6 April 2017
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Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 6-9 March 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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

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

The Chairperson opened the 6-9 March 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 **Error! Reference source not found.**). No new or additional conflicts were declared.

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

The PRAC Chair welcomed Patrick Batty as the new alternate for the United Kingdom, replacing Rafe Suvarna.

1.2. Agenda of the meeting on 6-9 March 2017

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

1.3. Adoption of the minutes of the previous meeting on 6-9 February 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 6-9 February 2017 were published on the EMA website on 5 May 2017 (EMA/PRAC/286717/2017).

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

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

3.1.1. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide (NAP)

Applicant: 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

The French Medicines Agency (ANSM) sent a letter of notification dated 08/03/2017 of a referral under Article 31 of Directive 2001/83/EC for the review of valproate-containing medicines in the treatment of women and girls who are pregnant or of childbearing potential, in relation to the risk of neurodevelopmental disorders in children, following the results of a national pharmacoepidemiological study programme[1] covering all the indications of valproate-containing medicines based on data from French national medico-administrative databases. In addition, the ANSM took into consideration the results of a study[2] performed in France between 2007-2014 on the use of valproate together with the results of a French national survey conducted in a sample of pharmacies in April-June 2016. It was considered of Union interest to assess the evidence in support of a contra-indication for valproate and related substances in the treatment of bipolar disorder during pregnancy and in women of childbearing potential who are not on effective contraception, as well as to review the effectiveness of the current risk minimisation measures across all indications.

Discussion

The PRAC noted the notification letter from the French Medicines Agency and also data from

[1] Chastel X., Essid A., Lesteven P. Enquête relative aux spécialités pharmaceutiques contenant du valproate de sodium. Février 2016, Inspection générale des affaires sociales (IGAS) Rapport No 2015-094R

[2] Agence nationale de sécurité du médicament et des produits de santé, Caisse Nationale. Rapport d'étude Exposition à l'acide valproïque et ses dérives au cours de la grossesse en France de 2007 à 2014: une étude observationnelle sur les données du SNIIRAM, April 2016

UK indicating a lack of impact on prescribing of valproate to women of childbearing potential following implementation of the risk minimisation measures after the previous referral. The PRAC discussed a list of questions to be addressed during the procedure as well as a timetable for conducting the review.

The PRAC appointed Sabine Straus as Rapporteur and Jean-Michel Dogné as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (LoQ) to the MAHs (EMA/PRAC/154222/2017) and a timetable for the procedure (EMA/PRAC/154221/2017). In addition, the PRAC adopted a LoQ to Healthcare Professional Organisations as well as a LoQ to patient representative organisations. Moreover, the PRAC agreed some questions to the NCAs to be circulated as part of a non-urgent information (NUI).

The PRAC discussed the option to conduct a public hearing according to the pre-defined criteria set out in the rules of procedure[3] (EMA/363479/2015). Based on the information currently available, a public hearing was considered appropriate in the context of this procedure and it was agreed that it would be of greatest benefit at a later stage of the procedure, following initial assessment of the matter by the Committee. Further information will be made available on the EMA website closer to the date.

3.2. Ongoing procedures

3.2.1. Human coagulation (plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP)
Recombinant factor VIII: antihemophilic factor (recombinant) (NAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY (CAP) - EMEA/H/A-31/1448

Applicant: Baxter AG (Advate), Bayer Pharma AG (Helixate Nexgen, Iblias, Kogenate, Kovaltry), CSL Behring GmbH (Voncento), Pfizer Limited (Refacto AF), various

PRAC Rapporteur: Julie Williams; PRAC Co-rapporteur: Brigitte Keller-Stanislawski

Scope: Review of the benefit-risk balance of factor VIII following notification by Germany 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 the review of factor VIII-containing medicines indicated for the treatment of haemophilia A to assess the impact of the results of the SIPPET study by *Peyvandi et al*.[4] recently published in the New England Journal of Medicine, on the benefit risk of factor-VIII containing medicines with further consideration of any potential for risk minimisation measures or other changes to the marketing authorisations of these medicinal products. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes January 2017 and PRAC minutes February 2017.

[3] Rules of procedure on the organisation and conduct of public hearings at the PRAC
[4] Peyvandi F. et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N Eng J Med. 2016 May 26;374(21):2054-64) (SIPPET study)

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusions reached by the ad-hoc expert group meeting held on 22 February 2017. An oral explanation took place at the meeting. In light of the oral explanation, the ad-hoc expert group's conclusions and the joint assessment report of the Rapporteurs, the PRAC adopted a third list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for the procedure (EMA/PRAC/471536/2016 rev. 3).

Post-meeting note: On 21/03/2017, the PRAC adopted via written procedure a further revised timetable (EMA/PRAC/471536/2016 rev. 4) for the procedure.

3.2.2. Lactose of bovine origin-containing medicinal products[5]: methylprednisolone (NAP) - EMEA/H/A-31/1449

Applicant: Pfizer Croatia d.o.o. (Solu-Medrol), various

PRAC Rapporteur: Jan Neuhauser; PRAC Co-rapporteur: Nikica Mirošević Skvrce

Scope: Review of the benefit-risk balance following notification by Croatia 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 methylprednisolone containing medicinal products for intravenous (IV)/intramuscular (IM) administration which contain lactose of bovine origin, indicated for the treatment of allergic conditions, following cases of hypersensitivity reactions, including life-threatening anaphylactic reactions, in patients allergic to cow's milk proteins. For further background, see PRAC minutes December 2016.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusion reached by the Rapporteurs and adopted a list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for conducting the review (EMA/PRAC/787809/2016 rev.1).

3.2.3. Paracetamol[6] (NAP) - EMEA/H/A-31/1445

Applicant: 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 paracetamol modified release medicinal 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 ongoing for the review of the benefit risk balance of modified- and prolonged-release paracetamol-containing medicines,

[5] For intravenous (IV) or intramuscular (IM) use indicated for the treatment of acute allergic reactions only
[6] Modified release formulations

following the recent publication by *Salmonson et al.*[7] 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. For further background, see PRAC minutes July 2016, PRAC minutes November 2016 and PRAC minutes February 2017.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusions reached by the ad-hoc expert group meeting held on 28 February 2017. In addition, the PRAC discussed the joint assessment report of the Rapporteurs and adopted a second list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/460935/2016).

3.2.4. Retinoids: acitretin (NAP); adapalene (NAP); alitretinoin - PANRETIN (CAP); bexarotene – TARGRETIN (CAP); isotretinoin (NAP); tazarotene (NAP); tretinoin (NAP) - EMEA/H/A-31/1446

Applicant: Eisai Ltd (Panretin, Targretin), various

PRAC Rapporteur: Ana Sofia Diniz Martins; PRAC Co-rapporteur: Julie Williams

Scope: Review of the benefit-risk balance following notification by the United Kingdom 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 oral and topical retinoid-containing medicines (acitretin; adapalene; alitretinoin; bexarotene; isotretinoin; tazarotene; tretinoin) indicated for the treatment of several conditions mainly affecting the skin such as acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders[8] to evaluate measures currently in place for pregnancy prevention and the possible risk of neuropsychiatric disorders. For further background, see PRAC minutes July 2016, PRAC minutes September 2016, PRAC Minutes October 2016, PRAC minutes December 2016 and PRAC minutes January 2017.

Summary of recommendation(s)/conclusions

The PRAC received preliminary feedback on the outcome of the dedicated meeting with patient/consumer and healthcare professionals organisations. This meeting focussed on understanding the HCPs' and patients' perspective on the communication, awareness and understanding of the teratogenic effects and was held on 3 March 2017. The perspective of patients and healthcare professionals will inform the ongoing review.

3.3. Procedures for finalisation

3.3.1. Gadolinium-containing contrast agents (GdCA): gadobenic acid (NAP); gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid

[7] 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, EAPCCT XXXVI International Congress 24-27 May, 2016, Madrid, Spain.

[8] Tretinoin may also be used to treat promyelocytic leukaemia

Applicant: Mallinckrodt Deutschland GmbH (Optimark); various

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Doris Stenver

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is to be concluded for gadolinium-containing contrast agents (GdCAs). The purpose of the referral procedure is to review the issue of accumulation of gadolinium in the brain, its clinical consequences and the overall safety profile of GdCAs. For further background, see PRAC minutes March 2016, PRAC minutes June 2016 and PRAC minutes July 2016, PRAC Minutes October 2016 and PRAC minutes December 2016.

Discussion

The PRAC reviewed the totality of the data submitted by the MAHs including at the oral explanations, as well as the views expressed by the ad-hoc expert group meeting, and discussed the conclusions reached by the Rapporteurs.

Data on product stability, as well as *in vitro* and non-clinical studies, strongly suggest that linear gadolinium-containing contrast agents (GdCAs) release gadolinium from the ligand molecules to a far greater extent than macrocyclic agents. Gadolinium (Gd) has been measured in the brain, both indirectly by studies showing signal intensity increases, and directly by studies measuring gadolinium concentrations with mass spectrometry, including methods that allow localisation in the brain (LA-ICP-MS) and separation of Gd species (GPC-MS). Based on non-clinical data, both linear and macrocyclic agents have the ability to distribute to the brain. However, linear agents are retained and persist for up to one year or longer. Macrocyclic agents show only a transient increase in Gd in the brain and undergo early washout.

Although no adverse neurological effects, such as cognitive or movement disorders, have yet been demonstrated to be caused by gadolinium accumulation in the brain, long-term safety data are limited. Harmful effects and potential interaction with disease processes are plausible in view of data supporting dechelation of linear agents in vivo and the known toxicity of unchelated gadolinium. Toxicity has been seen in other tissues where it accumulates (including nephrogenic systemic fibrosis (NSF), skin plaques) and in non-clinical data. Gadolinium accumulation has also been reported in a range of other tissues including the liver, kidney, muscle, skin and bone in non-clinical and clinical studies. The evidence strongly suggests a correlation between the potential for release of gadolinium from the ligand and the extent of retention in these tissues and organs. Linear GdCAs are associated with a significant risk of NSF, although current risk minimisation measures appear to be effective based on spontaneous adverse drug reaction reporting. In addition to NSF, there is also evidence that other harmful outcomes are associated with exposure to linear GdCAs, in particular gadolinium-associated skin plaques. Clinical studies, both observational and interventional, to fully address the serious concerns of potential neurological effects are not considered feasible within a reasonable period of time. This is due to the range of potential outcomes of interest, the requirement for long term follow-up, and the heterogeneity of the patient population that undergoes magnetic resonance imaging (MRI).

The PRAC considered options for risk minimisation measures. However, as no specific patient group with less risk of accumulation of gadolinium in the brain or a safe threshold level for retention in the brain could be identified, the restriction of the use of linear GdCAs to certain indications or certain groups of patients was considered not appropriate. The PRAC also concluded that there were practical difficulties for an effective restriction of the number of doses administered during the lifetime of a patient.

The PRAC considered that the risk related to the administration of linear intravenous GdCAs gadobenic acid, gadodiamide, gadopentetic acid, and gadoversetamide, taking into account the whole safety profile, including the additional potential risk of harm from brain and other tissues accumulation outweighs the benefits. The PRAC took into account that the liver-specific linear intravenous agent, Primovist (gadoxetic acid), undergoes substantial hepatic uptake, and requires a low dose. In addition, the time to the delayed phase scanning has clinical utility for imaging poorly vascularised hepatic lesions that cannot be adequately studied with agents without hepatic uptake. Therefore, the PRAC considered that the benefits of gadoxetic acid outweigh the risks related to this product. The PRAC also considered the linear intravenous agent with hepatic uptake, Multihance (gadobenic acid), authorised for liver imaging and which has utility in the delayed phase. However, in view of its time to onset of the delayed phase imaging, its authorised dose and its liver uptake, the PRAC considered that the benefit of gadobenic acid does not outweigh the risks related to this product in liver imaging. In relation to Magnevist (gadopentetic acid) for intra-articular injection, in view of the very low dose, the limited potential for repeated exposure for patients and the absence of evidence of brain accumulation, the PRAC considered that the benefits of this product outweigh its risks.

In view of the above, the Committee concluded that the benefit-risk balance of products containing intravenous gadobutrol, gadoteric acid, gadoteridol, and gadoxetic acid and intra-articular gadoteric acid and intra-articular gadopentetic acid remains favourable subject to the agreed amendments to the product information. The Committee recommended the variation to the terms of the marketing authorisations for products containing intravenous gadobutrol, gadoteric acid, gadoteridol, and gadoxetic acid and intra-articular gadoteric acid and intra-articular gadopentetic acid, to add information about use at the lowest dose and only when strictly necessary for imaging.The Committee also considered that the benefit-risk balance of intravenous gadobenic acid, gadodiamide, gadopentetic acid, and Optimark (gadoversetamide) is not favourable. Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommended the suspension of the marketing authorisations of the concerned products.

Summary of recommendation(s)/conclusions

The PRAC adopted a recommendation by a majority[9] to vary the terms of the marketing authorisations[10] for products containing intravenous gadobutrol, gadoteric acid, gadoteridol, and gadoxetic acid and intra-articular gadoteric acid and intra-articular gadopentetic acid, and to suspend the marketing authorisations for products containing gadodiamide, gadopentetic acid, gadobenic acid and gadoversetamide for intravenous use and adopted a recommendation to be considered by CHMP for an opinion. The Committee, having considered the data submitted in the procedure was of the opinion that the risk management plan (RMP) for products with a positive benefit-risk balance (except the intra-articular agents) should be revised accordingly and that MAHs should make proposals for conducting a further observational study into the effect of GdCA exposure during pregnancy on pregnancy outcomes. The PRAC considered also that a direct healthcare professional communication

[9] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded
[10] Update of SmPC sections 4.1, 4.2, 4.4 and 5.2. The package leaflet is to be updated accordingly

(DHPC) would be required to communicate the conclusion of this referral to healthcare professionals in relevant specialties. See Press Release (EMA/157486/2017) entitled 'PRAC concludes assessment of gadolinium agents used in body scans and recommends regulatory actions, including suspension for some marketing authorisations'.

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

None

3.5. Others

None

4. Signals assessment and prioritisation[11]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Docetaxel – TAXOTERE (CAP), DOCETAXEL ACCORD (CAP), TAXESPIRA (CAP)

Applicant(s): Aventis Pharma S.A. (Taxotere), Accord Healthcare Ltd (Docetaxel Accord), Hospira UK Limited (Taxespira), various

PRAC Rapporteur: Claire Ferard

Scope: Signal of unexpected seriousness of reported adverse drug reactions with docetaxel and suspicion of an increase in adverse drug reaction (ADR) reporting rate with docetaxel-containing products in France

EPITT 12059 – New signal

Lead Member State: FR

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. Taxotere is a centrally authorised product containing docetaxel.

