17. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0135

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include pre-exposure prophylaxis of human immunodeficiency virus (HIV) infection in adolescents aged 12 to <18 years at high risk. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on extrapolation of data for emtricitabine, tenofovir disoproxil fumarate, and Truvada in HIV-infected and uninfected subjects. The Package Leaflet and the RMP (version 15) are updated accordingly. In addition, the MAH took the opportunity to introduce minor linguistic amendments to the Product Information

15.3.18. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0017/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped variation consisting of an extension of indication to include the reduction of atherosclerotic cardiovascular disease risk in adults with high cardiovascular risk based on the results from study 20110118: a double-blind, randomised, placebo-controlled, multicentre study assessing the impact of additional low-density lipoprotein (LDL)-cholesterol reduction on major cardiovascular events when evolocumab (AMG 145) is used

in combination with statin therapy in patients with clinically evident cardiovascular disease (category 3 pharmacovigilance activity in the RMP, MEA 004). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update section 5.1 of the SmPC to include important mechanistic information for healthcare professionals based on study 20120153 (a double-blind, randomised, multicentre, placebo-controlled, parallel group study to determine the effects of evolocumab (AMG 145) treatment on stherosclerotic disease burden as measured by intravascular ultrasound in subjects undergoing coronary catheterisation, a category 3 pharmacovigilance activity, MEA 006). The RMP (version 2.0) is also updated in order to add two category 3 studies in the RMP (study 20160250: a multicentre, open-label, single-arm, extension study to assess long-term safety of evolocumab therapy in subjects with clinically evident cardiovascular disease in selected European countries and study 20150338: a multicentre, controlled, open-label extension (OLE) study to assess the long-term safety and efficacy of evolocumab (AMG 145)) as well as to update the milestones of five category 3 studies (study 20110110: multicentre, controlled, OLE study to assess the long-term safety and efficacy of evolocumab; study 20110271: multicentre, open-label study to assess the long-term safety, tolerability, and efficacy of evolocumab on low-density lipoprotein cholesterol (LDL-C) in subjects with severe familial hypercholesterolaemia (including homozygous familial hypercholesterolemia (HoFH)); study 20120138: a multicentre, controlled, OLE study to assess the long-term safety and efficacy of evolocumab; study 20130286: a double blind, randomised, placebo controlled, multicentre study to evaluate safety, tolerability, and efficacy on LDL-C of evolocumab in human immunodeficiency virus (HIV) positive patients with hyperlipidemia and mixed dyslipidemia; and study 20130295: a multicentre, OLE study to assess long-term safety and efficacy of evolocumab therapy in patients with clinically evident cardiovascular disease (FOURIER-OLE))

15.3.19. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0045

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include treatment in combination with basal insulin for Bydureon. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on study D5553C00002: a multicentre, randomised, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the safety and efficacy of once weekly exenatide therapy added to titrated basal insulin glargine compared to placebo added to titrated basal insulin glargine in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control on basal insulin glargine with or without metformin (Duration 7). The Package Leaflet and the RMP (version 25) are updated accordingly. In addition, the MAH took the opportunity to make minor corrections in sections 4.8 and 5.1 of the SmPC

15.3.20. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0085

Applicant: GSK Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of study EPI-HPV-069: a meta-analysis assessing the risk of three

autoimmune diseases following vaccination with Cervarix: autoimmune thyroiditis (AIT), Guillain-Barre syndrome (GBS) and inflammatory bowel disease (IBD). The RMP (version 18) is updated accordingly and includes minor updates related to other studies

15.3.21. Icatibant - FIRAZYR (CAP) - EMEA/H/C/000899/II/0034/G, Orphan

Applicant: Shire Orphan Therapies GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variation including: 1) extension of indication to include adolescents and children over 2 years old for the use of Firazyr for symptomatic treatment of acute attacks of hereditary angioedema. As a consequence, section 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6. of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to reflect the results of a juvenile toxicity study in SmPC section 5.3; 2) update section 5.2 of the SmPC to reflect the effect of age (elderly), gender and race on pharmacokinetics of icatibant. The Package Leaflet and the RMP (version 6.0) are updated accordingly. All relevant pharmacokinetics studies have been previously assessed, as part of prior submissions

15.3.22. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0003, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include treatment of patients with Duchenne muscular dystrophy in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids. The RMP (version 2.0) is updated accordingly

15.3.23. Insulin degludec - TRESIBA (CAP) - EMEA/H/C/002498/II/0028

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 5.1 of the SmPC based on new clinical data from a cardiovascular outcome trial EX1250-4080 (DEVOTE): a randomised, double-blind and event-driven clinical study with a median duration of 2 years comparing the cardiovascular safety of Tresiba (insulin degludec) versus insulin glargine (100 units/mL) in patients with type 2 diabetes mellitus (T2DM) at high risk of cardiovascular events. The RMP (version 8) is updated accordingly

15.3.24. Insulin glargine - ABASAGLAR (CAP) - EMEA/H/C/002835/II/0014

Applicant: Eli Lilly Regional Operations GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Submission of the final report from study I4L-MC-ABER (ABER): 'a prospective, randomised, open-label comparison of long-acting basal insulin analog Abasaglar (LY2963016) to the reference product (Lantus (insulin glargine)) in adult patients with type 2 diabetes mellitus (T2DM): the ELEMENT 5 study' conducted in non-European countries.

This study replaces the cancelled studies initially planned to be conducted in China and other countries. The RMP (version 1.6) is updated accordingly

15.3.25. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/WS1158/0154/G; LIPROLOG (CAP) - EMEA/H/C/000393/WS1158/0117/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Grouped worksharing variation including: 1) addition of a pre-filled pen: Humalog and Liprolog 100 U/mL Junior KwikPen to administer insulin in half unit increments and containing insulin lispro 3mL cartridge already approved for use; 2) addition of a new pack size of 10 (2x5) pre-filled pens (multipack) for Humalog and Liprolog 100 U/ml Junior KwikPen, including insulin lispro 3mL cartridge already approved for use.; 3) update of sections 4.2 and 4.4 of the SmPC of the already authorised 100 U/mL Humalog and Liprolog presentations to include the paediatric population. The Package Leaflet and the RMP (version 8.0) are updated accordingly

15.3.26. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0042

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC to reflect the final results of study CA184-169: a randomised double-blind phase III study of ipilimumab administered at 3 mg/kg versus at 10 mg/kg in subjects previously treated or untreated with unresectable or metastatic melanoma, in order to fulfil ANX 014.1. The MAH also provided with this variation application efficacy and safety data from study CA184-169 in two subgroups: female ≥ 50 years of age and with brain metastases in order to fulfil MEA 015.1. Annex II.D and the RMP (version 14.0) are updated accordingly. In addition the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to include some editorial changes and correct some typos throughout the product information, and to bring the product information in line with the latest QRD template (version 10)

