6 July 2017
EMA/PRAC/478147/2017

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 6-9 June 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).

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1. Introduction

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

The Chairperson opened the 6-9 June 2017 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed David Olsen, replacing Helga Haugom Olsen, as the new member for Norway and Peter Koren as the new alternate for Slovakia. In addition, Rhea Fitzgerald was announced as the new alternate for Ireland, replacing Ruchika Sharma. Furthermore, Agni Kapou moved from her position of alternate to member for Greece after Leonidas Klironomos stepped down from his role. The PRAC thanked all the past members and alternates for their contribution to the work of the Committee.

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

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

1.3. Minutes of the previous meeting on 2-5 May 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 2-5 May 2017 were published on the EMA website on 30 June 2017 (EMA/PRAC/419638/2017).

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

Applicant: Biogen Idec Ltd

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

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

Background

The European Commission (EC) sent a letter of notification dated 09 June 2017 triggering a procedure under Article 20 of Regulation (EC) No 726/2004 for the review of daclizumab (Zinbryta), a centrally authorised medicine, indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS).

The review was initiated following cases of serious liver injury, including a fatal case of fulminant liver failure reported in an ongoing observational study after the data lock point (DLP) for the PSUR under evaluation (PSUSA/00010518/201611, See under 6.1.3.). Taking into account the seriousness of the reactions including the fatal case, which occurred despite adherence to the current risk minimisation measures (RMMs) in place for the risk of liver injury, it was considered that further investigation of this risk was warranted to assess its impact on the benefit-risk balance of the medicinal product and the adequacy of the related RMMs. As a consequence, the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the EMA to assess the above concerns and their impact on the benefit-risk balance for daclizumab.

The EC also requested the EMA to give its opinion at the latest by 30 November 2017 on whether the marketing authorisation(s) for this medicinal product should be maintained, varied, suspended or revoked. In addition, the EC requested the EMA to consider as soon as possible whether provisional measures were necessary to protect public health.

Discussion

The PRAC noted the notification letter from the EC. The PRAC discussed the need for provisional measures to protect public health as well as a list of questions to be addressed during the procedure together with a timetable for conducting the review.

The PRAC appointed Eva Segovia as Rapporteur and Marcia Sofia Sanches de Castro Lopes Silva as Co-Rapporteur for the procedure.

The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure[1] (EMA/363479/2015). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/366034/2017) and a timetable for the ongoing procedure (EMA/PRAC/366037/2017). At its July 2017 meeting, the PRAC will further discuss the need for provisional measures, based on preliminary data that the MAH is requested to provide by 20 June 2017.

3.2. Ongoing procedures

3.2.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452

Applicant: Raptor Pharmaceuticals Europe BV (Quinsair), various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Martin Huber

Scope: Review of the benefit-risk balance 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 quinolone- and fluoroquinolone-containing medicines for systemic and inhalation use, indicated for the treatment of bacterial infections in particular those which are serious and life-threatening, in order to assess the persistence of side effects known to occur with quinolone and fluoroquinolone antibiotics following reports of long-lasting side effects mainly affecting musculoskeletal and nervous systems. The ongoing review also assesses the need for adequate and consistent risk minimisation measures (RMMs) and the impact of this safety concern if confirmed on the overall benefit risk balance of quinolones and fluoroquinolones for systemic and inhalation use especially in authorised indications which are related to treatment of non-serious/non severe infections. For further background, see PRAC minutes February 2017.

[1] Rules of procedure on the organisation and conduct of public hearings at the PRAC

Summary of recommendation(s)/conclusions

On 8 May 2017, the PRAC adopted by written procedure a revised timetable (EMA/PRAC/38618/2017 Rev. 1) for the conduct of the review in order to allow sufficient time to assess the recently available EudraVigilance analysis.

3.2.2. Lactose of bovine origin-containing medicinal products[2]: 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 acute 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 and PRAC minutes March 2017.

Summary of recommendation(s)/conclusions

The PRAC discussed the assessment reports prepared by the Rapporteurs and adopted a second 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.2).