Docetaxel is estimated to have been used in approximately 2.65 million patients worldwide in marketing experience, in the period from 2001 to 2016.

Following the spontaneous report of three cases of neutropenic enterocolitis with fatal outcome to the French pharmacovigilance system, a signal of unexpected seriousness of such reported adverse drug reactions with docetaxel and suspicion of an increase in adverse drug reaction (ADR) reporting rate with docetaxel-containing products was identified by France, based on 21

[11] 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

cases retrieved from EudraVigilance. France confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the evidence from preliminary analyses of data, including a time-series forecasting analysis performed in EudraVigilance, the PRAC considered that there was no apparent increase in frequency of occurrence of docetaxel-associated neutropenia and related events in the last two years. In addition, the Committee considered that further analysis of data available in EudraVigilance should be performed to identify whether there were any increases in the frequency of reports, for an extended time window from January 2010. The further EMA analysis should consider occurrence dates and also include additional adverse reactions. The PRAC noted that the product information of docetaxel-containing medicines includes warnings and advice about the risk of neutropenia and related adverse effects and monitoring of patients.

The PRAC appointed Claire Ferard as Rapporteur for the signal.

Summary of recommendation(s)

- EMA should perform, within 30 days, a detailed analysis of the data from EudraVigilance on adverse reactions related to neutropenia associated with docetaxel from January 2010 onwards. This further evaluation will be discussed along with the analysis being performed by the French regional pharmacovigilance centre of Toulouse. Further discussion is planned at the April 2017 PRAC meeting.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Ciprofloxacin (NAP); meropenem (NAP)

Applicant(s): various

PRAC Rapporteur: Jan Neuhauser

Scope: Signal of incompatibility leading to possible precipitation when co-administered intravenously

EPITT 18790 – Follow-up to December 2016

Background

The PRAC discussed the conclusions reached by the CHMP Quality Working Party (QWP) at their meeting held on 31 January to 02 February 2017 further to the list of questions (LoQ) agreed by PRAC at the December 2016 PRAC meeting. For further background, see PRAC minutes December 2016.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance of incompatibility and precipitation associated with concomitant administration of meropenem

and ciprofloxacin, and literature articles including the results from the study by *Chen et al.*[12]. The PRAC noted the advice given by the CHMP Quality Working Party (QWP), and agreed with the recommendation of the QWP to request the MAHs of the originator medicinal products containing meropenem and ciprofloxacin respectively to provide the results of an investigation of the risk for precipitate formation between meropenem and ciprofloxacin when administered intravenously as per routine clinical practice, as well as a cumulative review of all cases reporting 'product deposit' and related terms in association with co-suspect/interacting products meropenem and ciprofloxacin, and to discuss the potential mechanism for the formation of product deposit. Depending on the outcome of the review, the MAHs should discuss the need to amend the product information (PI) and/or the risk management plan (RMP).

Summary of recommendation(s)

- The MAHs of the originator medicinal products containing meropenem and ciprofloxacin respectively should submit to EMA, within 60 days, the results of an investigation of the risk for precipitate formation between meropenem and ciprofloxacin when administered intravenously as per routine clinical practice as well as a cumulative review of the signal, including an analysis of all case reports of product deposit and related terms, including a discussion on the potential mechanism for the formation of product deposit and a proposal for amending the product information and /or the risk management plan.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.2. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/SDA/012

Applicant(s): Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Signal of hepatotoxicity

EPITT 18754 – Follow-up to November 2016

Background

The MAH replied to the request for information on the signal of hepatotoxicity and the responses were assessed by the Rapporteur. For background information, see PRAC minutes November 2016.

Discussion

The PRAC considered the available evidence from the evaluation of the data submitted from clinical trial and post-marketing cases retrieved from the MAH's global database, pre-clinical data, and literature relating to the potential hepatotoxicity of the combination of enzalutamide and abiraterone, as well as the review of data from phase 2 studies with bicalutamide as comparator, and consequently agreed that the MAH should provide supplementary information.

Summary of recommendation(s)

- The MAH for Xtandi (enzalutamide) should submit to EMA, within 60 days, a review of all

[12] Chen LY., Chen J., Waters V., Boodhan S. Incompatibility of ciprofloxacin and meropenem injections, Am J Health-Syst. Pharm. 2013 Nov 15;70(22):1966, 1970

cases where potential hepatotoxicity may have been enhanced by concomitant use of other medications (especially those leading to a fatal outcome), in order to identify any relevant pattern of concomitant use not already included in the product information, and a proposal for amending the product information if such a pattern is identified. The MAH should also provide the narratives of cases originally assessed as inadequate or not related by the MAH, coded with MedDRA PTs[13] suggestive of drug-related hepatotoxicity, such as 'drug induced liver injury', 'hepatotoxicity', 'hepatocellular injury', 'jaundice' and 'acute liver failure' and discuss further the probable type of liver injury (e.g. cholestatic, hepatocellular, mixed) observed with enzalutamide. In addition, the MAH should discuss the need for any potential amendment of the product information and/ or the risk management plan and accordingly make a proposal for the changes to the relevant sections within this discussion.

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

4.3.3. Loperamide (NAP)

Applicant(s): various

PRAC Rapporteur: Andri Andreou

Scope: Signal of serious cardiac events with high doses of loperamide from abuse and misuse

EPITT 18339 – Follow-up to July 2016

Background

The MAH replied to the request for information on the signal of serious cardiac events with high doses of loperamide associated with abuse and misuse and the responses were assessed by the Rapporteur. For background information, see PRAC minutes July 2016.

Discussion

Having considered the available evidence from spontaneous reporting and the literature[14], including the cumulative review of all cases of Torsades de Pointes/ QT prolongation reported in the context of high doses of loperamide as well as the evaluation of the biological plausibility for a possible association and the comparison of the incidence of the cases reported in the EU and the USA, the PRAC concluded that the MAHs of loperamide-containing medicinal products should submit a variation within 2 months, to amend the product information as applicable. Taking into account the already existing wording in some nationally authorised products, the MAHs should propose to include a warning on cardiac events including QT prolongation and Torsades de Pointes reported in association with overdose as well as information on reported cardiac events further to overdose of loperamide and on related preclinical safety data.

Summary of recommendation(s)

- The MAHs for loperamide-containing products should submit to the national competent authorities of the Member States, within 60 days, a variation for amending the product information[15].

[13] Medical dictionary for regulatory activities – preferred terms (PTs)
[14] Kruse V., Somers A., Van Bortel L., De Both A., Van Belle S. and Rottey S. Sunitinib for metastatic renal cell cancer patients: observational study highlighting the risk of important drug–drug interactions. Journal of Clinical Pharmacy and Therapeutics, 2014, 39: 259–265. doi:10.1111/jcpt.12134
[15] Update of SmPC sections 4.4, 4.9 and 5.3. The package leaflet is to be updated accordingly

- The MAHs of loperamide-containing medicinal products should include cardiac events (QT prolongation and/or serious ventricular arrhythmias including Torsades de Pointes) in the RMP when applicable, as an important potential risk at the next regulatory opportunity and should closely monitor cardiac events (QT prolongation and/or serious ventricular arrhythmias including Torsades de Pointes) in future PSURs. New cases of cardiac events (QT prolongation and/or serious ventricular arrhythmias including Torsades de Pointes) should be evaluated and, if any new relevant information is found, it should be reported by the MAH(s) for further evaluation of causal relationship of cardiac events (QT prolongation and/or serious ventricular arrhythmias including Torsades de Pointes) and loperamide.
- The frequency of PSUR submission should be revised from eight-yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point (31/05/2020). The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

For the full PRAC recommendation, see EMA/PRAC/146565/2017 published on 04/04/2017 on the EMA website.

4.3.4. Nivolumab - OPDIVO (CAP)- EMEA/H/C/003985/SDA/015; pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/011

Applicant(s): Bristol-Myers Squibb Pharma EEIG (Opdivo), Merck Sharp & Dohme Limited (Keytruda)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of transplant rejection

EPITT 18781 – Follow-up to November 2016

Background

The MAH replied to the request for information on the signal of transplant rejection and the responses were assessed by the Rapporteur. For background information, see PRAC minutes November 2016.

Discussion

Having considered the available evidence from case reports in EudraVigilance and in the literature, as well as biological plausibility from the mechanism of action, the PRAC concluded that the MAHs of Opdivo (nivolumab) and of Keytruda (pembrolizumab) should, respectively for their products, submit a variation to amend the product information in order to add a warning on the risk of solid organ transplant rejection reported in the post-marketing setting in patients treated with PD-1 inhibitors. In addition, the undesirable effect of solid organ transplant rejection should be included in the product information with a frequency not known for nivolumab monotherapy as well as in combination with ipilimumab and for pembrolizumab, and the EU Risk Management Plans for these medicines should be amended to include 'solid organ rejection' as an important identified risk.

Summary of recommendation(s)

- The MAHs for Opdivo (nivolumab) and Keytruda (pembrolizumab) should submit to EMA, within 60 days, variation for amending the product information[16] and RMPs[17].

For the full PRAC recommendation, see EMA/PRAC/146565/2017 published on 04/04/2017 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. Alpha-1-antitrypsin - EMEA/H/C/003934, Orphan

Applicant: Kamada BioPharma Limited at Fieldfisher LLP

Scope: Treatment and maintenance therapy of adult patients with congenital deficiency of alpha-1 antitrypsin and lung disease with clinical evidence of emphysema and airway obstruction (forced expiratory volume in 1 second (FEV1)/slow vital capacity (SVC) <70%)

5.1.2. Dengue tetravalent vaccine (live, attenuated) - EMEA/H/C/004171

Scope: Prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4

5.1.3. Ocrelizumab - EMEA/H/C/004043

Scope: Treatment of multiple sclerosis

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

See Annex I 0

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

See also Annex I 0

5.3.1. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/II/0005/G

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations including an update of section 4.2 of the SmPC in order to include a revised dosing regimen as a result of the new 25 mg vial presentation. As a consequence, update of sections 6.5 and 6.6 of the SmPC to change the pack size of the finished product. The Annex II, Package Leaflet, Labelling and RMP (version 2.0) are updated accordingly

[16] Update of SmPC section 4.4 and 4.8. The package leaflet is to be updated accordingly
[17] Update of RMP important identified risk to add solid organ rejection

Background

Reslizumab is a humanised monoclonal antibody (immunoglobulin (Ig)G4, κ) indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

The CHMP is evaluating a grouped type II variation procedure for Cinqaero, a centrally authorised product containing reslizumab, to add a new presentation, at the same concentration (10mg/mL), of a 5-mL vial containing 25 mg of reslizumab in 2.5 mL concentrate, to support a vial-based dosing (VBD) regimen where the maximal doses will not exceed the approved 3.0 mg/kg dosing and reduce drug wastage compared to the currently approved body weight dosing regimen (3.0 mg/kg) where a specific volume is withdrawn from the vial and the remainder of the vial content has to be discarded. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 2.1 for Cinqaero (reslizumab) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that an updated risk management plan is submitted by the MAH.
- The PRAC supported including medication error related to confusion of the two doses (25 mg and 100 mg) as a potential important risk in the RMP and, additionally, a targeted follow-up questionnaire to investigate the root cause for medication error and lack of drug effect cases as part of the routine Pharmacovigilance activities.

  The PRAC agreed that the proposed routine risk minimisation measures are sufficient to ensure the safe and effective use of the product and that the direct healthcare professional communication (DHPC) proposed as additional risk minimisation measure is not necessary.

6. Periodic safety update reports (PSURs)

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

See also Annex I 0

6.1.1. Brimonidine[18] - MIRVASO (CAP) - PSUSA/00010093/201608 (with RMP)

Applicant: Galderma International

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Brimonidine is a selective alpha$_2$-adrenergic receptor agonist indicated[19] for the symptomatic treatment of facial erythema of rosacea in adult patients.

[18] Centrally authorised product only
[19] As a centrally authorised product (CAP)

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Mirvaso (brimonidine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the risk of haemodynamic effects following laser therapy and to include 'bradycardia' and 'dizziness' as undesirable effects with rare and uncommon frequencies, respectively. Therefore the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide a thorough assessment of the effectiveness of the updated risk minimisation measures relating to symptom exacerbation as well as a timetable to introduce fully on the market the updated product information reflecting all the approved variations, including the update proposed in this current PSUR procedure.

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

6.1.2. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/201608 (with RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Cobimetinib is a reversible, selective, allosteric inhibitor that blocks the mitogen-activated protein kinase (MAPK) pathway and is indicated for oral use for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation in combination with vemurafenib.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cotellic, a centrally authorised medicine containing cobimetinib, 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 Cotellic (cobimetinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add rhabdomyolysis as an undesirable effect with an uncommon frequency, as well as to include the warnings and the dose recommendations related to the risks of 'haemorrhage' and 'rhabdomyolysis / CPK elevations'. Therefore the current terms of the marketing authorisation(s) should be varied[21].

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

- In the next PSUR, the MAH should close the signal of 'acute renal injury and renal failure' (while being expected to re-open it in case of emergence of new relevant information), as well as the signal of 'hepatic toxicity', but should review this last topic under important potential risks unless otherwise justified. Moreover, the MAH is requested to provide a cumulative review and thorough analysis on neurological adverse reactions including a proposal for action.

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

6.1.3. Dabrafenib - TAFINLAR (CAP) - PSUSA/00010084/201608

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Dabrafenib is a protein kinase inhibitor indicated in monotherapy or in combination with trametinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tafinlar, a centrally authorised medicine containing dabrafenib, 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 Tafinlar (dabrafenib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a new warning on colitis and gastrointestinal perforation as well as to include as new undesirable effects 'photosensitivity reaction', 'colitis', 'gastrointestinal perforation', each with a common frequency, and myocarditis with a not known frequency. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- The MAH should delete the important potential risk 'photosensitivity' but include 'severe photosensitivity' as a new important identified risk in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP.
- In addition, the MAH should also, within 60 days, submit a cumulative review on severe cutaneous adverse reactions, including cases reported in clinical trials and in the post-marketing setting. The MAH should discuss causality and the need for an update of the product information.
- In the next PSUR, the MAH should closely monitor Guillain-Barre syndrome, and acute/chronic inflammatory demyelinating polyneuropathy (GBS/AIDP/CIDP).