15.3.27. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0044

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in children and adolescents 12 years of age and older. 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 and the RMP (version 15) are updated accordingly

15.3.28. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0047/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Grouped variations consisting of: 1) update of section 4.4 to revise the current warning on concurrent administration with vemurafenib to enhance awareness on the potential of hypersensitivity reactions when ipilimumab is used sequentially with vemurafenib as requested by the PRAC following the assessment of PSUSA/00009200/201603 completed in October 2016; 2) update of section 4.8 of the SmPC to amend the frequency of the adverse drug reaction (ADR) 'Vogt-Konyanagi-Haranda syndrome' from 'not know' to 'very rare'. The RMP (version 16) is updated accordingly. In addition, the MAH took the opportunity to implement some editorial changes to sections 4.2 and 4.4 of the SmPC to update the dose modification information for hepatotoxicity management guidelines in line with the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) recommendations (version 4)

15.3.29. Ivabradine - CORLENTOR (CAP) - EMEA/H/C/000598/WS1180/0047; IVABRADINE ANPHARM (CAP) - EMEA/H/C/004187/WS1180/0006; PROCORALAN (CAP) - EMEA/H/C/000597/WS1180/0046

Applicants: Anpharm Przedsiebiorstwo Farmaceutyczne (Ivabradine Anpharm), Les Laboratoires Servier (Corlentor, Procorolan)

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC with new adverse drug reactions (ADRs): ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. The Package Leaflet and the RMP (version 6) are updated accordingly. In addition, the MAH took the opportunity to align the Product Information in line with the latest QRD template (version 10.0)

15.3.30. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/II/0009

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include alone or in combination with conventional disease-modifying anti-rheumatic drug (cDMARD) the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARD therapies. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated to reflect the new safety and efficacy information. The Package Leaflet and the RMP (version 5) are updated accordingly

15.3.31. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0044/G, Orphan

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.4 of the SmPC in order to amend the warning regarding antibody response to injected insulin-like growth factor 1 (IGF-1). The RMP (version 9) is updated accordingly, including changes to the educational materials and changes to the instructions for antibody testing

15.3.32. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0017

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from phase 1 study NaltrexBuprop-1001 (TQT) to evaluate the potential effect of naltrexone/bupropion extended-release combination on cardiac repolarisation in healthy subjects. The RMP (version 10) is updated to include study NaltrexBuprop-1001 and additional studies recently completed (NB-CVOT (a multicentre, randomised, double-blind, placebo-controlled study assessing the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects with cardiovascular risk factors receiving naltrexone sustained release (SR)/bupropion SR), NaltrexBuprop-4001 (a multicentre, randomised, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone hydrochloride and bupropion hydrochloride extended release (ER) combination on the occurrence of MACE in overweight and obese subjects with cardiovascular disease), NaltrexBuprop-1004 (a phase 1, open-label, sequential design study to evaluate the potential effect of multiple oral doses of ER combination of naltrexone and bupropion on the pharmacokinetics (PK) of a single oral dose of metformin in healthy subjects) and NB-404 (a multicentre, randomised, open-label, controlled, method-of-use study assessing the effect of naltrexone SR/bupropion SR on body weight and cardiovascular risk factors in overweight and obese subjects (the Ignite study)). The MAH also took the opportunity to update the RMP to include references to the PASS protocols currently under discussion at PRAC

15.3.33. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0032

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to add administration guidance and update the safety information based on final results from imposed PAES CA209067: an interventional, randomised, double-blind study in subjects treated with nivolumab monotherapy, ipilimumab monotherapy and nivolumab combined with ipilimumab. Annex II, the Package Leaflet and the RMP (version 5.8) are updated accordingly. This submission fulfils ANX 016. In addition, the MAH took the opportunity to introduce minor editorial and formatting revisions in the Product Information

15.3.34. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0036/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.2, 5.1, 5.2 and 6.6 of the SmPC in order to introduce new dosing regimens and schedule; 2) update of sections 4.2, 5.1, 5.2 and 6.6 of the SmPC in order to introduce a change in the infusion time from 60 minutes to 30 minutes. These changes are based on interim results from study CA209153: a phase IIIb/IV safety trial of nivolumab in subjects with advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed during or after receiving at least one prior systemic regimen. The Package Leaflet and the RMP (version 10.0) are updated accordingly

15.3.35. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0038

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.8 of the SmPC with longer follow-up for subjects proceeding to allogeneic transplant following nivolumab treatment and update of section 5.1 of the SmPC with efficacy data from longer follow-up based on final results from study CA209205 (listed as a post-authorisation efficacy study (PAES) in Annex II): a phase 2, non-comparative, multi-cohort, single-arm, open-label study of nivolumab (BMS-936558) in classical Hodgkin lymphoma (cHL) subjects after failure of autologous stem cell transplant (ASCT). Annex II is updated to remove the commitment. The RMP (version 7.5) is updated accordingly

15.3.36. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/X/0016/G, Orphan

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Grouped application consisting of: 1) extension application (line extension) to add a new pharmaceutical form (film-coated tablets) associated with a new strength (100 mg and 150 mg); 2) Alignment of the Product Information (PI) for the approved capsule presentation with the PI proposed for the tablet presentation. The RMP (version 15) is updated accordingly

15.3.37. Palbociclib - IBRANCE (CAP) - EMEA/H/C/003853/II/0007

Applicant: Pfizer Limited

PRAC Rapporteur: Torbjorn Callreus

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC to reflect the results of study A5481013: a phase 1, open-label, single dose 75 mg palbociclib), parallel-cohort study to evaluate the pharmacokinetics of palbociclib in subjects with impaired hepatic function, and study A5481014: a phase 1, open-label, single dose (125 mg palbociclib), parallel-group study to evaluate the pharmacokinetics of palbociclib in subjects with impaired renal function. The RMP (version 1.4) is updated accordingly

15.3.38. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/II/0004/G, Orphan

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations to update sections 4.4, 4.5, 4.6 and 5.2 of the SmPC based on the final clinical study report (CSR) of study P15-02 assessing the mass balance recovery, metabolite profile and metabolite identification of [^{14}C] pitolisant at steady state conditions, in healthy cytochrome P450 2D6 (CYP2D6) phenotyped subjects, study P14-07 evaluating the pharmacokinetic interaction of pitolisant with sodium oxybate and modafinil in healthy male volunteers and study P15-15 evaluating the pharmacokinetic (PK) interaction of pitolisant with cytochrome P450 3A4 (CYP3A4) substrates (midazolam), cytochrome P450 2B6 (CYP2B6) substrates (bupropion), UDP-Glucuronosyltransferase-2B7 (UGT2B7)

inhibitors (probenecide)) in fulfilment of PAM (MEA 02, 03 and 04). The Package Leaflet and the RMP (version 5.0) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial change in section 4.8 of the SmPC