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

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

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

Summary of recommendation(s)/conclusions

[2] For intravenous (IV) or intramuscular (IM) use indicated for the treatment of acute allergic reactions only

The PRAC discussed the assessment reports prepared 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/154221/2017 Rev. 1). In addition, the PRAC agreed on the need for a Scientific Advisory Group (SAG) meeting to be organised in the course of the review and adopted a list of questions (LoQ) to the SAG on Neurology as well as a LoQ to the SAG on Psychiatry.

Furthermore, the PRAC decided to hold its first public hearing on 26 September 2017 during the PRAC meeting scheduled on 25-29 September 2017[3]. Further information, including a list of specific questions on which the public's views would be valuable and a summary of the safety concerns (SuSaC) will be discussed in July 2017. In addition, the PRAC will discuss a LoQ for a stakeholders meeting.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[4]

3.4.1. Gadolinium-containing contrast agents (GdCA): gadobenic acid (NAP); gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid (NAP); gadoteric acid (NAP); gadoteridol (NAP); gadoversetamide – OPTIMARK (CAP); gadoxetic acid (NAP) - EMEA/H/A-31/1437

Applicant(s): Mallinckrodt Deutschland GmbH (Optimark); various

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur: Valerie Strassmann

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

Background

Following the PRAC recommendation adopted at the March 2017 PRAC meeting, to vary the terms of the marketing authorisations for medicinal 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 medicinal products containing gadodiamide, gadopentetic acid, gadobenic acid and gadoversetamide, some of the MAHs concerned by this referral procedure conducted under Article 31 of Directive 2001/83/EC, requested a re-examination in line with Article 32 of Directive 2001/83/EC. For further background, see PRAC minutes March 2016, PRAC minutes June 2016 and PRAC minutes July 2016, PRAC Minutes October 2016, PRAC minutes December 2016, PRAC minutes March 2017, PRAC minutes April 2017 and PRAC minutes May 2017.

Summary of recommendation(s)/conclusions

The PRAC adopted a list of questions (LoQ) and discussed a list of experts (LoE) for the ad-hoc expert group meeting scheduled on 19 June 2017.

[3] Corresponding to the October 2017 PRAC plenary meeting
[4] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

Post-meeting note: on 16 June 2017, the PRAC adopted by written procedure the final LoE for the ad-hoc expert group meeting.

3.5. Others

3.5.1. 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: antihaemophilic factor (recombinant) (NAP); efmoroctocog alfa – ELOCTA (CAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY (CAP); turoctocog alfa – NOVOEIGHT (CAP); simoctocog alfa – NUWIQ (CAP); susoctocog alfa – OBIZUR (CAP) - EMEA/H/A-31/1448

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

PRAC Rapporteur: Jan Neuhauser; PRAC Co-rapporteur: Caroline Laborde

Scope: Request for re-examination under Article 32 of Directive 2001/83/EC of the review of the benefit-risk balance following notification by Germany of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

Following the PRAC recommendation adopted at the May 2017 PRAC meeting, to vary the terms of the marketing authorisations for human plasma derived factor VIII- and recombinant coagulation factor VIII-containing medicinal products, a marketing authorisation holder (MAH) concerned by this referral procedure requested a re-examination. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes January 2017, PRAC minutes February 2017, PRAC minutes March 2017 and PRAC minutes May 2017.

Upon receipt of the grounds for re-examination from a MAH concerned by this referral procedure, the PRAC will initiate a re-examination procedure[5], expected to conclude at the September 2017 PRAC meeting (scheduled on 29 August-1 September 2017).

Discussion

The PRAC noted the notification letter from one of the MAHs concerned by this referral procedure to request a re-examination of the recommendation adopted by the PRAC in May 2017.

The PRAC appointed Jan Neuhauser as Rapporteur and Caroline Laborde as Co-Rapporteur for the re-examination procedure.

Summary of recommendation(s)/conclusions

The Committee agreed on a preliminary timetable for the re-examination procedure expected to conclude at the September 2017 PRAC meeting (scheduled on 29 August-1

[5] Under Article 32 of Directive 2001/83/EC

September 2017). The timetable will be finalised further to the receipt of the MAH's grounds for re-examination of the PRAC recommendation.