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.

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

6.1.4. Deferiprone - FERRIPROX (CAP) - PSUSA/00000940/201608 (with RMP)

Applicant: Apotex Europe BV

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Deferiprone is an iron chelating agent indicated in monotherapy for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate, as well as in combination with another chelator in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ferriprox, a centrally authorised medicine containing deferiprone, 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 Ferriprox (deferiprone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the risk of neurological disorders, which can occur in children. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- The MAH is requested to submit an updated RMP within 60 days at the latest after the adoption of the variation resulting from this PSUSA assessment.
- In the next PSUR, the MAH should provide a thorough analysis of off-label use with a discussion on the clinical importance of risks related to off-label use in EU and non-EU countries respectively, and thoroughly discuss, if any ADR or a class of ADRs could be considered as an important risk with deferiprone used in specific off label indications, as well as long term use and cases with fatal outcome. Moreover, the MAH should provide a new comprehensive safety analysis of ear disorders and improve the literature analysis in view of the limited description of articles provided and its deficiency for signal detection.

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. Desloratadine, pseudoephedrine - AERINAZE (CAP) - PSUSA/00000963/201607

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

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

Desloratadine is a long-acting histamine antagonist (LABA) and pseudoephedrine a sympathomimetic agent with mostly α-mimetic activity. In combination, desloratadine / pseudoephedrine is indicated in adults and adolescents 12 years and older for the symptomatic treatment of seasonal allergic rhinitis when accompanied by nasal congestion.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aerinaze, a centrally authorised medicine containing desloratadine/pseudoephedrine, 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 Aerinaze (desloratadine / pseudoephedrine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning regarding convulsions as well as to add 'abnormal behaviour', 'aggression' and 'QT prolongation' as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].
- The MAH(s) of the centrally authorised desloratadine-containing products are requested within 90 days to provide a further analysis of all available data regarding movement disorders (including dystonia, tics and extrapyramidal symptoms) and discuss, whether 'movement disorders' should be included as a new undesirable effect in the product information.
- In the next PSUR, the MAH(s) should keep the safety signals of convulsions, movement disorders, QT prolongation, and abnormal behaviour including aggressive reactions as ongoing issues and provide a corresponding discussion. In addition, the MAHs should discuss cases of interactions with simvastatin and other statins leading to myopathies, and cases of cardiac disorders in pediatric patients. Finally, the MAH(s) should consider 'hypersensitivity' (including anaphylaxis, angioedema, dyspnoea, pruritus, rash and urticaria), 'abnormal hepatic function' (including hepatitis and elevated hepatic enzymes and bilirubin), and 'severe skin reactions' (including acute generalized exanthematous pustulosis) as important identified risks,' convulsion', 'movement disorder' (including psychomotor hyperactivity and restlessness), 'supraventricular tachyarrhythmia', 'QT prolonged', 'hallucination', 'abnormal behaviour including aggressive reactions', 'photosensitivity', 'abuse' and 'use in patients with cardiac disorders' as important potential risks and 'use in pregnancy', 'use in lactation' and 'use in children less than 12 years of age' as missing information for the baseline summary of safety concerns.

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. Dinutuximab - UNITUXIN (CAP) - PSUSA/00010420/201608

Applicant: United Therapeutics Europe Ltd

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

Background

Dinutuximab is a monoclonal chimeric antibody indicated for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation (ASCT). It is administered in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Unituxin, a centrally authorised medicine containing dinutuximab, 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 Unituxin (dinutuximab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the occurrence of transverse myelitis as well as transverse myelitis as undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should use the method of patient exposure calculation estimating the total number of patients exposed instead of patient-days and provide a justification for the proposed updates of the product information with regards to the events of posterior reversible encephalopathy syndrome (PRES) and prolonged urinary retention, based on the data discussed in the current PSUR. Depending on the assessment of the data provided in the next PSUR, the product information might be updated regarding the risks of PRES and prolonged urinary retention.

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

6.1.7. Linaclotide - CONSTELLA (CAP) - PSUSA/00010025/201608 (with RMP)

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Background

Linaclotide is a guanylate cyclase-C receptor agonist (GCCA) indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Constella (linaclotide), 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 further evaluate reports on 'thinking abnormal', 'hypersensitivity reactions', 'intestinal perforation' as well as reports of *Clostridium difficile* infection and discuss, if the latter should be considered as a safety concern. In addition, the MAH should discuss in details forms of reported off-label use. Moreover, viral gastroenteritis should remain a potential risk within the RMP, and an updated RMP including viral gastroenteritis as important potential risk should be submitted with the next PSUR at the latest.

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. Natalizumab - TYSABRI (CAP) - PSUSA/00002127/201608

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins and is indicated as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis for patients despite a full and adequate course of treatment with at least one disease modifying therapy (DMT), as well as for patients with rapidly evolving severe relapsing remitting multiple sclerosis 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.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Tysabri (natalizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH is requested within 90 days to provide more detailed information regarding the fatal events and to present fatal events by SOC[26] and PT[27] according to the country of origin.
- In the next PSUR, the MAH should address the risk of progressive multifocal leukoencephalopathy (PML) and the effectiveness of risk minimisation measures, analyse malignancies from pooled clinical studies and from all data sources with a specific focus on cases of melanoma, leukaemia and female breast malignancies, in accordance with

[26] Medical dictionary for regulatory activities – system organ class (SOC)
[27] Medical dictionary for regulatory activities – preferred term (PT)

committed refine approach, present a cumulative overview of cases of tuberculosis in natalizumab treated patients, monitor carefully the case reports of neuroblastoma in neonates/infants exposed during pregnancy, and discuss again whether L-selectin may present a suitable biomarker for additional PML risk stratification further to the publication of additional new data concerning the potential biomarker CD62L.

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. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/201608 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Panobinostat is a histone deacetylase (HDAC) inhibitor indicated in combination with bortezomib and dexamethasone for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Farydak, a centrally authorised medicine containing panobinostat, 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 Farydak (panobinostat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the statement with regards to the tabulated list of adverse drug reactions from clinical studies to clarify that these ADRs are those seen due to the addition of panobinostat to the combination of bortezomib and dexamethasone in the phase III study in multiple myeloma. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- The MAH should update the RMP at the next regulatory opportunity or at the latest with the submission of the next PSUR.
- In the next PSUR, the MAH should provide stratified patient exposure data and clarify the criteria used to grade non serious-cases.

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

6.1.10. Vemurafenib - ZELBORAF (CAP) - PSUSA/00009329/201608

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

[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

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Zelboraf (vemurafenib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on Dupuytren's contracture and plantar fascial fibromatosis as well as to add Dupuytren's contracture and plantar fascial fibromatosis as undesirable effects with a common and uncommon frequencies respectively. Therefore the current terms of the marketing authorisation(s) should be varied[29].
- The MAH should submit within 60 days a further analysis of posterior reversible encephalopathy syndrome (PRES) including a review of the published literature, data from spontaneous reports and reports from studies as well as a discussion on the need for any potential amendment to the product information. In addition, the MAH is requested to submit a further discussion on the signal of sarcoidosis including a proposed wording for the product information update, should the causal relationship be considered at least possible, and a cumulative review of lymphopenia to further discuss the event including causality assessment and a discussion on the need also to update the product information in this respect.
- In the next PSUR, the MAH should closely monitor the signal of 'gingival hyperplasia / hyperkeratosis' as well as discuss any new cases.

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

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

See also Annex I 16.2.

6.2.1. Busulfan - BUSILVEX (CAP); NAP - PSUSA/00000464/201607

Applicant(s): Pierre Fabre Medicament (Busilvex), various

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

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

Busulfan is a cytotoxic agent and a bifunctional alkylating agent indicated in combination with cyclophosphamide (BuCy2) as a conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option; in combination with fludarabine (FB) as a conditioning treatment prior to HPCT in adult patients who are candidates for a reduced-intensity conditioning (RIC) regimen as well as in combination with cyclophosphamide (BuCy4) or melphalan (BuMel) as a conditioning treatment prior to conventional HPCT in paediatric patients.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Busilvex, a centrally authorised medicine containing busulfan, and nationally authorised medicines containing busulfan, 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 busulfan-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information of both intravenous (i.v.) and oral formulations of busulfan-containing products should be updated to add the undesirable effect 'tooth hypoplasia' with a not known frequency. Moreover, the product information of oral busulfan-containing products should be updated to include the interaction with metronidazole among the special warnings and precautions for use as well as the interactions with other medicinal products and other forms of interaction. The product information of intravenous busulfan-containing products should be updated to include a warning on thrombotic microangiopathy reported after hematopoietic cell transplantation as well as to include the interaction with metronidazole. Therefore, the current terms of the marketing authorisations should be varied[30].
- In the next PSUR, the MAH should provide a cumulative search not only for reports of Stevens–Johnson syndrome (SJS), but overall for severe cutaneous adverse reactions (SCARs) including the relevant information to establish causality. In addition, the MAH should submit the follow-up time of the clinical trials performed with busulfan.

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. Desloratadine - AERIUS (CAP); AZOMYR (CAP); DASSELTA (CAP); DESLORATADINE ACTAVIS (CAP); DESLORATADINE RATIOPHARM (CAP); DESLORATADINE TEVA (CAP); NEOCLARITYN (CAP); NAP - PSUSA/00000962/201607

Applicant(s): Merck Sharp & Dohme Limited (Aerius, Azomyr, Neoclarityn), Krka, d.d., Novo mesto (Dasselta), Actavis Group PTC ehf (Desloratadine Actavis), Ratiopharm GmbH (Desloratadine Ratiopharm), Teva B.V. (Desloratadine Teva), various

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Desloratadine is a long-acting histamine antagonist (LABA) indicated for the relief of symptoms associated with allergic rhinitis or urticaria.

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

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Aerius, Azomyr, Dasselta, Desloratadine Actavis, Desloratadine Ratiopharm, Desloratadine Teva, Neoclarityn, centrally authorised medicines containing desloratadine, and nationally authorised medicines containing desloratadine, 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 desloratadine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning regarding convulsions and to add 'abnormal behavior', 'aggression' and 'QT prolongation' as undesirable effects with unknown frequencies. Therefore, the current terms of the marketing authorisations should be varied[31].
- The MAHs of the centrally authorised desloratadine-containing products are requested to provide, within 90 days, a further analysis of all available data regarding movement disorders (including dystonia, tics and extrapyramidal symptoms) and discuss, whether an update for the product information is warranted in order to include 'movement disorders' as a new undesirable effect.
- In the next PSUR, the MAH should keep the safety signals for 'convulsions', 'movement disorders', 'QT prolongation' and 'abnormal behaviour including aggressive reactions' as ongoing issues as well as discuss them. In addition, the MAHs are requested to discuss cases of interaction with simvastatin and other statins leading to myopathies, as well as cases of cardiac disorders in pediatric patients. Moreover, the MAHs should consider 'hypersensitivity' (including anaphylaxis, angioedema, dyspnea, pruritus, rash and urticarial) and 'abnormal hepatic function' (including hepatitis and elevated hepatic enzymes and bilirubin) as important identified risks, 'convulsion', 'movement disorder' (including psychomotor hyperactivity and restlessness), 'supraventricular tachyarrhythmia', 'QT prolonged', 'hallucination', 'abnormal behavior including aggressive reactions and photosensitivity' as important potential risks, and 'use in pregnancy', 'use in lactation' and 'use in children less than 6 months of age' as missing information for the baseline summary of safety concerns.
- All MAHs for the desloratadine medicinal products authorised in the EU are reminded to ensure that the product information is appropriately updated to reflect existing/approved information for the innovator product(s) if not already included in the product information for their products, where relevant.

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

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

See also Annex I 16.3.

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

6.3.1. Meloxicam (NAP) - PSUSA/00010474/201607

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class indicated in the symptomatic treatment of painful osteoarthritis (arthrosis, degenerative joint disease), rheumatoid arthritis and ankylosing spondylitis.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing meloxicam, 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 meloxicam-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'pancreatitis' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[32].
- In the next PSUR, the MAHs should monitor cases of diverticulitis and cases of psoriasis (induction or exacerbation). In addition, given the suggestion of a possible interaction between meloxicam and tenofovir leading to acute kidney injury, MAHs should monitor reports of the interaction and further investigate the pharmacodynamic and/or pharmacokinetic interactions between meloxicam and tenofovir.

6.3.2. Ropinirole (NAP) - PSUSA/00002661/201607

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Ropinirole is a non-ergoline D2/D3 dopamine agonist indicated for the treatment of Parkinson's disease (PD) and restless legs syndrome (RLS) under certain conditions.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing ropinirole, 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 ropinirole-containing medicinal products in the approved indications remains unchanged.

[32] 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

- Nevertheless, the product information should be updated to include the risk of dopamine agonist withdrawal syndrome (DAWS) and a warning to ensure that ropinirole should be tapered off when treatment of patients with Parkinson's disease is discontinued. DAWS should also be added as an undesirable effect with an unknown frequency. In addition, the product information should include a warning on the risk of hallucinations. Therefore the current terms of the marketing authorisations should be varied[33].
- In the next PSUR, the MAH should provide detailed reviews of 'dopamine dysregulation syndrome' (DDS), 'impulse control disorders' (ICD) including hypersexuality and increased libido, medication errors, 'pregnancy' (especially for RLS), 'fatal cases', 'fibrotic complications' (lungs and cardiac valves), as well as 'atrial fibrillation / cardiac rhythm disorders'. In addition, following the emergence of any new data, the MAHs should provide a discussion on the issues of hypotension (including orthostatic hypotension), syncope, augmentation and early morning rebound (RLS indication only), melanoma, rhabdomyolysis or creatine phosphokinase (CPK) increased, serious diarrhoea, cardiac failure and serious events for standardised MedDRA queries (SMQ) 'haemorrhages' and 'embolic and thrombotic 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.