15.3.39. Plerixafor - MOZOBIL (CAP) - EMEA/H/C/001030/II/0032, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to reflect the results of the completed study MSC12830 (MOZ11809): a phase 4, multicentre, randomised, comparator trial evaluating the standard weight-based dose (0.24 mg/kg) compared to a fixed dose (20 mg) of plerixafor injection in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize and collect ≥5 x 10^6 $CD34^+$ cells/kg in ≤4 days and to evaluate the difference in total systemic exposure in patients with non-Hodgkin's lymphoma weighing ≤70 kg' listed as a category 3 study in the RMP. The Package Leaflet and the RMP (version 9.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.40. Rasagiline - AZILECT (CAP) - EMEA/H/C/000574/WS1168/0077; RASAGILINE RATIOPHARM (CAP) - EMEA/H/C/003957/WS1168/0010

Applicant: Teva B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.4, 4.7 and 4.8 to include a new warning on excessive daytime sleepiness and sudden sleep onset episodes as well as update of section 4.9 to remove 'dysphoria' as a symptom reported following overdose of rasagiline based on a company core data sheet (CCDS) update. The Package Leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to make editorial changes throughout the Product Information to correct the invented name for Rasagiline Ratiopharm in the Czech annexes and to bring the Product Information (PI) in line with the latest QRD template (version 10)

15.3.41. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0052/G

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations consisting of: 1) addition to the authorised indications: treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults, to Xarelto 10 mg. The RMP (version 10) is updated accordingly; 2) change in pack sizes of the finished product: change in the number of units in a pack; 3) change in immediate packaging of the finished product: change in type of container or addition of a new container- solid, semi-solid and non-sterile liquid pharmaceutical forms; 4) addition of information on interactions with selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) in

section 4.5 and a related warning in section 4.4 of the SmPC. In addition, MedDRA[68] terminology is updated in the adverse drug reactions; 5) deletion of 'patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery' and 'remedial pro-coagulant therapy for excessive haemorrhage' from the summary of safety concerns

15.3.42. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0060/G, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variation consisting of: 1) extension of indication to include the paediatric population for the use in the paediatric chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients from 1 year of age and older. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 6.5, 6.6 and 8 of the SmPC are updated accordingly. The RMP (version 18) is updated accordingly. Furthermore, the Product information is brought in line with the latest QRD template (version 10); 2) addition of a low-dose romiplostim 125 microgram vial presentation for powder for solution for injection (4 vials pack); 3) addition of a 1 vial pack size of a low-dose romiplostim 125 microgram presentation

15.3.43. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/X/0020

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application (line extension) to add new strengths of 2500 IU, 3000 IU, 4000 IU for Nuwiq, powder and solvent for solution for injection. The RMP (version 5.4) is updated accordingly

15.3.44. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/II/0017/G

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variation consisting of an update of sections 4.2, 4.8 and 5.1 of the SmPC to reflect available data from previously untreated patients (PUP) based on the interim report of interventional GENA-05 study: an immunogenicity, efficacy and safety of treatment with human cell line-derived recombinant factor VIII (human-cl-rhFVIII) in previously untreated patients with severe haemophilia A. The Package Leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the Product Information throughout to bring it in line with the core Summary of Product Characteristics for human plasma-derived and recombinant coagulation factor VIII products (EMA/CHMP/BPWP/1619/1999 rev. 2) and with the latest QRD template (version 10). Moreover, the MAH proposed to combine the SmPC for all strengths and to update Annex A with detailed information on the packaging

[68] Medical Dictionary for Regulatory Activities

15.3.45. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/WS1211/0059; RISTABEN (CAP) - EMEA/H/C/001234/WS1211/0051; TESAVEL (CAP) - EMEA/H/C/000910/WS1211/0059; XELEVIA (CAP) - EMEA/H/C/000762/WS1211/0063

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to modify the information on dosing, an existing warning and administration instructions, respectively for use of sitagliptin in patients with type 2 diabetes mellitus (T2DM) and renal impairment. The RMP (version 8) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet for Tesavel and to bring the product information in line with the latest QRD template (version 10). Minor editorial changes are also introduced in the Product Information

15.3.46. Sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/WS1212/0085/G; JANUMET (CAP) - EMEA/H/C/000861/WS1212/0085/G; RISTFOR (CAP) - EMEA/H/C/001235/WS1212/0072/G; VELMETIA (CAP) - EMEA/H/C/000862/WS1212/0088/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2. and 5.2 of the SmPC in order to modify the information on dosing, and administration instructions respectively for use of sitagliptin/metformin in patients with type 2 diabetes mellitus (T2DM) and moderate renal impairment. The RMP (version 8) is updated accordingly. In addition, section 4.5 of the SmPC is updated to include information on the concomitant use of ranolazine, vandetanib, dolutegravir and cimetidine. Furthermore, the MAH took the opportunity to update the list of local representatives in the Package Leaflet for Efficib and to bring the product information (PI) in line with the latest QRD template (version 10). Minor editorial changes are also introduced in the Product Information

16. ANNEX I - Periodic safety update reports (PSURs)

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

16.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only

16.1.1. Agomelatine - THYMANAX (CAP); VALDOXAN (CAP) - PSUSA/00000071/201702

Applicants: Servier (Ireland) Industries Ltd. (Thymanax), Les Laboratoires Servier (Valdoxan)

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

16.1.2. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201701

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.3. Asparaginase[69] - SPECTRILA (CAP) - PSUSA/00010445/201701

Applicant: Medac Gesellschaft fur klinische Spezialpraparate mbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.4. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/201701

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.5. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/201701 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.1.6. Axitinib - INLYTA (CAP) - PSUSA/00010022/201701

Applicant: Pfizer Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

[69] Centrally authorised product only

16.1.7. Besilesomab - SCINTIMUN (CAP) - PSUSA/00000385/201701 (with RMP)

Applicant: Cis Bio International

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.8. Birch bark extract - EPISALVAN (CAP) - PSUSA/00010446/201701

Applicant: Birken AG

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.9. Brimonidine[70] - MIRVASO (CAP) - PSUSA/00010093/201702 (with RMP)

Applicant: Galderma International

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.10. Brivaracetam - BRIVIACT (CAP) - PSUSA/00010447/201701