4. Signals assessment and prioritisation[6]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. mTOR[7] inhibitors: everolimus – AFINITOR (CAP), VOTUBIA (CAP), NAP; sirolimus – RAPAMUNE (CAP); temsirolimus – TORISEL (CAP)

Applicant(s): Novartis Europharm Ltd (Afinitor, Votubia), Pfizer Limited (Rapamune, Torisel), various

PRAC Rapporteur: Martin Huber

Scope: Signal of optic neuropathy and papilloedema

EPITT 18901 – New signal

Lead Member State(s): SE, DE

Background

Everolimus is an antineoplasic agent selectively inhibiting mTOR protein kinase. The exposure of Afinitor a centrally authorised medicine containing everolimus, indicated for the treatment of hormone receptor-positive, HER2/neu[8] negative advanced breast cancer under conditions, of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease, of unresectable or metastatic, well-differentiated (grade 1 or grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease, and of patients with advanced renal cell carcinoma under conditions, is estimated to have been 106,497 patient-years worldwide in the period from first authorisation in 2009 to 2016. The exposure of Votubia a centrally authorised medicine containing everolimus, indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) under conditions and for the treatment of subependymal giant cell astrocytoma (SEGA) associated with TSC under certain conditions, is estimated to have been 4,965 patient-years worldwide in the period from first authorisation in 2011 to 2015. The exposure of Certican, a nationally authorised medicine containing everolimus, indicated for the prophylaxis of organ rejection in adult patients receiving renal, cardiac or hepatic transplant under conditions, is estimated to have been 300,838 patient-years worldwide in the period from first authorisation in 2003 to 2015.

Sirolimus is an immunosuppressant indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant under certain conditions. The exposure for Rapamune a centrally authorised medicine containing sirolimus,

[6] 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

[7] Mechanistic target of rapamycin

[8] Human epidermal growth factor receptor 2, proto-oncogene Neu

is estimated to have been 528,144 patient-years worldwide, in the period from first authorisation in 2001 to 2014.

Temsirolimus is an antineoplasic agent selectively inhibiting mTOR protein kinase indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) under conditions as well as for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). The exposure for Torisel a centrally authorised medicine containing temsirolimus, is estimated to have been more than 50,567 patient-years worldwide, in the period from first authorisation in 2007 to 2015.

During routine signal detection activities, a signal of optic neuropathy and papilloedema with mTOR inhibitors was identified by France, based on 3 cases of papilloedema and 1 case of ischaemic optic neuropathy with everolimus retrieved from the French pharmacovigilance database and additional relevant cases retrieved in EudraVigilance with everolimus, sirolimus and temsirolimus. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having discussed the available evidence from the case reports of papilloedema, ischaemic optic neuropathy/optic neuritis, blindness and ocular toxicity, and optic neuropathy associated with blindness in EudraVigilance, in the French national pharmacovigilance database and from the literature, the PRAC considered that further evaluation of the association between mTOR inhibitors and optic neuropathy and papilloedema was warranted. The PRAC recommended that the MAHs should submit supplementary information to EMA in order to assess this signal.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH(s) for Afinitor, Votubia and Certican (everolimus), as well as the MAH(s) of Rapamune (sirolimus) and Torisel (temsilorimus) should submit to EMA, within 90 days, a cumulative review of the signal, i.e. events of 'optic neuropathy' and 'papilloedema', including an analysis of relevant data from post-marketing sources, clinical trials, non-clinical data and relevant literature, and evaluate the plausibility of a possible association, and a discussion of a potential class effect of mTOR inhibitors as well as the need for any potential amendment to the product information and/ or the risk management plan with a proposal for the changes accordingly.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Telmisartan – KINZALMONO (CAP), MICARDIS (CAP), PRITOR (CAP), TELMISARTAN ACTAVIS (CAP), TELMISARTAN TEVA (CAP), TELMISARTAN TEVA PHARMA (CAP), TOLURA (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDIS PLUS (CAP), PRITOR PLUS (CAP), TOLUCOMBI (CAP); telmisartan, amlodipine – TWYNSTA (CAP); NAP