6.3.3. Trimetazidine (NAP) - PSUSA/00003043/201608

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Trimetazidine (TMZ) is currently indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapy.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing trimetazidine, 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 trimetazidine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'vertigo' as an undesirable effect with a not known frequency. Therefore the current terms of the marketing authorisations should be varied[34].
- In the next PSUR, the MAHs should review and discuss the adverse reactions of 'fall' and 'hyponatremia' as well as address all the safety issues currently under monitoring: extrapyramidal symptoms (including choreiform movements and chorea), falls, orthostatic

[33] Update of SmPC sections 4.4 and 4.8 with a cross-reference in section 4.2 to 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
[34] 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

hypotension/hypotension, hyponatremia, confusional state, parkinsonian symptoms (parkinsonism, extrapyramidal disorders and gait disturbance particularly in elderly patients of 75 years old or more) and patients with renal impairment, coagulation disorders (including haemorrhage and stroke), thrombocytopenia, agranulocytosis and liver dysfunction.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 0

6.4.1. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/LEG 052

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of an analysis of data collected through a follow-up questionnaire regarding spontaneous reports on abuse, misuse, dependence and withdrawal symptoms including a discussion on the potential added value of the collected data. In addition, the MAH submitted a detailed analysis of cases of 'hepatobiliary disorders' as requested in the conclusions of PSUSA/00002511/201601 adopted by PRAC in September 2016

Background

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

In the context of the evaluation of a post-authorisation measure submitted following the conclusions of the PSUR single assessment PSUSA (EMEA/H/C/PSUSA/00002511/201601) for the above mentioned pregabalin-containing medicine(s), the PRAC requested the MAH to submit further data (for background, see PRAC minutes September 2016). 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, either a variation[35], or a justification for not doing so, to update the product information of pregabalin-containing products by adding 'elevated liver enzymes', 'hepatitis', 'jaundice', 'hepatic failure' as undesirable effects with uncommon, very rare, rare and very rare frequencies respectively as well as changing the undesirable effects 'alanine aminotransferase increased' and 'aspartate aminotransferase increased', both of uncommon frequency, in 'elevated liver enzymes' among the hepatobiliary disorders.
- In addition, the MAH should submit in next PSUR a review of the Lyrica target questionnaire[36] (TQ) to assess the possibility of a more concise TQ in order to facilitate a better response. Therefore, each question should be carefully reviewed to verify the need

[35] Update of SmPC section 4.8. The package leaflet is to be updated accordingly
[36] A follow up survey of 12 questions sent to healthcare professionals (HCPs) following report of an adverse event related to potential abuse, misuse, dependence or withdrawal symptoms of pregabalin

for it and the relevance of the information that is sought, taking into account the results from the current review and the information in the current product information. If applicable, an updated version of the TQ should be submitted with the response.

6.4.2. Pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/LEG 005

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of an analysis of data collected through a follow-up questionnaire regarding spontaneous reports on abuse, misuse, dependence and withdrawal symptoms including a discussion on the potential added value of the collected data. In addition, the MAH submitted a detailed analysis of cases of 'hepatobiliary disorders' as requested in the conclusions of PSUSA/00002511/201601 adopted by PRAC in September 2016

Background

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

In the context of the evaluation of a post-authorisation measure submitted following the conclusions of the PSUR single assessment PSUSA (EMEA/H/C/PSUSA/00002511/201601) for the above mentioned pregabalin-containing medicine(s), the PRAC requested the MAH to submit further data (for background, see PRAC minutes September 2016). 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, either a variation[37], or a justification for not doing so, to update the product information of pregabalin-containing products by adding 'elevated liver enzymes', 'hepatitis', 'jaundice', 'hepatic failure' as undesirable effects with uncommon, very rare, rare and very rare frequencies respectively as well as changing the undesirable effects 'alanine aminotransferase increased' and 'aspartate aminotransferase increased', both of uncommon frequency, in 'elevated liver enzymes' among the hepatobiliary disorders.
- In addition, the MAH should submit in next PSUR, a review of the target questionnaire[38] (TQ) to assess the possibility of a more concise TQ in order to facilitate a better response. Therefore, each question should be carefully reviewed to verify the need for it and the relevance of the information that is sought, taking into account the results from the current review and the information in the current product information. If applicable, an updated version of the TQ should be submitted with the response.

[37] Update of SmPC section 4.8. The package leaflet is to be updated accordingly
[38] A follow up survey of 12 questions sent to healthcare professionals (HCPs) following report of an adverse event related to potential abuse, misuse, dependence or withdrawal symptoms of pregabalin

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[39]

7.1.1. Iron intravenous (IV) (NAP) - EMEA/H/N/PSP/J/0053

Applicant: Mesama Consulting

PRAC Rapporteur: Claire Ferard

Scope: 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

Background

Intravenous (IV) iron-containing medicines are indicated in iron deficiency situations when the oral route is insufficient or poorly tolerated especially in chronic kidney disease (CKD) patients (haemodialysis), but also in pre- or post-operative situations, or in case of intestinal absorption disorders.

A protocol for a post-authorisation safety study to assess the risk of severe hypersensitivity reactions to the use of IV iron-containing medicines, was submitted to the PRAC by a consortium of MAHs in accordance with the conditions to the marketing authorisation included in the EC decision (Annex IV) for the referral under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1322) for IV iron-containing medicines. For further background, see PRAC minutes February 2013.

Endorsement/Refusal of the protocol

- The PRAC, having considered the 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 that the design of the study did not fulfil the study objectives.
- The PRAC therefore recommended that the MAH IV iron-consortium should complete the proposed protocol with more details regarding the anaphylaxis markers compounds administered to treat anaphylaxis (i.e. names and number administered) using all available information. The MAH IV consortium should provide, in particular, information on those medicines from the classes of antihistamine (allergy treatment), HIV treatment, nonsteroidal anti-inflammatory drugs (and any other medications which can trigger an allergic reaction), to capture more individuals with comorbidities, separately analysing IV-iron and marker compounds users; and estimate, in new IV-iron users, the risk of anaphylaxis according to number of administrations by IV-iron types[40] to study the phenomenon of patient sensitisation at first exposure with subsequent exposure leading to a reaction. In addition, the IV-iron consortium should undertake additional sensitivity analyses using other pooling methods and also alternative continuity corrections to test the validity of assumptions, to collect all available data in Q1 2018, to provide further details on the indirect validation; to clarify the six-month proposed period for inclusion in

[39] In accordance with Article 107n of Directive 2001/83/EC
[40] Wang C. et al. Comparative Risk of Anaphylactic Reactions Associated with Intravenous Iron Products. JAMA. 2015;314(19):2062-2068. doi:10.1001/jama.2015.15572

the cohort and for the variables related to treatment of anaemia and possible indications for IV-iron treatment; and to capture the route of administration given that Cosmofer may be administered both intravenously and intramuscularly. Finally, the MAH IV iron-consortium should provide the method for analysing the impact of the referral assessment, taking into consideration the incidence of reactions before and after the referral date.

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

7.1.2. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/PSA/S/0016

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Amended PASS protocol (amendment 1, version 3.0) for study CC-5013-MDS-012: a retrospective drug-utilisation study to describe patterns of Revlimid use (from II/56 (extension of indication)

Background

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

In April 2014, the PRAC adopted the protocol for a non-interventional PASS (study CC-5013-MDS-012) designed as a retrospective drug-utilisation study to describe patterns of Revlimid use. The MAH has submitted a substantial protocol amendment further to the feasibility results, to revise various timelines and introduce major changes including the specification of data sources, reduction of the sample size (from 1,000 to 500 MDS patients) and the modification of the study secondary objectives. For further background, see PRAC minutes April 2014.

Endorsement/Refusal of the protocol

- The PRAC, having considered the updated protocol Amendment 1, version 3.0 in accordance with Article 107o of Directive 2001/83/EC, objected to the amended protocol for the above listed medicinal product(s), as the Committee considered that the design of the study did not fulfil the study objectives. The PRAC did not consider acceptable the MAH's proposal to reduce the sample size, given that it may consequently jeopardize the secondary safety objectives. In addition, the MAH should consider modifying the timelines as those proposed would not enable the assessment of the utilisation of lenalidomide in Europe in a timely manner. Therefore, the PRAC recommended that the MAH should revise the protocol in line with the study objectives finally imposed by the PRAC.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 days-assessment timetable will be applied.

7.1.3. Valproate (NAP) - EMEA/H/N/PSA/J/0015

Applicant: Sanofi

PRAC Rapporteur: Sabine Straus

Scope: 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

Background

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

The PRAC adopted in January 2016 a revised protocol (version 3.1) for a post-authorisation safety study (drug utilisation study) to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate further to its submission to the PRAC by a consortium of MAHs in accordance with conditions to the marketing authorisation included in the EC decision Annex IV for the referral under Article 31 of Directive 2001/83/EC (EMA/612389/2014) for valproate-containing medicines. For further background, see PRAC minutes July 2015 PRAC minutes September 2015 and PRAC minutes January 2016. The applicant on behalf of the consortium has submitted a substantial protocol amendment to replace the Spanish database initially included, as well as the consortium composition.

Endorsement/Refusal of the protocol

- The PRAC, having considered the amended protocol version 4.0 in accordance with Article 107o 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 objectives. The PRAC did not consider acceptable to reduce the sample size given that for the study population of interest (female incident users aged between 13-49 years) the minimum number of 384 patients included in the main pre- implementation period for this age category is not reached using IMS LPD[41]. Concerns regarding the representativeness of valproate prescribers and treated patients included in the proposed Spanish database IMS (LPD) were acknowledged. Therefore, the PRAC recommended finding alternatives to enlarge the study population including the pre-intervention period from Spain, to be able to study the primary objective of this DUS, and clarifying whether the characteristics of the prescribers and patients included in IMS (LPD) in Spain and their patterns of use could represent the pattern of use in this country.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[42]

See Annex I 17.2.

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

7.3. Results of PASS imposed in the marketing authorisation(s)[43]

7.3.1. Flupirtine maleate - EMEA/H/N/PSR/J/0007

Applicant(s): Meda Pharma GmbH & Co KG (Flupigil); Meda Pharma - Produtos Farmaceuticos, S.A. (Metanor)

PRAC Rapporteur: Valerie Strassmann

Scope: Submission of the final study results for an imposed non-interventional PASS: retrospective chart review to evaluate the effectiveness of the risk minimisation measures for the use of flupirtine 100 mg immediate-release capsules in daily practice

Background

In line with the conclusions of a referral under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for flupirtine-containing medicines (EMEA/H/107i/1363), MAHs were required (Annex VI) as a condition to the marketing authorisations to conduct a PASS to evaluate the effectiveness of the risk minimisation activities. The protocol for this retrospective chart review to evaluate the effectiveness of the risk minimisation measures for the use of flupirtine 100 mg immediate-release capsules in daily practice was assessed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. For background information, see PRAC minutes March 2013, PRAC minutes May 2013, PRAC minutes June 2013, PRAC minutes May 2014, PRAC minutes June 2014, PRAC Minutes December 2014, PRAC minutes March 2015, PRAC minutes July 2015.

Summary of advice

- Based on the review of the final report of the non-interventional PASS, the PRAC considered that supplementary information should be requested before a recommendation can be made.
- The PRAC considered that the missing data from Portugal (due to problems at the study site recruitment) were necessary to complement the German data and further determine the existence or not of a similar trend to the one observed in Germany. In addition, the PRAC agreed on the need to understand the reasons for the limited effectiveness of the current risk minimisation measures in Germany before reassessing the most appropriate way to effectively minimise the risk of hepatotoxicity with flupirtine. In this regard, the MAH should, as part of the Request for Supplementary Information, elaborate on the reasons for the observed non-compliance rates. The MAH should make all possible efforts to understand their lack of adherence to the current safety restrictions and monitoring requirements.
- The MAH should submit responses to the request for supplementary information within 60 days to EMA. A 60 days-assessment timetable will be applied.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[44]

See Annex I 17.4.

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

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

See Annex I 0

7.6. Others

See Annex I 0

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 0

8.2. Conditional renewals of the marketing authorisation

See Annex I 0

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 EMA

10.1. Safety related variations of the marketing authorisation

10.1.1. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/II/0026; canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0023

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: PRAC consultation on type II variations to update the safety information in section 4.4 of the SmPC in relation to the existing warning on diabetic ketoacidosis (DKA): the term 'and fatal' is added when describing the DKA cases that have been reported. The Package Leaflet is updated accordingly: term 'rare but serious, sometimes life-threatening and fatal' is added when describing DKA. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

Background

Canagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor indicated in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control as monotherapy or as add-on therapy. Canagliflozin, in combination with metformin, a biguanide, is indicated in adults aged 18 years and older with T2DM as an adjunct to diet and exercise to improve glycaemic control under certain conditions.

A type II variation is under evaluation at the CHMP proposing to update the product information of canaglifozin-containing products (Invokana and Vokanamet) on an extension of the warning statement regarding diabetic ketoacidosis (DKA) to add that fatal cases of DKA have been reported in patients taking canagliflozin. Recently, the PRAC concluded in a referral under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1419) that DKA can be associated with all three SGLT2-inhibitors-containing medicines currently on the market. This suggests a class effect. The incidence of cases of DKA was low with all SGLT2 inhibitors products. Currently, it is not possible to decide whether the risk is comparable for the three products. The PRAC was requested to provide advice on this variation and whether the cases of fatal DKA would also apply to the other authorised representatives of the class of SGLT2 inhibitors. For further background, see PRAC minutes June 2015, PRAC minutes October 2015, and PRAC minutes February 2016.

Summary of advice

- Based on the review of the available information, including case reports in EudraVigilance, the PRAC agreed that the product information of canagliflozin-containing medicines should be revised[45] to include the information on fatal cases of DKA in the existing warning, and that this revised warning on DKA should also apply to the other authorised representatives of the SGLT2- inhibitors class, i.e. dapagliflozin and empagliflozin-containing medicines. Consequently, the PRAC suggested an updated wording related to the existing warning on DKA to introduce the notion that some cases of DKA have had a fatal outcome, for all authorised SGLT2-inhibitors medicines.
- In addition, the Committee recommended that further evaluation of cases of fatal DKA and the revision of the existing warning on DKA in the product information for empagliflozin and dapagliflozin are handled in their ongoing PSUSA procedures, i.e. respectively PSUSA/00010388/201610 for empagliflozin and PSUSA/00010029/201610 for dapagliflozin, which will both conclude at the May 2017 PRAC meeting.

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

None

10.3. Other requests

10.3.1. Brodalumab – EMEA/H/C/003959

Scope: PRAC consultation on an initial application for brodalumab with a proposed indication for the treatment of moderate to severe plaque psoriasis

For further background, see PRAC minutes September 2016 and PRAC minutes November 2016.

10.3.2. Rituximab – MABTHERA (CAP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Background

Rituximab is a monoclonal antibody that binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes and is indicated for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), and rheumatoid arthritis as well as for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis under certain conditions.