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.11. Colistimethate sodium[71] - COLOBREATHE (CAP) - PSUSA/00009112/201702

Applicant: Teva B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.12. Dapagliflozin, metformin - EBYMECT (CAP); XIGDUO (CAP) - PSUSA/00010294/201701 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[70] Centrally authorised product only
[71] Dry inhalation powder only

16.1.13. Dolutegravir - TIVICAY (CAP); dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - PSUSA/00010075/201701

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.14. Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/201701

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.15. Elosulfase alfa - VIMIZIM (CAP) - PSUSA/00010218/201702

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.16. Eptifibatide - INTEGRILIN (CAP) - PSUSA/00001246/201701

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.1.17. Etanercept - ENBREL (CAP) - PSUSA/00001295/201702

Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.18. Etanercept - BENEPALI (CAP) - PSUSA/00010452/201701

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.19. Evolocumab - REPATHA (CAP) - PSUSA/00010405/201701

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.20. Fampridine - FAMPYRA (CAP) - PSUSA/00001352/201701

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.21. Gadoversetamide - OPTIMARK[72] - PSUSA/00001508/201701

Applicant: Guerbet

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.22. Infliximab[73] - FLIXABI (CAP); INFLECTRA (CAP); REMSIMA (CAP) - PSUSA/00010106/201701

Applicants: Samsung Bioepis UK Limited (SBUK) (Flixabi), Hospira UK Limited (Inflectra), Celltrion Healthcare Hungary Kft. (Remsima)

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.23. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201701

Applicant: Leo Laboratories Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.24. Ivacaftor - KALYDECO (CAP) - PSUSA/00009204/201701

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.25. Lenvatinib - KISPLYX (CAP); LENVIMA (CAP) - PSUSA/00010380/201702

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

[72] Marketing authorisation(s) expiry date: 25 July 2017
[73] Biosimilars only

16.1.26. Meningococcal group-B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - PSUSA/00010043/201701

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.27. Modified vaccinia Ankara virus - IMVANEX (CAP) - PSUSA/00010119/201701 (with RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.28. Nilotinib - TASIGNA (CAP) - PSUSA/00002162/201701

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.29. Pegaspargase - ONCASPAR (CAP) - PSUSA/00010457/201701

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.30. Perampanel - FYCOMPA (CAP) - PSUSA/00009255/201701

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.31. Phenylephrine, ketorolac - OMIDRIA (CAP) - PSUSA/00010419/201701

Applicant: Omeros London Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.32. Pomalidomide - IMNOVID (CAP) - PSUSA/00010127/201702

Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.33. Pregabalin - LYRICA (CAP); PREGABALIN PFIZER (CAP) - PSUSA/00002511/201701

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.34. Pyronaridine, artesunate - PYRAMAX (Art 58[74]) - EMEA/H/W/002319/PSUV/0016

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUR procedure

16.1.35. Roflumilast - DALIRESP (CAP); DAXAS (CAP); LIBERTEK (CAP) - PSUSA/00002658/201701

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.36. Rufinamide - INOVELON (CAP) - PSUSA/00002671/201701

Applicant: Eisai Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.37. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/201701

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.38. Saxagliptin, dapagliflozin - QTERN (CAP) - PSUSA/00010520/201701

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

16.1.39. Silodosin - SILODYX (CAP); UROREC (CAP) - PSUSA/00002701/201701

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.40. Simoctocog alfa - NUWIQ (CAP) - PSUSA/00010276/201701

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.41. Vismodegib - ERIVEDGE (CAP) - PSUSA/00010140/201701

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.42. Vorapaxar - ZONTIVITY (CAP) - PSUSA/00010357/201701

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

16.2.1. Abacavir - ZIAGEN (CAP); NAP - PSUSA/00000010/201612

Applicants: ViiV Healthcare UK Limited (Ziagen), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.2.2. Abacavir, lamivudine - KIVEXA (CAP); NAP - PSUSA/00000011/201612

Applicants: ViiV Healthcare UK Limited (Kivexa), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.2.3. Abacavir, lamivudine, zidovudine - TRIZIVIR (CAP); NAP - PSUSA/00003144/201612

Applicants: ViiV Healthcare UK Limited (Trizivir), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.2.4. Caspofungin - CANCIDAS (CAP); CASPOFUNGIN ACCORD (CAP); NAP - PSUSA/00000576/201612

Applicants: Merck Sharp & Dohme Limited (Cancidas), Accord Healthcare Ltd (Caspofungin Accord), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.2.5. Sildenafil[75] - VIAGRA (CAP); NAP - PSUSA/00002699/201612

Applicants: Pfizer Limited (Viagra), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

16.3.1. Allergen for therapy[76]: Dactylis Glomerata L., Phleum Pratense L., Anthoxanthum Odoratum L., Lolium Perenne L., Poa Pratensis L. (NAP) - PSUSA/00010465/201612

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.2. Amino acid combinations, glucose, triglyceride combinations[77]- NUMETA (NAP) - PSUSA/00010190/201612

Applicant(s): Baxter Healthcare Limited

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

[75] Erectile dysfunction indication only
[76] Sublingual tablet only
[77] Only for Numeta (e.g. olive oil, soya bean oil, fish oil), with or without electrolytes, mineral compounds (intravenous (IV) application)

16.3.3. Amlodipine, lisinopril (NAP) - PSUSA/00010192/201612

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.4. Aprotinin, calcium chloride, human factor XIII, human fibrinogen, human thrombin (NAP); aprotinin, fibrinogen, fibronectin, human coagulation factor XIII, plasma protein fraction, plasminogen, thrombin (NAP); aprotinin, human fibrinogen, thrombin, calcium chloride (NAP); aprotinin, calcium chloride, factor XIII, human thrombin, human clottable protein containing mainly fibrinogen and fibronectin (NAP); bovine aprotinin, calcium chloride, human fibrinogen, factor XIII, fibronectin, plasminogen, human thrombin (NAP); bovine aprotinin, calcium chloride, human fibrinogen, factor XIII, fibronectin, human thrombin (NAP); bovine aprotinin, human fibrinogen, calcium chloride dihydrate, plasma fibronectin, thrombin, human coagulation factor XIII (NAP), bovine aprotinin, human fibrinogen, calcium chloride dihydrate, plasma protein fraction, fibronectin, thrombin, human coagulation factor XIII (NAP); bovine aprotinin, human fibrinogen, plasminogen, human thrombin, human coagulation factor XIII, human fibronectin (NAP) - PSUSA/00010346/201611

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.5. Beclometasone (NAP) - PSUSA/00000306/201612