Applicant(s): Bayer Pharma AG (Kinzalmono, Kinzalkomb, Pritor, Pritor Plus), Boehringer Ingelheim International GmbH (Micardis, Micardis Plus, Twynsta), Actavis Group PTC ehf (Telmisartan Actavis, Actelsar HCT), Teva B.V.(Telmisartan Teva, Telmisartan Teva Pharma), Krka, d.d., Novo mesto (Tolura, Tolucombi); various

PRAC Rapporteur: Not applicable

Scope: Signal of risk of psoriasis or exacerbation of psoriasis

EPITT 18882 – New signal

Lead Member State(s): IT

Background

Telmisartan is an angiotensin II receptor blocker (ARB) also known as angiotensin II receptor antagonist indicated for the treatment of essential hypertension under certain conditions as well as for the reduction of cardiovascular morbidity under certain conditions.

The exposure for Micardis, a centrally authorised medicine containing telmisartan, is estimated to have been more than 53,793,396 patient-years worldwide, in the period from first authorisation in 1998 to 2016.

During routine signal detection activities, a signal of psoriasis or exacerbation of psoriasis with ARBs was identified by France, based on 819 cases of 'psoriatic conditions' retrieved from EudraVigilance. Italy confirmed that the signal needed initial analysis and prioritisation by the PRAC for telmisartan.

Discussion

Having considered the available evidence from case reports and from the literature, and taking into consideration the patient exposure, the PRAC agreed that a causal relationship between treatment with telmisartan and psoriasis and exacerbation of psoriasis was not established and consequently changes in the product information were not warranted at this stage. Therefore, the PRAC recommended that MAH(s) for telmisartan-containing medicinal products should continue to monitor these events as part of routine safety surveillance.

Summary of recommendation(s)

- The MAHs for telmisartan-containing medicines should continue to monitor the events of psoriasis and exacerbation of psoriasis as part of routine safety surveillance.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Phenprocoumon (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal

EPITT 18902 – New signal

Lead Member State(s): DE

Background

Phenprocoumon is a vitamin K antagonist indicated as an antithrombotic agent, for the treatment and prevention of thromboembolic diseases.

Following the publication by *Hüttel et al.*[9], a recently published observational cohort study, a signal of risk of birth defects and spontaneous foetal loss was identified by Germany, suggesting that the risk of birth defects and spontaneous foetal loss was related to the time of phenprocoumon withdrawal. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the known embryotoxic risk of phenprocoumon, and the evidence provided by the literature, the PRAC recommended that the MAH of phenprocoumon should submit supplementary information to EMA in order to assess this signal.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH(s) for phenprocoumon-containing medicines should submit to EMA, within 60 days, a discussion on the need for amending the product information considering the results of the study by *Hüttel et al.* and all other available evidence on the embryotoxic risk of phenprocoumon following first trimester exposure, especially as regards its potential relationship to the time of withdrawal as well as the appropriate changes proposal.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Prednisolone (NAP), prednisone (NAP)

Applicant(s): various

PRAC Rapporteur: Doris Stenver

Scope: Signal of induced scleroderma renal crisis

EPITT 18888 – New signal

Lead Member State(s): DK

Background

Prednisolone is a corticosteroid with mainly glucocorticoid activity used to treat inflammatory conditions such as arthritis or dermatitis and as adjunctive therapy for conditions such as autoimmune diseases.

Following the submission of a type II variation in Germany for a nationally authorised product containing prednisolone to include a new warning in the product information on a possible risk of scleroderma renal crisis in patients with systemic sclerosis, in the context of a signal of scleroderma renal crisis for prednisolone raised in 2014 by a MAH for a prednisolone-containing product, a signal of scleroderma renal crisis was identified by Germany. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

[9] Hüttel E, Padberg S, Meister R, Beck E, Schaefer C. Pregnancy outcome of first trimester exposure to the vitamin K antagonist phenprocoumon depends on duration of treatment. Thromb Haemost. 2017 Feb 23. doi: 10.1160/TH16-11-0838

Having considered the available evidence, including from published literature, the PRAC recommended that the MAHs of systemic formulations of prednisolone-containing medicinal products and prednisone-containing medicinal products in doses which provide a systemic concentration equivalent to more than 15 mg prednisolone daily should vary their marketing authorisations. For topical formulations, since the systemic absorption of prednisolone-containing medicinal products and prednisone-containing medicinal products is expected to be low and consequently systemic concentrations corresponding to more than 15 mg prednisolone daily unlikely, the PRAC did not consider it warranted to update the product information for these medicinal products in light of the current knowledge.