The PRAC was consulted by EMA following a third party enquiry regarding the impact of rituximab on T-cell counts, in particular CD4, in rituximab-treated patients as well as the need for stratification of rituximab patients for the risk of developing progressive multifocal leukoencephalopathy (PML) based on the JC virus[46] status and raising concerns that the incidence of PML in rituximab patients is greater than stated in the Mabthera (rituximab)

[45] Update of SmPC section 4.4 The package leaflet is to be updated accordingly
[46] John Cunningham virus

product information and that applying the STRATIFY 2 test in rituximab patients would reduce the PML related mortality. Correspondence with the enquirer, including EMA's response, was shared with the Committee.

Summary of advice

- Having considered the information presented by the PRAC Rapporteur, the PRAC acknowledged that the impact of rituximab on T-cell counts, in particular CD4, in rituximab-treated patients and risk of PML are part of the ongoing PSUR assessment. The PRAC also agreed that the frequency of PML associated with rituximab in the different indications as well as the current risk minimisation strategy should be reviewed in this procedure.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh

None

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 - update

PRAC lead: Jolanta Gulbinovič

The topic was deferred to a later PRAC meeting. The Committee will be updated in due

course.

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

At the organisational matters teleconference held on 23 March 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 help 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. An overview of the stakeholder engagement meetings held since November 2016 was presented: the Flagship event on 23 November 2016 in London, the SCOPE stakeholder event on 20-21 March 2017 in London as well as the forthcoming local stakeholder meetings scheduled on 25 April 2017 in Croatia and 23 March 2017 in Hungary, and the SCOPE signal management training scheduled on 24-25 April 2017 in the Netherlands. In addition, an update on SCOPE deliverables, the SCOPE and EURORDIS training, the pilot exchange program and the upcoming activities was given. The PRAC welcomed receiving regular updates on the progress of SCOPE. Any questions can be sent to the MHRA as coordinator of the project: scope@mhra.gsi.gov.uk.

12.5. Cooperation with International Regulators

12.5.1. Gaucher disease - a strategic collaborative approach between EMA and FDA

A strategic collaborative approach between EMA and FDA was developed to facilitate paediatric drug development particularly in the field of Gaucher disease. A draft document was released for public consultation in May 2014. At the organisational matters teleconference held on 23 March 2017, the PRAC was updated on the outcome of the public consultation and the timelines for a further synchronised publication between EMA and FDA.

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

At the organisational matters teleconference on 23 March 2017, the PRAC Secretariat presented to the Committee the draft final PRAC work plan for 2017 as consolidated following previous discussions (for background, see PRAC minutes February 2017). The PRAC adopted the work plan 2017.

Post-meeting note: On 04/04/2017, the PRAC work plan 2017 (EMA/PRAC/213230/2017) was published on the EMA website.

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Good Pharmacovigilance Practices (GVP) module II on 'Pharmacovigilance system master file' – Revision 2

The PRAC adopted the 'GVP Module II – Pharmacovigilance system master file (PMSF)' revision 2, implementing some administrative revisions following the adoption at the Pharmacovigilance Inspectors' Working Group (PhV IWG) in light of recent regulatory changes, and minor edits. See also PRAC minutes December 2016.

12.9.2. Pharmacovigilance systems and their quality systems

None

12.9.3. Pharmacovigilance inspections

None

12.9.4. Pharmacovigilance audits

None

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

12.10.1. PSUR single assessment (PSUSA) for CAPs only - editorial changes to product information

At the organisational matters teleconference on 23 March 2017, the EMA Secretariat presented the possibility now provided to MAHs to implement minor editorial changes not requiring assessment[47] in the product information in the PSUR procedures (CAPs only) with an outcome of variation of the conditions of the marketing authorisation. Of note, changes in the scientific content cannot be accepted as an editorial change. This implementation of minor editorial changes is acceptable when a variation is not foreseen in the near future and consequently the MAH cannot comply with the EMA recommendation to implement this type of editorial changes within a separate upcoming variation.

[47] The EMA defines minor editorial changes as 'formatting changes, correction of typographical errors and/or mistakes to the English Product Information or other linguistic versions of the Product Information provided that the meaning of the text is not altered'. Examples of acceptable editorial changes include update of local representatives and minor alignment with the last QRD template

12.10.2. Roadmap for PSUR issues - explanatory note to Good Pharmacovigilance Practice (GVP) module VII on 'Periodic safety update report' and 'Questions & Answers (Q&A)' document to assessors

PRAC lead: Menno van Der Elst

Following the previous PRAC discussions (see PRAC minutes February 2016, PRAC minutes March 2016, PRAC minutes April 2016, PRAC minutes May 2016, and PRAC minutes November 2016), the EMA Secretariat presented to the PRAC an overview of the comments received from the Industry stakeholders, at the tenth industry platform on the operation of EU pharmacovigilance legislation hold on 3 February 2017, on the explanatory note to GVP module VII on 'Periodic safety update reports (PSURs)', and the Q and A document for assessors (EMA/518909/2016), developed as follow-up actions from the joint PRAC/CMDh recommendation paper on common understanding on EU PSUR single assessment. The PRAC endorsed the 'explanatory note' to GVP module VII following the comments from the stakeholders (EMA/102307/2017).

12.10.3. 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 welcomed the progress being made.

12.10.4. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version March 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 March 2017, the updated EURD list was adopted by the CHMP and CMDh at their March 2017 meetings and published on the EMA website on 28 March 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

The PRAC was updated on the outcome of the March 2017 SMART Working Group (SMART WG) work stream WS1. Further to the discussions in the December 2016 and February SMART WG WS1 of the pilot for the adoption of signal recommendations without an initial discussion at the plenary meeting, SMART took into account the comments received from the PRAC working group on efficiency. As agreed, the pilot is to be extended for another 6 months, until June 2017. In addition, a reflection is being undertaken on an appropriate set of criteria for MAHs to prioritise safety issues to be channelled via signal procedures. Moreover, the group discussed further the ongoing development of the MAH signal validation form.

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 29 March 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

Following the last discussion on the EudraVigilance (EV) auditable requirement project (see PRAC minutes June 2016 and PRAC minutes January 2016), the EMA secretariat presented a status update on the latest developments, activities and outcomes relating to the audit plan. The Committee confirmed the steps to prepare the corresponding PRAC recommendation at the May 2017 PRAC meeting.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Good Pharmacovigilance Practice (GVP) module V on 'Risk management systems' - finalisation

The EMA Secretariat presented to the PRAC the revised good pharmacovigilance practice (GVP) module V on 'Risk management systems'. Some changes in terms of terminology, guidance and updated requirements have been implemented. In parallel the RMP template for industry has also been revised to get aligned with the ongoing GVP module V revision. See 0

The Committee adopted the revised GVP module V (EMA/838713/2011 Rev 2) and agreed the following transitional arrangements:

- RMP template revision 1 will be accepted until 30 September 2017 for initial marketing authorisation applications (MAA) and responses to day 120 list of questions (LoQ) but, after this date, RMP template revision 2 should be used;
- All other RMP submissions, pre-authorisation or post-authorisation (including responses to day 90 LoQ for an initial application under accelerated assessment) using the RMP template revision 1 will be accepted until 30 March 2018.

Post-meeting note: The GVP Module V on 'Risk management systems (rev.2)' was published on 30 March 2017 on the EMA website (see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Good pharmacovigilance practices>Guideline on good pharmacovigilance practices: Module V – Risk management systems).

12.14.2. Good Pharmacovigilance Practice (GVP) module V on 'Risk management systems' - outcome of PRAC survey

PRAC lead: Sabine Straus

The PRAC welcomed the presentation by the EMA Secretariat of the survey results where PRAC members were consulted on several aspects of the GVP module V, including their opinion on new definitions, generics, and the most important changes.

12.14.3. Risk management plan (RMP) template for industry - finalisation

In parallel to the revision of the good pharmacovigilance practice (GVP) module V on risk management systems, the PRAC adopted the revised RMP template. See 12.14.1.

Post-meeting note: The second revision of the RMP template was published on 30 March 2017 on the EMA website (see: Home>Human Regulatory>Marketing authorisation>Pharmacovigilance> Risk management>Risk management plans).

12.14.4. Risk management plan (RMP) review process - review of experience with the revised process and quantitative survey results

The PRAC welcomed the presentation by the EMA Secretariat of the outcome of a quantitative survey on the experience with the revised RMP review process implemented for MAAs starting in May 2015 with a collaborative approach between PRAC and CHMP and where more than 80 marketing authorisation applications were included in the review set.

12.14.5. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Good Pharmacovigilance Practices (GVP) – PRAC review and adoption of revised GVP modules in 2017: update on GVP status and overview

The PRAC was provided with an overview of the good pharmacovigilance practices (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. Industry stakeholder platform on the operation of the EU pharmacovigilance – Feedback from the tenth industry stakeholder platform meeting held on 3 February 2017

The PRAC welcomed the feedback provided by the EMA Secretariat on the tenth industry stakeholder platform meeting on the operation of EU pharmacovigilance hosted by EMA on 3 February 2017. At the meeting, the Regulators updated the industry stakeholders on the matters arising in the field including the 2017 PRAC work plan, and gave an overview of the GVP work for 2017 (e.g. the finalisation of the revised GVP module V), as well as the regulatory requirements for post-authorisation studies, in particular the publication of the information related to study protocols and results. In addition, the Regulators gave some updates on the PSUR developments, on the registries initiative, as well as on a review of the MAHs' compliance with PRAC signal recommendations requesting variations of the product information (PI) for the CAPs (reference period: May 2015 - April 2016) with an overall positive results.

12.20.3. Strategy on measuring the impact of pharmacovigilance activities – report from the workshop held on 5-6 December 2016

The EMA Secretariat presented the report of the Workshop on measuring the impact of pharmacovigilance activities held on 5-6 December 2016. For further background, see PRAC minutes January 2016. The PRAC endorsed the publication of the workshop report (EMA/59474/2017).

Post-meeting note: The workshop report has been published on the EMA website on 27 March 2017.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[48]

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[49].

14.1.1. Fulvestrant - FASLODEX (CAP)

Applicant: AstraZeneca UK Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of anaphylactic reactions

EPITT 18832 – New signal

Lead Member State: SE

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. Efavirenz, emtricitabine, tenofovir disoproxil – EMEA/H/C/004250

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

15.1.2. Etirinotecan pegol - EMEA/H/C/003874

Scope: Treatment of breast cancer with brain metastases

15.1.3. Nitisinone - EMEA/H/C/004281

Scope: Treatment of hepatorenal tyrosinemia type 1

[48] 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

[49] 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

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. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS1103/0018; XIGDUO (CAP) - EMEA/H/C/002672/WS1103/0029

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 8.3) to implement the outcome of the Article 31 referral procedure (EMEA/H/A-31/1432) on metformin and metformin-containing medicines regarding the use in patients with moderate renal impairment (Commission Decision dated 12 December 2016)

15.2.2. Darunavir - PREZISTA (CAP) - EMEA/H/C/000707/WS1059/0084; Darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/WS1059/0015

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 3.1) in order to delete the category 3 study TMC114HIV3015: a single arm, open label trial to assess the pharmacokinetics of darunavir/ritonavir, darunavir/cobistat, etravirine and rilpivirine in human immunodeficiency virus (HIV)-1 infected pregnant women, and replace it by pharmacokinetics data in HIV-1 pregnant women

15.2.3. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS1063/0022; Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS1063/0027

Applicant: AbbVie Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the RMP for Exviera and Viekirax to: 1) add information on cases of hepatic decompensation observed in patients with Child-Pugh B hepatic impairment, and to reflect the changes of the SmPC to change the dose recommendation of these patients to 'not recommended', as well as the addition of statements recommending the monitoring of hepatic function in these patients as approved on WS/0873; 2) add a reference to nine drug-drug interaction studies as approved in WS0896/G; 3) include a reference to the completion of rat 2 year carcinogenicity studies as recently approved in variations II-06 (Exviera) and II-04 (Viekirax) respectively; 4) reflect the update of section 4.2 of SmPC for Viekirax to recommend a decrease in treatment duration of 12 weeks in genotype 4 (GT4) cirrhotic patients, with a consequential change to sections 4.4 and 5.1 as approved in II-22-G; 5) remove the non-clinical PAMS 1-3, (MEA/003, MEA/002, MEA/003)

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. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0107

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information following the MAH's initiative to update its clinical trials safety database to include all currently completed clinical trials for both the intravenous (IV) and subcutaneous (SC) formulations. The adverse reactions' table in section 4.8 as well as the description of selected adverse reactions of special interest is amended. As a consequence, section 4.4 is brought in line with the amended section 4.8. The Package Leaflet and the RMP (version 22) are updated accordingly

15.3.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0163

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of chronic non-infectious uveitis in paediatric patients. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 13.0) are updated accordingly. In addition, the MAH took the opportunity to implement an alternative format statement for blind/partially sighted patients into the Package Leaflet as introduced with procedure EMEA/H/C/000481/N/0155. Furthermore, the MAH made some editorial changes to the package leaflet

15.3.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0047

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report for study LBSL99/BEL112626 (RMP, category 3, MEA 010): a multicentre, open label, continuation trial of monoclonal anti-BLyS antibody in subjects with systemic lupus erythematosus (SLE) who completed the phase 2 protocol LBSL02. The RMP (version 22) is updated accordingly

15.3.4. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0012

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include Zykadia as first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). As

a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated to update the information based primarily on the supporting study CLDK378A2301 (ASCEND-4: a phase III multicentre, randomized study of oral ceritinib versus standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK-positive), stage IIIB or IV, non-squamous NSCLC). The Package Leaflet and the RMP (version 6.0) are updated accordingly

15.3.5. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/X/0055/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications including: 1) line extension to introduce a new pharmaceutical form associated with new strengths (1 mg, 2.5 mg and 5 mg hard capsules), 2) variation to include paediatric use in the approved indication. As a consequence, sections 4.2 and 4.4 of the SmPC are updated to detail the posology in paediatric patients and to update the safety information respectively. The Package Leaflet, Labelling and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the product information is brought in line with the latest QRD template (version 10)

15.3.6. Cobicistat - TYBOST (CAP) - EMEA/H/C/002572/WS1086/0034 Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/WS1086/0077

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for study GS-US-236-0140: a phase IV, randomized, open-label study evaluating the renal effect of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (DF) or other tenofovir DF-containing regimens (ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF or efavirenz/emtricitabine/tenofovir DF) compared to ritonavir-boosted atazanavir plus abacavir/lamivudine in antiretroviral treatment-naïve human immunodeficiency virus (HIV)-1 infected adults with an estimated glomerular filtration rate (eGFR)≥70 mL/min. The RMP (version 2.0) is updated accordingly