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.6. Beclometasone, salbutamol (NAP) - PSUSA/00000309/201701

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.7. Brotizolam (NAP) - PSUSA/00000444/201612

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.8. Cefazolin (NAP) - PSUSA/00000589/201611

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.9. Ciprofibrate (NAP) - PSUSA/00000771/201612

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.10. Citalopram (NAP) - PSUSA/00000779/201612

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.11. Dienogest (NAP) - PSUSA/00003167/201612

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.12. Donepezil (NAP) - PSUSA/00001160/201611

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.13. Escitalopram (NAP) - PSUSA/00001265/201612

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.14. Gaxilose (NAP) - PSUSA/00010283/201701

Applicant(s): various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.3.15. Idarubicin (NAP) - PSUSA/00001720/201611

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.16. Indapamide, perindopril (NAP) - PSUSA/00010230/201611

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.17. Levonorgestrel, ethinylestradiol (NAP); ethinylestradiol[78] (NAP) - PSUSA/00010442/201701

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.3.18. Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide (NAP) - PSUSA/00010390/201701

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.19. Lubiprostone (NAP) - PSUSA/00010290/201701

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.20. Pergolide (NAP) - PSUSA/00002351/201612

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.21. Rupatadine (NAP) - PSUSA/00002673/201612

Applicant(s): various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

[78] Combination pack

16.3.22. Sertindole (NAP) - PSUSA/00002695/201701

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.23. Sulbactam (NAP) - PSUSA/00002800/201611

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.24. Terbutaline (NAP) - PSUSA/00002897/201612

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.25. Testosterone undecanoate[79] (NAP) - PSUSA/00010161/201612

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.26. Tibolone (NAP) - PSUSA/00002947/201612

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.27. Ursodeoxycholic acid (NAP) - PSUSA/00003084/201611

Applicant(s): various

PRAC Lead: Amy Tanti

Scope: Evaluation of a PSUSA procedure

16.3.28. Varicella zoster-immunoglobin (NAP) - PSUSA/00010266/201612

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

[79] Injection route only

Scope: Evaluation of a PSUSA procedure

16.3.29. Vecuronium bromide (NAP) - PSUSA/00003102/201611

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.30. Yellow fever vaccine (live) (NAP) - PSUSA/00003135/201612

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

16.4.1. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/LEG 065

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Detailed review of fatal events in line with the MedDRA[80] hierarchy terms sorted by country of origin as requested in the conclusions of PSUSA/2127/201608/0099 adopted by PRAC in March 2017

16.4.2. Vardenafil - LEVITRA (CAP) - EMEA/H/C/000475/LEG 026.1

Applicant: Bayer AG

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to LEG 026 [submission of a cumulative review and a discussion on cerebrovascular disorders with data from all available sources (clinical trials, post-marketing experience, literature) including information regarding time to onset, age of patients, dose of vardenafil, confounding or risk factors as well as any information on dechallenge/rechallenge as requested in the conclusions of PSUSA/00003098/201603 adopted by PRAC in November 2016] as per the request for supplementary information (RSI) adopted in March 2017

16.4.3. Vardenafil - VIVANZA (CAP) - EMEA/H/C/000488/LEG 026.1

Applicant: Bayer AG

PRAC Rapporteur: Dolores Montero Corominas

[80] Medical Dictionary for Regulatory Activities

Scope: MAH's response to LEG 026 [submission of a cumulative review and a discussion on cerebrovascular disorders with data from all available sources (clinical trials, post-marketing experience, literature) including information regarding time to onset, age of patients, dose of vardenafil, confounding or risk factors as well as any information on dechallenge/rechallenge as requested in the conclusions of PSUSA/00003098/201603 adopted by PRAC in November 2016] as per the request for supplementary information (RSI) adopted in March 2017

16.5. Follow-up to PSUR procedures

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[81]

17.1.1. Cholic acid – KOLBAM (CAP) - EMEA/H/C/PSA/S/0021

Applicant: Retrophin Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: Amendment to PASS protocol for a prospective, observational, non-interventional, post-marketing, patient registry to collect data on routine clinical care in patients treated with Kolbam (cholic acid) [protocol previously adopted within procedure EMEA/H/C/PSP/0017.2 at November 2016 PRAC meeting]

17.1.2. Iron intravenous (IV) (NAP) - EMEA/H/N/PSP/J/0053.1

Applicant: Mesama Consulting

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to EMEA/H/N/PSP/J/0053.1 [PASS protocol for a study evaluating the risk of severe hypersensitivity reactions and assessing the risk of anaphylactic or severe immediate hypersensitivity reactions on the day of or the day after first IV iron use] as per the request for supplementary information (RSI) adopted in March 2017

17.1.3. Ketoconazole – KETOCONAZOLE HRA (CAP) - EMEA/H/C/PSP/S/0040.4

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

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

Scope: MAH's response to PSP/S/0040.3 [revised PASS protocol for a prospective, multinational, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole (using the existing European Registry on Cushing's syndrome (ERCUSYN)), to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole] as per the request for supplementary information (RSI) adopted in June 2017

17.1.4. Ethinylestradiol (NAP), levonorgestrel, ethinylestradiol (NAP) - EMEA/H/N/PSP/J/0054.1

Applicant: Teva Pharma B.V. (Seasonique)

PRAC Rapporteur: Caroline Laborde

Scope: MAH's response to PSP/J/0054 [PASS protocol for a drug utilisation study of Seasonique (ethinylestradiol, levonorgestrel) in Europe aiming at assessing both safety outcomes and drug utilisation patterns] as per the request for supplementary information (RSI) adopted in April 2017

17.1.5. Valproate (NAP) - EMEA/H/N/PSA/J/0015.1

Applicant: Sanofi

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to PSA/J/0015 including a revised protocol [updated protocol for a joint drug utilisation study (DUS) using EU databases to study the effectiveness of the imposed risk minimisation measures following the conclusion of the referral procedure under Article 31 of Directive 2001/83/EC completed in 2014 (EMEA/H/A-31/1387) and to further characterise the prescribing patterns for valproate] as per the request for supplementary information (RSI) adopted in March 2017

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[82]

17.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.4

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: MAH's response to MEA 007.2 and MEA 007.3 [revised PASS protocol for study OBS13434: a prospective, multicentre, observational, PASS to evaluate the long term safety profile of alemtuzumab treatment in patients with relapsing forms of multiple sclerosis (RMS)] as per the request for supplementary information (RSI) adopted in April 2017

17.2.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 002

Applicant: Eli Lilly Nederland B.V.