The PRAC appointed Doris Stenver as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for originator medicinal products systemic formulations containing prednisolone or prednisone, should comment on a proposal for amendments. The PRAC will discuss a consolidated product information proposal and adopt a further recommendation at its July 2017 meeting.

4.3. Signals follow-up and prioritisation

4.3.1. Dabigatran – PRADAXA (CAP) – EMEA/H/C/000829/SDA/047; lovastatin (NAP); simvastatin (NAP)

Applicant(s): Boehringer Ingelheim International GmbH (Pradaxa), various

PRAC Rapporteur: Torbjorn Callreus

Scope: Signal of major haemorrhage following dabigatran interaction with simvastatin or lovastatin

EPITT 18819 – Follow-up to February 2017

Background

The MAH replied to the request for information on the signal of major haemorrhage following dabigatran interaction with simvastatin or lovastatin and the responses were assessed by the Rapporteur. For background information, see PRAC minutes February 2017.

Discussion

Having considered the data provided by the MAH for Pradaxa (dabigatran) on the drug interaction between dabigatran and statins and the limitations of the study by *Antoniou T, et al.*[10], the PRAC agreed that no changes to the product information were warranted at this stage. Moreover, requesting interaction studies in healthy volunteers was not considered informative on the issue at present. However, the PRAC acknowledged that the concomitant use of statins in the population receiving dabigatran is common and took into account the potentially serious clinical consequences of an increase in dabigatran plasma levels. Therefore, the PRAC recommended that the MAH for Pradaxa (dabigatran) should submit supplementary information to EMA in order to investigate further this potential interaction.

[10] Antoniou T, et al. Association between statin use and ischemic stroke or major hemorrhage in patients taking dabigatran for atrial fibrillation. J CMAJ. 2016 Nov 21. doi: 10.1503/cmaj.160303

Summary of recommendation(s)

- The MAH for Pradaxa (dabigatran), should submit to EMA, an analysis of this potential interaction between dabigatran and most commonly used statins in ongoing clinical trials and observational studies (e.g. GLORIA-AF[11]) taking into account relevant co-variates such as patient age and renal function.

4.3.2. Dabrafenib – TAFINLAR (CAP) - EMEA/H/C/002604/SDA/012; trametinib – MEKINIST (CAP) - EMEA/H/C/002643/SDA/009

Applicant(s): Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of sepsis

EPITT 18779 – Follow-up to December 2016

Background

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

Discussion

Having considered the available evidence from the cumulative review provided by the MAH for Tafinlar (dabrafenib) and Mekinist (trametinib), the PRAC concluded that the current evidence did not warrant regulatory action at this stage. The MAH of Tafinlar (dabrafenib) and Mekinist (trametinib) should closely monitor these events as part of routine safety surveillance.

Summary of recommendation(s)

- The MAH for Tafinlar (dabrafenib) and Mekinist (trametinib) should closely monitor events of sepsis as part of routine safety surveillance.

4.3.3. 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 (ADRs) with docetaxel in particular neutropenic enterocolitis and suspicion of an increase in ADR reporting rate in France with docetaxel-containing products

EPITT 12059 – Follow up to April 2017

Background

[11] Huisman MV, et al. Global registry on long-term oral antithrombotic treatment in patients with atrial fibrillation, Am Heart J. 2014 Mar;167(3):329-34. doi: 10.1016/j.ahj.2013.12.006. Epub 2013 Dec 19

The signal was further explored with the updated report of the French regional pharmacovigilance centre of Toulouse and an EMA analysis of the time-trend of reports for docetaxel, in France. For background information, see PRAC minutes April 2017.