15.3.7. Darunavir - PREZISTA (CAP) - EMEA/H/C/000707/WS1089/0086/G; Darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/WS1089/0018/G

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variation including: 1) submission of the final report for study GS-US-236-0140 (RMP, category 3): a phase IV, randomized, open-label study evaluating the renal effect of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (DF) or other tenofovir DF-containing regimens (ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF or efavirenz/emtricitabine/tenofovir DF) compared to ritonavir-boosted atazanavir plus abacavir/lamivudine in antiretroviral treatment-naïve human immunodeficiency virus (HIV)-1 infected adults with an estimated glomerular filtration rate (eGFR)≥70 mL/min. The RMP (version 25.0 for Prezista and version 4.0 for Rezolsta) are updated accordingly. The RMP are

also updated to remove the important potential risks of 'renal toxicity'.; 2) based on a cumulative review of the available data, the RMPs are also updated to remove the important risks of 'pancreatis', 'convulsions' and 'cardiac conduction abnormalities' and the important risk 'development of drug resistance'

15.3.8. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0086/G, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations including: 1) update of section 4.8 of the SmPC with the adverse drug reactions (ADR) frequencies to reflect overall exposure to eculizumab in clinical trials; 2) update of section 4.4 of the SmPC with warning and precautions on meningococcal vaccination timing as recommended by PRAC. The Package Leaflet, Annex II and the RMP (version 13) are updated accordingly. In addition, the RMP is updated in order to implement the previous PRAC recommendation to remove the off label use from missing information, to provide the exposure data from PSUR#13 and to update the epidemiology sections with more complete and recent scientific literature data. Moreover, the MAH took the opportunity to update the Product Information to add editorial changes and to bring it in line with the latest QRD template

15.3.9. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0090, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include the 'treatment of refractory generalised myasthenia gravis (gMG) patients who are antiacetylcholine receptor (AChR) antibody-positive'. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated to include information on the new indication and to include the new methodology to calculate the adverse drug reaction frequencies in section 4.8. The RMP (version 14.0) is updated accordingly

15.3.10. Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/II/0026

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include paediatric patients from 6 to less than 12 years of age, with a body weight of at least 25kg, infected with human immunodeficiency virus (HIV)-1 without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir. As a consequence, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated based on the analysis of the paediatric study GS-US-292-0106 (cohort 2): a phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 Infected antiretroviral treatment naive adolescents and virologically suppressed children. The Package Leaflet and the RMP (version 3) are updated accordingly

15.3.11. Emtricitabine, tenofovir disoproxil – EMTRICITABINE,TENOFOVIR DISOPROXIL MYLAN (CAP) - EMEA/H/C/004050/II/0001

Applicant: Mylan S.A.S

PRAC Rapporteur: Julie Williams

Scope: Update of the SmPC following the assessment of the extension of indication for the reference product, Truvada, for pre-exposure prophylaxis. The Package Leaflet, Annex II and Labelling are updated accordingly

15.3.12. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0034

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of section 5.1 of the SmPC in order to reflect the final results of the post authorisation efficacy study (PAES) CL-9785-0410 which was a study of enzalutamide in patients with progressive mCRPC previously treated with abiraterone acetate, listed as a category 3 in the RMP. The RMP (version 11.0) is updated accordingly

15.3.13. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0035

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.4 and 4.8 of the SmPC to reflect the final results of PASS CL-9785-0403 (UPWARD): a multicentre, single-arm, open-label, post-marketing safety study to evaluate the risk of seizure among subjects with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide who are at potential increased risk of seizure (RMP category 3). The RMP (version 11.0) is updated accordingly. In addition, the MAH took the opportunity to introduce a correction in section 5.1 of the SmPC

15.3.14. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0036

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.6 and 5.3 of the SmPC to reflect the final results of study AE-7592-G on transfer of radioactivity into foetuses and breast milk in rats after a single oral administration of [^{14}C] enzalutamide - ISN: 9785-ME-0046. The Package Leaflet and the RMP (version 11.0) are updated accordingly

15.3.15. Eslicarbazepine acetate - ZEBINIX (CAP) - EMEA/H/C/000988/II/0053

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication for the tablet formulation to include the use of Zebinix as monotherapy in adults, in addition to the previously authorised indication as adjunctive

therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 15.0) are updated accordingly.

15.3.16. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0041

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.1 of the SmPC in order to align it with more recently approved glucose-lowering agents and with the 'reflection paper on the wording of indication for medicinal products for treatment of type 2 diabetes' In addition, update of section 5.1 based on study D5553C00003 (Duration 8 study): a 28-week, multicentre, randomized, double-blind, active-controlled, Phase 3 study with a 24-week extension phase followed by a 52-week extension phase to evaluate the efficacy and safety of simultaneous administration of exenatide once weekly 2 mg and dapagliflozin once daily 10 mg compared to exenatide once weekly 2 mg alone and dapagliflozin once daily 10 mg alone in patients with type 2 diabetes who have inadequate glycemic control on metformin. The Package Leaflet and the RMP (version 24) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes in the SmPC and Package Leaflet

15.3.17. Fampridine - FAMPYRA (CAP) - EMEA/H/C/002097/II/0036/G

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Sabine Straus

Scope: Grouped variations to: 1) update sections 4.2 and 5.1 of the SmPC, Annex II and the Package Leaflet based on the results of the clinical study ENHANCE: a multicentre, randomized, double blind, placebo controlled study to assess the long-term efficacy and safety of prolonged release fampridine 10 mg, administered twice daily in subjects with multiple sclerosis; 2) update of section 4.6 of the SmPC based on the data from pregnancy registry; 3) update of section 4.2 and 5.2 of the SmPC based on the core data sheet (CDS) and PRAC review of the Fampyra PSUR#03. The RMP (version 11) is updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10.0). Finally, a switch from a conditional to a standard marketing authorisation (MA) is assessed as part of this procedure

15.3.18. Follitropin delta - REKOVELLE (CAP) - EMEA/H/C/003994/II/0003/G

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations including: 1) introduction of a pre-filled cartridge as a new presentation for Rekovelle strength 12 µg/0.36mL; 2) addition of a new pack size for the strength 36 µg/1.08mL and addition of a new pack size for the strength 72 µg/2.16mL. As a consequence, sections 2, 4.2, 6.3, 6.5, 6.6 and 8 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly

15.3.19. Human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP) - EMEA/H/C/002493/II/0017/G

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Grouped variations including: 1) update of section 4.8 of the SmPC in order to amend the frequencies of undesirable effects to reflect the final clinical study report (CSR) from study CSLCT-BIO-08-53: a phase III, open-label, multicentre study to evaluate efficacy, pharmacokinetics, and safety of Voncento in paediatric subjects with haemophilia A. The Package Leaflet and the RMP (version 6.1) are updated accordingly. The revised RMP also includes the removal of the commitment to conduct a post-marketing study for haemophilia A patients (study CSLCT-BIO-12-78) for Voncento as a consequence of new data from study CSLCT-BIO-08-53. In addition, the MAH took the opportunity to combine different strengths in the SmPC and Package Leaflet

15.3.20. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP) - EMEA/H/C/000703/WS1128/0071; SILGARD (CAP) - EMEA/H/C/000732/WS1128/0062

Applicant: Sanofi Pasteur MSD SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 5.1 of the SmPC based on the final report for study P019-21: a long-term follow-up study of safety, immunogenicity, and effectiveness of human papillomavirus [types 6, 11, 16, 18] recombinant vaccine in mid-adult women (FUTURE III (females united to unilaterally reduce endo-/ecto-cervical cancer)) (Gardasil MEA 060.2; Silgard MEA 059.2) and fourth interim report for study P015-21: a registry-based study of protocol V501-015 subjects, and recipients of human papillomavirus [types 6, 11, 16, 18] recombinant vaccine in countries with centralised cervical cancer screening infrastructures to evaluate the long-term effectiveness, immunogenicity, and safety of human papillomavirus [types 6, 11, 16, 18] recombinant vaccine (Gardasil/Silgard MEA 019.7). The RMP (version 11) is updated accordingly

15.3.21. 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. Section 4.6 of the SmPC, the Package Leaflet and the RMP (version 13.2) are updated accordingly. The MAH also took the opportunity to bring the product information in line with the QRD template and update the local representatives of the Package Leaflet

15.3.22. Insulin degludec - TRESIBA (CAP) - EMEA/H/C/002498/II/0024/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations to update sections 4.2 and 5.1 of the SmPC in order to include updated information on the use of Tresiba in terms of transfer from other basal insulin regimens and the effects of Tresiba on hypoglycaemia following the completion of studies NN1250-3995 (SWITCH 1: a randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, both with insulin aspart as mealtime insulin in subjects with type 1 diabetes) and NN1250-3998 (SWITCH 2: a randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, with or without oral antidiabetic drugs in subjects with type 2 diabetes), comparing the safety and efficacy of Tresiba (insulin degludec) and insulin glargine U-100. The Package Leaflet, Labelling and RMP (version 7.0) are updated accordingly. The MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10). Finally, minor changes have been made to the SmPC section 4.2 and the corresponding section of the Package Leaflet to clarify the correct use of Tresiba (insulin degludec)

15.3.23. Insulin degludec, liraglutide - XULTOPHY (CAP) - EMEA/H/C/002647/II/0017

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.2 of the SmPC in order to update the information on use of Xultophy in patients with hepatic impairment based on clinical trial NN2211-1328 (a single-centre, open-label trial investigating the pharmacokinetics and the safety profile after a single dose of liraglutide in subjects with hepatic impairment and in subjects with normal hepatic function), the LEAD 1-6 meta-analysis as well as other liraglutide trials. In addition, 'fatigue' has been added to the tabulated list of adverse reactions in section 4.8 of the SmPC. The Package Leaflet and the RMP (version 6.0) are updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10)

15.3.24. Lapatinib - TYVERB (CAP) - EMEA/H/C/000795/II/0048/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations to: 1) update sections 4.4, 4.8, and 5.1 of the SmPC in order to add a warning on QTc prolongation and update safety information following the submission of study report EGF114271: a phase IV placebo controlled single sequence crossover study to evaluate the effect of repeat oral doses of lapatinib on cardiac repolarization in patients with advanced cancer; 2) update section 4.8 of the SmPC in order to further elaborate on the undesirable effect 'serious cutaneous reactions' based on the review of the MAH's safety database. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the product information (PI) in line with the latest QRD template (version 10) and to update Annex II to delete a condition which was fulfilled with procedure ANX 28.2. The RMP (version 32) is updated accordingly also introducing template-related changes, study milestones updates, and to upgrade 'food effect' to an important identified risk (from procedure EMEA/H/C/000795/II/0024)

15.3.25. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/X/0088/G, Orphan

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Grouped application including: 1) extension of indication to include the treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP), or with Ph+ CML-CP resistant or intolerant to prior therapy including imatinib, based on results from two clinical studies in paediatric patients conducted in accordance with the approved Tasigna paediatric investigation plan (PIP): a phase I pharmacokinetic (PK) study CAMN107A2120 (a multicentre, open-label, pharmacokinetic study of oral nilotinib in paediatric patients with newly diagnosed chronic phase (CP) Ph+ CML, with CP or accelerated phase (AP) Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or with refractory/relapsed Ph+ ALL) and a Phase II safety and efficacy study CAMN107A2203 (a multicentre, open label, non-controlled phase II study to evaluate efficacy and safety of oral nilotinib in paediatric patients with newly diagnosed Ph+ CML in CP or with Ph+ CML in CP or AP resistant or intolerant to either imatinib or dasatinib). The RMP (version 18.0) is updated accordingly; 2) line extension to add a new strength of 50mg hard capsules. In addition, the MAH proposed to merge the SmPCs for the 50 mg and 200 mg strengths

15.3.26. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0017

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) after platinum-based therapy in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, of the SmPC are updated in order to add the proposed new indication, add a warning that patients with a baseline performance score ≥ 2, untreated brain metastasis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the SCCHN clinical trial and update the undesirable effects and safety information. The Labelling and RMP (version 6.0) are updated accordingly

15.3.27. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0029

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of hepatocellular carcinoma after prior sorafenib therapy in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (version 8.0) are updated accordingly

15.3.28. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0030

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine based therapy. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add the new indication and update the safety information. The Package Leaflet and the RMP (version 9.0) are updated accordingly

15.3.29. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0014

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of classical Hodgkin lymphoma (cHL) in adults who have refractory disease, or who have relapsed after greater than 3 prior lines of therapy, based on the results from study KEYNOTE-087, an open-label phase II trial of pembrolizumab in subjects with relapsed or refractory cHL and study KEYNOTE-013, a phase Ib multi-cohort trial of pembrolizumab in subjects with hematologic malignancies. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 5.0) are updated accordingly

15.3.30. 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

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations including: 1) extension of indication to include paediatric population to register Nplate 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

15.3.32. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS1075/0037; Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS1075/0006; Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/WS1075/0043

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final non-clinical study report PC-334-2035 assessing the potential for a pharmacokinetic (PK) interaction via transporter or enzyme based inhibition when sofosbuvir and other direct acting antivirals (DAAs) are used concomitantly with amiodarone. The RMPs (version 1.0 for Epclusa, version 2.0 for Harvoni, version 5.0 for Sovaldi) are updated accordingly

15.3.33. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0066

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the use in adult patients for the treatment of giant cell arteritis for the subcutaneous formulation of RoActemra. 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 information relevant to this indication. The Package Leaflet and the RMP (version 21) are updated accordingly

15.3.34. Trifluridine, tipiracil - LONSURF (CAP) - EMEA/H/C/003897/II/0002/G

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations to: 1) update of sections 4.2, 4.4 and 5.2 of the SmPC following availability of the final clinical study report for study TO-TAS-102-106: a phase I, open-label study evaluating the safety, tolerability, and pharmacokinetics of TAS-102 in patients with advanced solid tumours and varying degrees of hepatic impairment (requested in MEA 002). The RMP (version 5.0) is updated accordingly to remove the missing information 'use in patients with moderate to severe hepatic impairment' and to add 'hyperbilirubinaemia in patients with baseline moderate to severe hepatic impairment' as important potential risk; 2) update of sections 4.5 and 5.2 of the SmPC following availability of the results in vitro CYP induction study of tipiracil hydrochloride (TPI) using the appropriate concentration of TPI (requested in a recommendation). The RMP is updated accordingly; 3) update of section 4.2 of the SmPC in order to correct inconsistencies in the dose calculation according to body surface area. The package leaflet is updated to add 'interstitial lung disease'. Finally, the MAH took the opportunity to update Annex IIIA in accordance with the latest QRD template