[82] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

PRAC Rapporteur: Patrick Batty

Scope: PASS protocol for study I4V-MC-B003: a prospective observational US post-marketing registry study to assess the long-term safety of baricitinib compared with other therapies used in the treatment of adults with moderate-to-severe rheumatoid arthritis in the course of routine clinical care [final report expected by March 2031] (as requested in the initial opinion)

17.2.3. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 012.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 012.1 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as requested in the request for supplementary information (RSI) adopted in April 2017

17.2.4. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 013

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: PASS protocol for a US epidemiology database study l to further characterise the incidence of lower limb amputation in patients taking canagliflozin (category 3 PASS) as well as a feasibility assessment report for the conduct of a similar observational database study in the EU (category 3 PASS) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)

17.2.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 011.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 011 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as requested in the request for supplementary information (RSI) adopted in April 2017

17.2.6. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 012

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: PASS protocol for a US epidemiology database study to further characterise the incidence of lower limb amputation in patients taking canagliflozin (category 3 PASS) as well as a feasibility assessment report for the conduct of a similar observational database study in the EU (category 3 PASS) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)

17.2.7. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/MEA 024

Applicant: Pfizer Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Amendment of a protocol for study A8081062: a PASS descriptive study evaluating the frequency of risk factors for and sequelae of potential sight threatening event and severe visual loss among patients being treated with crizotinib following exposure to Xalkori (crizotinib) required by the US FDA (RMP category 3 study) (from the outcome of II/39 variation procedure)

17.2.8. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/MEA 001.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 001.1 [updated protocol for PASS L01XC24: a survey measuring the effectiveness of the educational materials regarding the minimisation of risk of interference for blood typing with daratumumab] as per the request for supplementary information (RSI) adopted in May 2017

17.2.9. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/MEA 067.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 067.1 [revised PASS protocol and questionnaire for a cross sectional physician survey (study N6987) to assess the impact of educational materials on prescribers' awareness of doses and biological monitoring recommendations and also to assess the awareness and appropriate use of both formulations (orodispersible tablets and film-coated tablets) as per request for supplementary information (RSI) adopted in April 2017

17.2.10. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 009

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: PASS protocol for study 109MS303: a dose-blind, multicentre, extension study to determine the long-term safety and efficacy of two doses of BG00012 monotherapy in subjects with relapsing-remitting multiple sclerosis (ENDORSE) [final clinical study report

expected in Q1 2024]

17.2.11. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/MEA 005.1

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's responses to MEA 005 [PASS protocol for study EVM-19596-00-001: a drug utilisation study (DUS) (RMP category 3) using relevant healthcare databases at two different time periods in order to define the compliance to contraindications over time and the number of subjects diagnosed with pancreatitis after eluxadoline treatment] as requested in the request for supplementary information (RSI) adopted in March 2017

17.2.12. Fenofibrate, simvastatin - CHOLIB (CAP) - EMEA/H/C/002559/MEA 002.6

Applicant: Mylan Products Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002.5 [PASS protocol to assess the clinical practice regarding concomitant use of fenofibrate and simvastatin both as free and fixed combination (Cholib): a European study in Austria, Croatia, Czech Republic, Portugal, Slovakia and Slovenia and a corresponding study web questionnaire] as per the request for supplementary information (RSI) adopted in March 2017

17.2.13. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/MEA 015.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Patrick Batty

Scope: MAH's responses to MEA 015 [PASS protocol for study GS-EU-313-4172: a non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL)] as per the request for supplementary information (RSI) adopted in March 2017

17.2.14. Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/MEA 004

Applicant: Plethora Solutions Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Protocol for a drug utilisation study (DUS) of Fortacin (lidocaine, prilocaine) in Europe: a retrospective cohort study using electronic medical records database aiming at characterising the population of patients who are prescribed the medicinal product and at describing the real-life prescribing patterns (listed as a category 3 study in RMP)

17.2.15. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/MEA 014.2

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Proposed amendment to the drug utilisation study (DUS), study NN8022-4241 evaluating in-market utilisation of Saxenda (liraglutide) used for weight management in Europe: a retrospective medical record review study to be conducted in Italy and Germany [PASS protocol agreed in September 2015 and protocol amendment agreed in February 2016], relating to a smaller sample size of patients in Germany for a pilot study to be conducted prior to the DUS

17.2.16. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 004.1

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 004 [PASS protocol for study C38072-AS-50026, a non-interventional phase IV study active pregnancy surveillance: effect of reslizumab exposure on pregnancy outcomes] as per the request for supplementary information (RSI) adopted in April 2017

17.2.17. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.1

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 005 [submission of a protocol for study C38072-AS-50027: a long-term non-interventional cohort study comparing the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using secondary administrative healthcare data (RMP category 3)] as per the request for supplementary information (RSI) adopted in May 2017

17.2.18. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/MEA 019.1

Applicant: UCB Pharma Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 019 [Protocol for study NA0001 (EU PAS register EUPAS15024): a non-interventional PASS on the effectiveness of the educational materials] as per the request for supplementary information (RSI) adopted in April 2017

17.2.19. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 025.2

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 025.1 [PASS protocol: to evaluate the effectiveness of risk minimisation measures: a survey among healthcare professionals and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of velaglucerase alfa in six European countries] as per the request for supplementary information (RSI) adopted in May 2017

17.3. Results of PASS imposed in the marketing authorisation(s)[83]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[84]

17.4.1. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/WS1182/0001; SOLYMBIC (CAP) - EMEA/H/C/004373/WS1182/0001

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report for study 20130258: an open-label, single-arm extension study to evaluate the long-term safety and efficacy of ABP 501 (adalimumab biosimilar) in subjects with moderate to severe rheumatoid arthritis (listed as a category 3 study in the RMP (MEA 002)). The RMP (version 2.0) is updated accordingly

17.4.2. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/II/0043

Applicant: Bristol-Myers Squibb, Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report for study CV185-365: a PASS evaluating the effectiveness of Eliquis (apixaban) risk minimisation tools in the European Economic Area countries (listed as a category 3 study in the RMP). The RMP (version 17.0) is updated accordingly

17.4.3. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/WS1188/0157; LIPROLOG (CAP) - EMEA/H/C/000393/WS1188/0120

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for a non-interventional PASS EUPAS 13422 evaluating the impact of additional risk minimisation measures on healthcare professionals and on patients' understanding and their behaviour regarding the risk of hypoglycaemia and/or hyperglycaemia due to medication errors associated with administration of Humalog 200 U/mL KwikPen or Liprolog 200 U/mL KwikPen

17.4.4. Paliperidone - XEPLION (CAP) - EMEA/H/C/002105/II/0031

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final study report for a PASS using European Union databases to