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 procedures including centrally authorised products only

16.1.1. Agalsidase beta - FABRAZYME (CAP) - PSUSA/00000070/201607

Applicant: Genzyme Europe BV

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.2. Asenapine - SYCREST (CAP) - PSUSA/00000256/201608

Applicant: N.V. Organon

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.3. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/201608

Applicant: AstraZeneca AB

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.4. Cobicistat - TYBOST (CAP) - PSUSA/00010081/201608

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.5. Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - PSUSA/00010082/201608

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.6. Collagenase clostridium histolyticum[50] - XIAPEX (CAP) - PSUSA/00000871/201608

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.7. Copper (^{64}Cu) chloride - CUPRYMINA (CAP) - PSUSA/00010040/201608

Applicant: Sparkle S.r.l.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.8. Crizotinib - XALKORI (CAP) - PSUSA/00010042/201608

Applicant: Pfizer Limited

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.1.9. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) - VAXELIS (CAP) - PSUSA/00010469/201608

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.10. Dronedarone - MULTAQ (CAP) - PSUSA/00001180/201607

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.11. Eliglustat - CERDELGA (CAP) - PSUSA/00010351/201608

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.12. Elosulfase alfa - VIMIZIM (CAP) - PSUSA/00010218/201608

Applicant: BioMarin Europe Ltd

[50] Indicated in the treatment of Dupuytren's contracture and treatment of Peyronie's disease only

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.13. Elvitegravir - VITEKTA (CAP) - PSUSA/00002577/201608

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.14. Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - PSUSA/00010514/201608 (with RMP)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.15. Emtricitabine, rilpivirine, tenofovir disoproxil - EVIPLERA (CAP) - PSUSA/00009142/201608

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.16. Enzalutamide - XTANDI (CAP) - PSUSA/00010095/201608

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.17. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/201608

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.18. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/201608

Applicant: Shield TX (UK) Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Florbetaben (^{18}F) - NEURACEQ (CAP) - PSUSA/00010094/201608

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.20. Pioglitazone - ACTOS (CAP), GLUSTIN (CAP); pioglitazone, glimepiride - TANDEMACT (CAP); pioglitazone, metformin - COMPETACT (CAP), GLUBRAVA (CAP); PSUSA/00002417/201607

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.21. Human alpha$_1$-proteinase inhibitor - RESPREEZA (CAP) - PSUSA/00010410/201608

Applicant: CSL Behring GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.22. Human coagulation factor VIII, human von Willebrand factor[51] - VONCENTO (CAP) - PSUSA/00010102/201608

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.23. Lenvatinib - KISPLYX (CAP), LENVIMA (CAP) - PSUSA/00010380/201608 (with RMP)

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.24. Loxapine[52] - ADASUVE (CAP) - PSUSA/00010113/201608 (with RMP)

Applicant: Ferrer Internacional S.A.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

[51] Centrally authorised product only
[52] As pre-dispensed inhalation powder

16.1.25. Mecasermin - INCRELEX (CAP) - PSUSA/00001942/201608 (with RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.26. Nonacog alfa - BENEFIX (CAP) - PSUSA/00002183/201608

Applicant: Pfizer Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.27. Ospemifene - SENSHIO (CAP) - PSUSA/00010340/201608

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.28. Pandemic influenza vaccine (H5N1) (whole virion, vero cell derived, inactivated) - PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP); prepandemic influenza vaccine (H5N1) (whole virion, vero cell derived, inactivated) - VEPACEL (CAP) - PSUSA/00002282/201608

Applicant: Nanotherapeutics Bohumil Sro

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.29. Peginterferon alpha-2b - PEGINTRON (CAP); VIRAFERONPEG (CAP) - PSUSA/00002327/201607 (with RMP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.30. Pomalidomide - IMNOVID (CAP) - PSUSA/00010127/201608

Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.31. Safinamide - XADAGO (CAP) - PSUSA/00010356/201608

Applicant: Zambon SpA

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.32. Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/201608

Applicant: Alexion Europe SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.33. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/201608

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.34. Vernakalant hydrochloride - BRINAVESS (CAP) - PSUSA/00003109/201608

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Amlodipine, valsartan - COPALIA (CAP), DAFIRO (CAP), EXFORGE (CAP), IMPRIDA (CAP); amlodipine, hydrochlorothiazide, valsartan - COPALIA HCT (CAP), DAFIRO HCT (CAP), EXFORGE HCT (CAP); NAP - PSUSA/00010344/201606

Applicant(s): Novartis Europharm Ltd (Copalia, Copalia HCT, Dafiro, Dafiro HCT, Exforge, Exforge HCT, Imprida), various

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.2.2. Human coagulation factor IX - NONAFACT (CAP); NAP - PSUSA/00001617/201607

Applicant(s): Sanquin Plasma Products B.V. (Nonafact), various

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.2.3. Human protein C - CEPROTIN (CAP); NAP - PSUSA/00002563/201607

Applicant(s): Baxter AG (Ceprotin), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.2.4. Palonosetron - ALOXI (CAP); NAP - PSUSA/00002268/201607

Applicant(s): Helsinn Birex Pharmaceuticals Ltd (Aloxi), various

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Beclometasone, formoterol[53] (NAP) - PSUSA/00010068/201607

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.2. Desogestrel (NAP) - PSUSA/00000966/201607

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.3. Fluticasone propionate, formoterol fumarate dihydrate (NAP)– PSUSA/00010339/201607

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.4. Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide (NAP) - PSUSA/00010390/201607

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.5. Lovastatin (NAP) - PSUSA/00010051/201607

Applicant: various

PRAC Lead: Dolores Montero Corominas

[53] Inhalative application

Scope: Evaluation of a PSUSA procedure

16.3.6. Lubiprostone (NAP) - PSUSA/00010290/201607

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.7. Magnesium sulphate, sodium sulphate, potassium sulphate (NAP) - PSUSA/00010239/201608

Applicant: various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.8. Mitoxantrone (NAP) - PSUSA/00002076/201606

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.9. Phleum pratense[54] (NAP) - PSUSA/00010475/201607

Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.10. Pilocarpinel, timolol (NAP) - PSUSA/00002408/201607

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.11. Poliovirus type 1, poliovirus type 2, poliovirus type 3 vaccine (oral, live, attenuated) (NAP) - PSUSA/00002458/201607

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[54] Allergen for therapy, oromucosal use, authorised via mutually recognition procedure

16.3.12. Tamsulosin (NAP) - PSUSA/00002847/201607

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/LEG 168

Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of a review on the apparent increase in reports of adverse events (AEs) linked to elevated liver function tests (LFT) and the possible need for additional risk minimisation measures. The review also includes an analysis of underlying reasons for the change in frequency of the LFT abnormalities from the time of granting of the marketing authorisation (MA) to any other adverse drug reactions currently listed in section 4.8 of the SmPC and details on the results of the statistical analysis of studies from registers such as the British Society for Rheumatology Biologicals Register (BSRBR), German register for the long-term observation of therapy with biologics in adult patients with rheumatoid arthritis (RABBIT), as requested in the conclusions of EMEA/H/C/PSUSA/00001295/201602 adopted by PRAC in September 2016

16.4.2. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/LEG 034

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Submission of a 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

16.4.3. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/LEG 084

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Submission of a 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

16.4.4. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/LEG 104

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of a cumulative summary table of serious adverse events (SAEs) from clinical trials as requested in the conclusions of EMEA/H/C/PSUSA/00002225/201509 adopted by PRAC in May 2016

16.4.5. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[55]) - EMEA/H/W/002300/LEG 013

Applicant: GSK Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of further information on studies Malaria-055 (an efficacy study of GSK Biologicals' candidate malaria vaccine 257049 against malaria disease in infants and children in Africa) and Malaria-076 (an extension to study Malaria-055 PRI to evaluate the long-term efficacy, safety and immunogenicity of GSK Biologicals' candidate malaria vaccine in infants and children in Africa), as well as on the ad-hoc analysis of mortality by gender, on the post-hoc analysis of cerebral malaria and regarding the risk-benefit analysis, as requested in the conclusions of EMEA/H/W/002300/PSUV/011 adopted by PRAC in November 2016

16.4.6. Vardenafil - LEVITRA (CAP) - EMEA/H/C/000475/LEG 026

Applicant: Bayer Pharma AG

PRAC Rapporteur: Dolores Montero Corominas

Scope: 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

16.4.7. Vardenafil - VIVANZA (CAP) - EMEA/H/C/000488/LEG 026

Applicant: Bayer Pharma AG

PRAC Rapporteur: Dolores Montero Corominas

Scope: 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

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.

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[56]

None

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[57]

17.2.1. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/MEA 005

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: PASS protocol for study EVM-19596-00-001: a drug utilisation study (DUS) (RMP category 3) using relevant health care 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 initial MAA opinion)

17.2.2. Fenofibrate, simvastatin - CHOLIB (CAP) - EMEA/H/C/002559/MEA 002.5

Applicant: Mylan Products Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002.4: submission of a revised protocol in addition to the third status report for study ABT285.E.001: a drug utilisation research (DUR) study on the use of fenofibrate and simvastatin fixed combination: a European multinational study using secondary health records databases as per the request for supplementary information (RSI) adopted in September 2016. Submission of a revised protocol and questionnaire for the questionnaire-based study EUPAS15741: assessment of prescribing conditions of Cholib: a European study in Austria, Croatia, Czech Republic, Portugal, Slovakia and Slovenia, as per the request for supplementary information (RSI) adopted in October 2016

17.2.3. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/MEA 015

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Patrick Batty

Scope: 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)

17.2.4. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/MEA 016

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Patrick Batty

Scope: PASS protocol for study GS-EU-313-4226: a cross-sectional PASS to assess healthcare provider awareness of risks associated with Zydelig in the European Union

[56] In accordance with Article 107n of Directive 2001/83/EC
[57] 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

17.2.5. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 001.3

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's responses to MEA 001.1 and MEA 001.2 on PASS protocol for study 178-CL-114: 'evaluation of cardiovascular events in users of mirabegron and other treatments for overactive bladder: on cardiovascular events' as adopted in October 2013 and July 2016 respectively

17.2.6. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 008

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Protocol for study D3820R00008: a US post-marketing, comparative, observational study to evaluate the cardiovascular safety of naloxegol in patients with non-cancer pain in comparison to other treatments for opioid induced constipation

17.2.7. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 002.1: PASS protocol for study CLCZ696B2014: a non-interventional post-authorisation European database safety study (RMP category 3) to characterize the risk of angioedema and other specific safety events of interest in association with use of Entresto (sacubitril/valsartan) in adult patients with heart failure, as per request for supplementary information (RSI) adopted in November 2016

17.2.8. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA/004.1: PASS protocol for study CLCZ696B2015: a non-interventional post-authorisation European database safety study (category 3) to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of sacubitril/valsartan, as per request for supplementary information (RSI) adopted in November 2016

17.2.9. Zonisamide - ZONEGRAN (CAP) - EMEA/H/C/000577/MEA 038

Applicant: Eisai Ltd

PRAC Rapporteur: Almath Spooner

Scope: PASS protocol for study E2090-E044-501: a non-interventional PASS: a retrospective database study of the prescribing of zonisamide in UK general practice: a drug utilisation study (DUS) as part of post marketing safety surveillance (from II/65)

17.3. Results of PASS imposed in the marketing authorisation(s)[58]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[59]

17.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0108/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations including 1) submission of the final clinical study report from epidemiological IM101045A study: safety of non-biologic disease-modifying antirheumatic drugs (DMARDs) and biologic treatment for rheumatoid arthritis (RMP category 3 study); 2) submission of the final clinical study report from epidemiological IM101045B study: safety and outcomes in patients treated with abatacept and other anti-rheumatic therapies (RMP category 3 study). IM101045A and IM101045B are both observational studies, sharing overlapping safety objectives (assessment of the risk of infections, infusion-related reactions, autoimmune disorders, injection reactions and combination use)

17.4.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0159

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final clinical study report (CSR) for study P06-134: a long-term non-interventional registry to assess safety and effectiveness of Humira in subjects with moderately to severely active Crohn's disease in fulfilment of MEA 056.9. The study includes also some paediatric patients and fulfils Article 46 paediatric obligations

17.4.3. Buprenorphine, naloxone - SUBOXONE (CAP) - EMEA/H/C/000697/II/0035

Applicant: Indivior UK Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final study report for PEUS004: a retrospective observational survey on Suboxone use in France. The RMP (version 12.1) is updated accordingly

17.4.4. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/II/0100

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final report for study 1160.144 evaluating the potential off-label use of dabigatran etexilate in Europe: a drug utilisation study (DUS) in Cegedim France, Denmark, and Clinical Practice Research Datalink (CPRD) UK

[58] In accordance with Article 107p-q of Directive 2001/83/EC
[59] 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

17.4.5. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/II/0101

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final report for study 1160.162: an observational study assessing the management of gastrointestinal and urogenital bleeding events in patients with non valvular atrial fibrillation treated with dabigatran etexilate

17.4.6. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/II/0025

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for PASS 206207-025: a prospective observational study to evaluate the long-term safety in real-world clinical practice

17.4.7. Human rotavirus, live attenuated - ROTARIX (CAP) - EMEA/H/C/000639/II/0094

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final study report for EPI-ROTA-007 VS US DB: a phase IV, open, observational study of the safety of Rotarix, administered to a birth cohort in US States health insurance plans. The RMP (version 17) is updated in order to amend information in relation to EPI-ROTA-007 VS US DB study, EPI-ROTA-052 BOD EU SUPP (an observational community-based strain surveillance study) as agreed in the conclusions of variation II/86. In addition, the MAH took this opportunity to further update the RMP with the new due date for submission of the final study report for ROTA-085 PMS (a special drug use investigation for Rotarix (investigation of incidence of intussusception after vaccination for rotavirus gastroenteritis) conducted with the objective to determine the incidence of intussusception after vaccination with Rotarix in Japan)

17.4.8. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/II/0064

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final study report for study MI-MA194: a post-marketing observational evaluation of the safety of Fluenz in children and adolescents with high-risk conditions

17.4.9. Levodopa, carbidopa, entacapone - CORBILTA (CAP) - EMEA/H/C/002785/II/0009

Applicant: Orion Corporation

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of the final report of pharmacoepidemiological registry study

CCOM998A2001 (RMP category 3) evaluating the risk of incident myocardial infarction in Parkinson's disease patients with add-on entacapone to levodopa/dopa-decarboxylase inhibitor (DDCI) compared to other add-on Parkinson's disease therapy without entacapone - a retrospective cohort study using data from MarketScan, as requested by PRAC in the conclusions of EMEA/H/C/PSUSA/00000547/201510 in May 2016. The RMP (version 2.0) is updated accordingly

17.4.10. Levodopa, carbidopa, entacapone - CORBILTA (CAP) - EMEA/H/C/002785/II/0010

Applicant: Orion Corporation

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of the final report of pharmacoepidemiological registry study ER11-9411 (RMP category 3) evaluating the risk of developing prostate cancer in entacapone and levodopa/dopa-decarboxylase inhibitor (DDCI) users compared to levodopa/DDCI users without entacapone - a nation-wide retrospective register-based study, as requested by PRAC in the conclusions of EMEA/H/C/PSUSA/00000547/201510 in May 2016. The RMP (version 2.0) is updated accordingly

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[60]

17.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 053.3

Applicant: Genzyme Europe BV

PRAC Rapporteur: Claire Ferard

Scope: Epidemiology PASS study report for study ALGMYC07390 evaluating the prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions

17.5.2. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 005

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: First and second interim reports for study MB102134, a drug utilisation study (DUS): observational single-cohort data base study with descriptive data analyses among patients receiving dapagliflozin within electronic medical records (EMRs) in Europe. This study aims at describing the utilisation patterns of dapagliflozin during the first 3.5 years after marketing authorisation and launch in Europe and the characteristics of European patients prescribed dapagliflozin by age, sex, dapagliflozin dose, country, selected comorbidities, and selected concomitant medications

17.5.3. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 008.3

Applicant: AstraZeneca AB

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

PRAC Rapporteur: Qun-Ying Yue

Scope: First and second interim reports for study MB102134, a drug utilisation study (DUS): observational single-cohort data base study with descriptive data analyses among patients receiving dapagliflozin within electronic medical records (EMRs) in Europe. This study aims at describing the utilisation patterns of dapagliflozin during the first 3.5 years after marketing authorisation and launch in Europe and the characteristics of European patients prescribed dapagliflozin by age, sex, dapagliflozin dose, country, selected comorbidities, and selected concomitant medications

17.5.4. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 004

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First and second interim reports for study MB102134, a drug utilisation study (DUS): observational single-cohort data base study with descriptive data analyses among patients receiving dapagliflozin within electronic medical records (EMRs) in Europe. This study aims at describing the utilisation patterns of dapagliflozin during the first 3.5 years after marketing authorisation and launch in Europe and the characteristics of European patients prescribed dapagliflozin by age, sex, dapagliflozin dose, country, selected comorbidities, and selected concomitant medications

17.5.5. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 007

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First and second interim reports for study MB102134, a drug utilisation study (DUS): observational single-cohort data base study with descriptive data analyses among patients receiving dapagliflozin within electronic medical records (EMRs) in Europe. This study aims at describing the utilisation patterns of dapagliflozin during the first 3.5 years after marketing authorisation and launch in Europe and the characteristics of European patients prescribed dapagliflozin by age, sex, dapagliflozin dose, country, selected comorbidities, and selected concomitant medications

17.5.6. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.7

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: 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

17.5.7. Efavirenz, emtricitabine , tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/MEA 039.5

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 039.4: third annual report for malignant events associated with efavirenz: Diagnostic Consulting Network (DCN) report as a routine risk minimisation measures, as adopted by PRAC in November 2016

17.5.8. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 027.4

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First progress report of the ENEIDA registry: a long-term, non-interventional observational study of patients with inflammatory bowel disease (IBD) in Spain to evaluate whether the use of golimumab is associated with a risk of colectomy for intractable disease, advanced neoplasia (colorectal cancer or high grade dysplasia), and hepatosplenic T-cell lymphoma (HSTCL) in patients with ulcerative colitis (UC) as compared with alternative therapies for similar severity of disease

17.5.9. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/ANX 191.5

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Third progress report for study CSTI571I2201: a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Philadelphia positive (Ph+) acute lymphoblastic leukaemia (ALL) patients treated with chemotherapy + imatinib ± hematopoietic stem cell treatment (±HSCT)

17.5.10. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 133.11

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Ninth annual paediatric inflammatory bowel disease (IBD) registry (DEVELOP) report on long-term safety and efficacy of infliximab and other therapies, safety and efficacy of variable infliximab dosing intervals, episodic therapy, monotherapy (initiated de novo or following discontinuation of concomitant immunomodulators), combined infliximab and immunomodulator therapy (azathioprine/6-mercaptopurine (AZA/6-MP) or methotrexate (MTX))

17.5.11. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/ANX 001.4

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Fourth interim study results of a five-year long-term observational study with ivacaftor in patients with cystic fibrosis (CF), including also microbiological and clinical endpoints

17.5.12. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/001252/ANX 002.9

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Seventh interim analysis of the cystic fibrosis (CF) study, which aims to compare the rate of identified and potential risks for Bronchitol in CF between Bronchitol-exposed patients and an unexposed patient group matched (via propensity score modelling) for age, disease severity (FEV1 % predicted), concomitant medications and presence of chronic *Pseudomonas*

17.5.13. Nalmefene - SELINCRO (CAP) - EMEA/H/C/002583/MEA 001.2

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Interim study report for PASS 14910A (EUPAS5678): a non-interventional multi-country prospective cohort study investigating patterns of use of Selincro and frequency of adverse drug reactions in routine clinical practice

17.5.14. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 009

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Annual progress study report for study D3820R00008: a US post-marketing, comparative, observational study to evaluate the cardiovascular safety of naloxegol in patients with non-cancer pain in comparison to other treatments for opioid induced constipation

17.5.15. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/LEG 087.4

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Fourth annual review on pregnancy cases

17.5.16. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/MEA 099.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Interim study report for study BV29684: a non-interventional cohort study assessing the safety of oseltamivir exposure in pregnant women

17.5.17. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/MEA 004.5

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Annual progress report for PASS study E2007-G000-402: a post-marketing observational safety study to evaluate the long-term safety and tolerability of Fycompa (perampanel) as add-on therapy in epilepsy patients

17.5.18. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 256.9

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Caroline Laborde

Scope: Second interim study report for a drug utilisation study (DUS) GS-EU-104-0433 in paediatric patients with human immunodeficiency virus (HIV)-1 infection, to describe the characteristics of HIV-1 infected patients up to 18 years of age treated with Viread within the EU in order to determine if they are being managed in accordance with the European SmPC. In addition, MAH's responses to the request for supplementary information (RSI) as adopted by PRAC in March 2016 for MEA 0256.6 on the first interim study report

17.5.19. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 273.2

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Caroline Laborde

Scope: Six-monthly interim results including a status report regarding the inclusion of patients and the matching process within the planned cohort for PASS study GS-EU-174-1846: a multicentre, non-interventional, retrospective cohort study of patients with chronic hepatitis B and with moderate or severe renal impairment treated with Viread

17.6. Others

17.6.1. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.8

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Statistical analysis plan of the ongoing EU B1781044 PASS for bazedoxifene: a cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe) for the period from October 2015 to October 2016, as per the request for supplementary information (RSI) adopted in July 2016

17.6.2. Desloratadine - AERIUS (CAP) - EMEA/H/C/000313/MEA 065.2; AZOMYR (CAP) - EMEA/H/C/000310/MEA 065.2; NEOCLARITYN (CAP) - EMEA/H/C/000314/MEA 065.2

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Statistical analysis plan for a Nordic register-based study exploring the association between the use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter (from WS/0641, CHMP adoption dated 26 March 2015)

17.6.3. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 064

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Feasibility study for an observational cohort study (RMP category 3) utilising the Tysabri outreach: unified commitment to health (TOUCH) prescribing programme (5 year enrolment: January 2016-December 2020 + 3 year follow up) including a feasibility assessment for inclusion of EU registry data to estimate the risk of progressive multifocal leukoencephalopathy (PML) among patients on Tysabri switching from the newer disease-modifying therapies (DMTs) and from established DMTs

17.6.4. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/MEA 102.2

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Annual report for study NV20234: a double-blind, randomized, stratified multicentre trial evaluating conventional and double dose oseltamivir in the treatment of immunocompromised patients with influenza exploring the safety and efficacy of oseltamivir in immunocompromised patients

17.7. New Scientific Advice

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

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. Anagrelide - XAGRID (CAP) - EMEA/H/C/000480/S/0077 (without RMP)

Applicant: Shire Pharmaceutical Contracts Ltd.

PRAC Rapporteur: Claire Ferard

Scope: Annual reassessment of the marketing authorisation

18.1.2. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0020 (without RMP)

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

18.1.3. Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/S/0030 (without RMP)

Applicant: Meda AB

PRAC Rapporteur: Almath Spooner

Scope: Annual reassessment of the marketing authorisation

18.1.4. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0005 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Annual reassessment of the marketing authorisation

18.1.5. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0036 (with RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Claire Ferard

Scope: Annual reassessment of the marketing authorisation

18.1.6. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0019 (without RMP)

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

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Fampridine - FAMPYRA (CAP) - EMEA/H/C/002097/R/0037 (without RMP)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Sabine Straus

Scope: 1-year conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Aliskiren - RASILEZ (CAP) - EMEA/H/C/002406/R/110112 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: 5-year renewal of the marketing authorisation

18.3.2. Axitinib - INLYTA (CAP) - EMEA/H/C/002406/R/0021 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Helga Haugom Olsen

Scope: 5-year renewal of the marketing authorisation

18.3.3. Catridecacog - NOVOTHIRTEEN (CAP) - EMEA/H/C/002284/R/0020 (without RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Claire Ferard

Scope: 5-year renewal of the marketing authorisation

18.3.4. Copper (^{64}Cu) chloride - CUPRYMINA (CAP) - EMEA/H/C/002136/R/0014 (with RMP)

Applicant: Sparkle S.r.l.

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.5. Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/R/0030 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Claire Ferard

Scope: 5-year renewal of the marketing authorisation

18.3.6. Glycopyrronium bromide - SEEBRI BREEZHALER (CAP) - EMEA/H/C/002430/R/0020 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.7. Glycopyrronium bromide - TOVANOR BREEZHALER (CAP) - EMEA/H/C/002690/R/0022 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.8. Glycopyrronium bromide - ENUREV BREEZHALER (CAP) - EMEA/H/C/002691/R/0020 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.9. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/R/0038 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.10. Temsirolimus - TORISEL (CAP) - EMEA/H/C/000799/R/0065 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.11. Zoledronic acid - ZOLEDRONIC ACID MYLAN (CAP) - EMEA/H/C/002482/R/0013 (with RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

18.3.12. Zoledronic acid - ZOLEDRONIC ACID TEVA (CAP) - EMEA/H/C/002439/R/0018 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.13. Zoledronic acid - ZOLEDRONIC ACID TEVA PHARMA (CAP) - EMEA/H/C/002437/R/0014 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 6-9 March 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	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	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Claire Ferard	Member	France	No interests declared	Full involvement
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
Leonidas Klironomos	Member	Greece	No participation in final deliberations and voting on:	3.2.1. Lactose of bovine origin-containing medicinal products: methylprednisolone; 3.3.2. Human coagulation (plasma-derived) factor VIII;

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				6.1.10. Crizotinib – XALKORI; 6.1.34. Nonacog alfa – BENEFIX; 6.4.1. Etanercept – ENBREL; 6.4.6. Pregabalin – LYRICA; 6.4.7. Pregabalin - PREGABALIN PFIZER; 7.6.1 Bazedoxifene – CONBRIZA; 8.1.5. Tafamidis - VYNDAQEL (CAP); 8.3.2. Axitinib – INLYTA; 8.3.10. Temsirolimus - TORISEL
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Alternate	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Helga Haugom Olsen	Member	Norway	No interests declared	Full involvement
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No participation in final deliberations and voting on:	3.2.2. Paracetamol (NAP); 6.2.3. Desloratadine - AERIUS (CAP); AZOMYR (CAP); DASSELTA (CAP); DESLORATADINE ACTAVIS (CAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				DESLORATADINE RATIOPHARM (CAP); DESLORATADINE TEVA (CAP); NEOCLARITYN (CAP); 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
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	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
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
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Flora Musuamba Tshinanu	Expert - via telephone*	Belgium	No interests declared	Full involvement
Charlotte Selvais	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Adriana Andrić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Morana Pavičić	Expert -	Croatia	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	via telephone*			
Martin Erik Nyeland	Expert - in person*	Denmark	No participation in discussion, final deliberations and voting on:	5.3.22. Insulin degludec - TRESIBA (CAP); 5.3.23. Insulin degludec, liraglutide - XULTOPHY (CAP); 8.3.3. Catridecacog - NOVOTHIRTEEN (CAP)
Kaarlo Hoppu	Expert - via telephone*	Finland	No interests declared	Full involvement
Kim Bouillon	Expert - via telephone*	France	No interests declared	Full involvement
Catherine Deguines	Expert - via telephone*	France	No interests declared	Full involvement
Pierre Demolis	Expert - in person*	France	No interests declared	Full involvement
Sara Miranda	Expert - via telephone*	France	No interests declared	Full involvement
Alexandre Moreau	Expert - in person*	France	No interests declared	Full involvement
Fanny Raguideau	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Tobias Lamkemeyer	Expert - via telephone*	Germany	No interests declared	Full involvement
Johannes Pohly	Expert - via telephone*	Germany	No interests declared	Full involvement
Niamh Buckley	Expert - in person*	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Johann Lodewijk Hillege	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Bianca Mulder	Expert - in person*	Netherlands	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Jacob Brogren	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Bengt Ljungberg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Helena Möllby	Expert - via telephone*	Sweden	No interests declared	Full involvement
Helene Salmonson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Tomas Salmonson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jan Sjöberg	Expert - in person*	Sweden	No interests declared	Full involvement
Akosua Adjei	Expert - in person*	United Kingdom	No interests declared	Full involvement
Phil Bryan	Expert - in person*	United Kingdom	No interests declared	Full involvement
John Clements	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Katherine Donegan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Abidali Fazal	Expert - in person*	United Kingdom	No interests declared	Full involvement
Anna Radecka	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Angela Thomas	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Expert - in person*	United Kingdom	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in

20. 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

21. 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