[83] In accordance with Article 107p-q of Directive 2001/83/EC
[84] 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

assess the risk of cardiovascular and cerebrovascular adverse events in elderly patients treated with paliperidone palmitate, paliperidone prolonged-release, and other antipsychotics

17.4.5. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/II/0066

Applicant: UCB Pharma Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study C00302 (post marketing non-interventional surveillance pharmacoepidemiology study (PMSS) to evaluate long-term safety, tolerability and compliance in administration of Xyrem (sodium oxybate) oral solution in patients who receive treatment with this medication in regular clinical practice) listed as a category 3 study in the RMP. The RMP (version 8) is updated accordingly

17.4.6. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0182

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Caroline Laborde

Scope: Submission of the final report for study GX-US-174-0172: a 5-year observational (non-interventional) renal safety registry conducted to provide further safety data in hepatitis B virus (HBV)-infected patients with decompensated liver disease (listed as a category 3 study in the RMP)

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[85]

17.5.1. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.8

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to ANX 038.7 [third annual interim report for study CICL670E2422: an observational, multicentre study to evaluate the safety of deferasirox in the treatment of paediatric patients with non-transfusion-dependent iron overload] as per the request for supplementary information (RSI) adopted in April 2017

17.5.2. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.4

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Second annual interim report for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients

[85] In line with the revised variations regulation for any submission before 4 August 2013

treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors [final report expected in July 2020]

17.5.3. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 004

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Second annual interim report for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors [final report expected in July 2020]

17.5.4. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Second annual interim report for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors [final report expected in July 2020]

17.5.5. Epoetin beta - NEORECORMON (CAP) - EMEA/H/C/000116/MEA 045.6

Applicant: Roche Registration Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Sixth interim report summarising the progress on studies to assess the functional activity of epoetin receptors in different tumour types, and at different stages in the life-cycle of tumour evaluation

17.5.6. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 007.2

Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Third annual interim safety and efficacy report for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra (infliximab) in patients with rheumatoid arthritis (EU and Korea) and MAH's responses to EMEA/H/C/002778/MEA 007.1 procedure as per the request for supplementary information (RSI) adopted in September 2016 [final report expected by May 2026]

17.5.7. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 010.2

Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Annual interim safety and efficacy report for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra (infliximab) in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea) and MAH's responses to EMEA/H/C/002778/MEA 010.1 procedure as per the request for supplementary information (RSI) adopted in September 2016 [final report expected by May 2026]

17.5.8. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 007.2

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Third annual interim safety and efficacy report for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Remsima (infliximab) in patients with rheumatoid arthritis (EU and Korea) and MAH's responses to EMEA/H/C/002576/MEA 007.1 procedure as per the request for supplementary information (RSI) adopted in September 2016 [final report expected by May 2026]

17.5.9. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 010.2

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Annual interim safety and efficacy report for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Remsima (infliximab) in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea) and MAH's responses to EMEA/H/C/002576/MEA 010.1 procedure as per the request for supplementary information (RSI) adopted in September 2016 [final report expected by May 2026]

17.5.10. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.7

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual interim report for the passive enhanced safety surveillance study (ESS) D2560C00008: a postmarketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age

17.5.11. Meningococcal group B vaccine(rDNA, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 017.3

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Third interim report for study V72_36OB: a post-licensure observational safety study after meningococcal B vaccine 4CMenB (Bexsero) vaccination in routine UK care [final report expected in December 2019]

17.5.12. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 013.4

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 013.3 [annual interim report from an observational database-assisted comparative cohort study to investigate the risk of hepatotoxicity and

hepatocellular carcinoma (protocol number: ISN 9463-CL-140): a multicentre cohort study of the short and long-term safety of micafungin and other parenteral antifungal agents (MYCOS)] as per the request for supplementary information (RSI) adopted in January 2017

17.5.13. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - EMEA/H/C/002705/MEA 002.4

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Second biannual interim report for the VERIFIE study (VFMCRP-MEAF-PA21-01-EU): a non-interventional study to investigate the short and long-term real-life safety, effectiveness, and adherence of Velphoro in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis (PD) and MAH's responses to the request for supplementary information (RSI) for MEA 002.3 adopted in February 2017 on the first interim study report

17.5.14. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/ANX 011.3

Applicant: Teva B.V.

PRAC Rapporteur: Caroline Laborde

Scope: Third interim report (covering the period from the start of recruitment in August 2014 until April 2017) for a prospective PASS observational study (ZEG2013_08) to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrol/estradiol users compared with the VTE risk in users of combined oral contraceptives containing levonorgestrel (as imposed in accordance with Article 10(a) of Regulation (EC) No 726/2004

17.5.15. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/ANX 001.3

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Second annual interim report for PASS ENCEPP/SDPP/8585: an observational retrospective cohort study for ospemifene utilising existing databases in Germany, Italy, Spain, and the United States to evaluate the incidence of venous thromboembolism and other adverse events, as agreed in the RMP, in vulvar and vaginal atrophy (VVA) patients treated with ospemifene as compared to: 1) patients newly prescribed selective estrogen receptor modulators (SERMs) for oestrogen-deficiency conditions or breast cancer prevention and; 2) the incidence in untreated VVA patients (category 1) [final report expected in February 2021]

17.5.16. Pegvisomant - SOMAVERT (CAP) - EMEA/H/C/000409/MEA 061

Applicant: Pfizer Limited

PRAC Rapporteur: Caroline Laborde

Scope: Interim report from study A6291010 (ACROSTUDY): a multicentre, post marketing surveillance study of pegvisomant therapy in patients with acromegaly as agreed in the opinion for the initial MAA [due date: final report due in 2018, extended to 2019 (MEA 059)]

17.5.17. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/MEA 011.3

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Fourth annual interim report for study H4621g (MotHER pregnancy register): an observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with Herceptin (trastuzumab), Perjeta (pertuzumab) in combination with Herceptin, or Kadcyla during pregnancy or within 7 months prior to conception [final report expected by May 2024]

17.5.18. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 023.9

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Seventh annual interim report for study CNTO1275PSO4005 (Nordic database initiative): a prospective cohort registry, five-year observational study of adverse events (AEs) observed in patients exposed to ustekinumab

17.5.19. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.10

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Seventh annual interim report for study CNTO1275PSO4007 (pregnancy research initiative) (C0743T): exposure to ustekinumab during pregnancy in patients with psoriasis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers. In addition, the submission includes a summary document on pregnancy outcomes from study CNT01275PS04037: pregnancy exposure registry OTIS (Organisation of Teratology Information Specialists) study conducted in North America on autoimmune diseases in pregnancy; study C0168Z03: a multicentre, prospective, observational PSOLAR (Psoriasis Longitudinal Assessment and Registry) study tracking the long-term safety experience and clinical status of patients with psoriasis who are eligible to receive (or are actively receiving) systemic therapies for psoriasis; and study CNT01275PS04007: a prospective, observational, exposure-based cohort Nordic Pregnancy Registry study analysing maternal and birth outcome data obtained from the Swedish Medical Birth Register (SMBR), Danish Medical Birth Register (DMBR) and Finnish Medical Birth Register (FMBR)

17.6. Others

17.6.1. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.10

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of a statistical analysis plan (SAP) for PASS B1781044: a cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe, as per the request for supplementary information (RSI) agreed in the conclusion of MEA 012.9 adopted in May 2017

17.6.2. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/MEA 004

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Feasibility study for conducting a PASS using multiple sclerosis registries to address specific safety concerns or to measure effectiveness of risk minimisation measures (from initial opinion)

17.6.3. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 011

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Statistical analysis plan (SAP) outlining the meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)

17.6.4. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 003

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Statistical analysis plan (SAP) outlining the meta-analysis of three clinical trials: 1)

study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)

17.6.5. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 007

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Statistical analysis plan (SAP) outlining the meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)

17.6.6. Palonosetron - PALONOSETRON ACCORD (CAP) - EMEA/H/C/004129/LEG 002.1

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Almath Spooner

Scope: Six-monthly cumulative review of cases of injection site reactions classified as an important potential risk (1 October 2016-31 March 2017) as requested at the time of the opinion for marketing authorisation(s) for Palonosetron Accord 250 micrograms solution for injection until further market experience is acquired

17.6.7. Valproate (NAP) - EMEA/H/N/PSI/J/0001

Applicant(s): Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to PSI/J/0001 [first interim study report of a non-interventional imposed PASS, designed to assess the effectiveness of risk minimisation measures in the outpatient setting, including the 3-year data collected for the pre-implementation period in 4 out of 5 countries (France, Germany, Spain, Sweden and United Kingdom) versus the 6-month data collected for the post-implementation period in all of the five EU selected countries, and submission of the final study report of the Joint PASS survey among healthcare professionals (HCPs) to assess their knowledge and attitudes on the prescribing conditions of valproate in France, Germany, Spain, Sweden and United Kingdom] as per the request for supplementary information (RSI) adopted in April 2017

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

18. 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.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0049 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/R/0051 (with RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.2.2. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0002 (without RMP), Orphan

Applicant: Intercept Pharma Ltd

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.2.3. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/R/0005 (without RMP)

Applicant: AbbVie Ltd.

PRAC Rapporteur: Patrick Batty

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - EMEA/H/C/002246/R/0031 (with RMP)

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Valerie Strassmann

Scope: 5-year renewal of the marketing authorisation

18.3.2. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/R/0105 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.3. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/R/0024 (with RMP)

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

18.3.4. Nalmefene - SELINCRO (CAP) - EMEA/H/C/002583/R/0022 (without RMP)

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.5. Ocriplasmin - JETREA (CAP) - EMEA/H/C/002381/R/0033 (without RMP)

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.6. Pioglitazone, metformin hydrochloride - GLUBRAVA (CAP) - EMEA/H/C/000893/R/0054 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

19. Annex I – Other safety issues for discussion requested by the CHMP or EMA

19.1. Safety related variations of the marketing authorisation

None

19.2. Timing and message content in relation to Member states' safety announcements

None

19.3. Other requests

None

19.4. Scientific advice

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

20. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 29 August–1 September 2017 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 - via telephone*	Austria	No interests declared	Full involvement
Marianne Lunzer	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsovà	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
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussions,	6.1.6 Eluxadoline - TRUBERZI (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			final deliberations and voting on:	
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Member	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	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	Member	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
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations	3.4.1. Human coagulation (plasma - derived) factor VIII; 6.1.14.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	Sorafenib - NEXAVAR (CAP); 6.3.5. Chlormadinone (NAP) 11.1.1. Moxifloxacin (NAP)
Kristin Thorseng Kvande	Alternate	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
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Sanches de Castro Lopes Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Peter Koren	Alternate	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No participation in final deliberations and voting on:	3.3.1. Paracetamol (NAP); paracetamol, tramadol (NAP) 4.2.1. Amlodipine (NAP); rifampicin (NAP) 4.2.2. Azithromycin (NAP) 4.2.3. Doxycycline (NAP) 4.3.1. Azithromycin (NAP); tobramycin 4.3.5. Pramipexole –

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP) 11.1.1. Moxifloxacin (NAP)
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Thomas Lang	Expert - via telephone*	Austria	No interests declared	Full involvement
Daniela Philadelphy	Expert - in person*	Austria	No interests declared	Full involvement
Jamila Hamdani	Expert - via telephone*	Belgium	No interests declared	Full involvement
Flora Musuamba Tshinanu	Expert - via telephone*	Belgium	No interests declared	Full involvement
Carine Condy	Expert - via telephone*	France	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Catherine Deguines	Expert - via telephone*	France	No interests declared	Full involvement
Sara Franco	Expert - in person*	France	No interests declared	Full involvement
Marie Gadeyne	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Marc Martin	Expert - in person*	France	No interests declared	Full involvement
Christine Diesinger	Expert - via telephone*	Germany	No interests declared	Full involvement
Thomas Grüger	Expert - via telephone*	Germany	No interests declared	Full involvement
Anna Marie Coleman	Expert - via telephone*	Ireland	No interests declared	Full involvement
Negar Babae	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Lotte Minnema	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Peter Mol	Expert - in person*	Netherlands	No interests declared	Full involvement
Maartje van der Sar	Expert - in person*	Netherlands	No restrictions applicable to this meeting	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Monika Trojan	Expert - via telephone*	Poland	No restrictions applicable to this meeting	Full involvement
Sílvia Duarte	Expert - via telephone*	Portugal	No interests declared	Full involvement
Mário Miguel Rosa	Expert - in person*	Portugal	No restrictions applicable to this meeting	Full involvement
Almudena López-Fando Sandafe	Expert - in person*	Spain	No interests declared	Full involvement
Miguel Angel Macia	Expert - via telephone*	Spain	No interests declared	Full involvement
Ferran Torres	Expert - in person*	Spain	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - in person*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Karl-Mikael Kälkner	Expert - via telephone*	Sweden	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
Darius Matusevicius	Expert - via telephone*	Sweden	No interests declared	Full involvement
Helena Möllby	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jessica Mwinyi	Expert - via telephone*	Sweden	No interests declared	Full involvement
Claire Hearnden	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 agenda topics or activities they participated in.

21. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

22. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

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

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

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