Discussion

Having considered the available evidence from the analyses conducted by ANSM and EMA, the PRAC agreed that a change in frequency of reports of neutropenic colitis was not observed across the Member States and that there was insufficient evidence that the change in frequency of reports in France was directly related to the docetaxel formulation. Thus, no changes in the product information were considered warranted at this stage. The PRAC considered the relevance of requesting a bioequivalence test from the MAHs and agreed that the current level of evidence is not strong enough to require additional studies, including studies of bioequivalence.

Summary of recommendation(s)

- The MAHs for docetaxel-containing medicinal products should continue to monitor the events of neutropenic enterocolitis and their frequency as part of routine safety surveillance.

Post-meeting note: See PRAC press release (EMA/365357/2017) dated 9 June 2017 entitled 'PRAC concludes there is no evidence of a change in known risk of neutropenic enterocolitis with docetaxel'.

4.3.4. Gabapentin (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of respiratory depression without concomitant opioid use

EPITT 18814 - Follow-up to January 2017

Background

The MAH replied to the request for information on the signal of respiratory depression without concomitant opioid use and the responses were assessed by the Rapporteur. For background information, see PRAC minutes January 2017.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, and the supplementary information provided by the MAH, the PRAC recommended that the MAH(s) of gabapentin-containing medicinal products should vary their marketing authorisations to update the product information.

Summary of recommendation(s)

- The MAHs for gabapentin-containing medicinal products should submit to relevant national competent authorities, within 60 days, a variation to amend the product information[12] to add a warning on respiratory depression highlighting patient groups

[12] Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly

being at higher risk of experiencing this adverse reaction and to include respiratory depression as an undesirable effect of rare frequency.

For the full PRAC recommendation, see EMA/PRAC/337620/2017 published on 03/07/2017 on the EMA website.

4.3.5. Intravenous (IV) fluids containing electrolytes and/or carbohydrates (NAP)

Applicant(s): various

PRAC Rapporteur: Doris Stenver

Scope: Signal of hyponatremia

EPITT 18631 – Follow-up to April 2017

Background

The signal of hyponatremia associated with intravenous fluids containing electrolytes and/or carbohydrates was further explored with the analysis of data available in EudraVigilance, along with a proposed wording to be included in the product information (PI) and any possibility of further risk minimisation measures (RMMs) that could be deemed necessary. For background information, see PRAC minutes April 2017.

Discussion

Having considered the evidence from the literature as well as from EudraVigilance, the PRAC confirmed an increased risk of hospital acquired hyponatraemia (HAH), eventually leading to irreversible brain injury and death, in association with the administration of intravenous (IV) fluids. Thus, the PRAC agreed to strengthen risk minimization by implementing adequate risk minimisation measures. Moreover an update of the product information was considered warranted with consideration to be given to consultation of HCPs.

Summary of recommendation(s)

- Based on the available evidence, changes to the product information were deemed warranted. Consequently, to ensure clarity and completeness of the product information, the PRAC considered necessary to further reflect on these changes and discuss a consolidated proposal at the PRAC meeting July 2017.

4.3.6. Levonorgestrel (intrauterine device) (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of anxiety, panic attacks, mood changes, sleep disorders and restlessness

EPITT 18849 – Follow-up to February 2017

Background

The MAH replied to the request for information on the signal of anxiety, panic attacks, mood changes, sleep disorders and restlessness and the responses were assessed by the Rapporteur. For background information, see PRAC minutes February 2017.

Discussion

Having reviewed the available evidence, including the data submitted by the MAH, the PRAC agreed that further exploratory analysis in EudraVigilance and electronic health records should be performed by EMA and that additionally the MAHs should provide supplementary information.

Summary of recommendation(s)

- The MAH for Jaydess, Kyleena, Luadei, Mirena, Skyla, Sofitta (levonorgestrel IUD) should submit to EMA, within 60 days, a detailed single-case analysis including a causality assessment in line with the WHO criteria for all cases with positive dechallenge for its levonorgestrel intrauterine devices (IUDs), a detailed analysis of the reasons for discontinuation of the levonorgestrel IUD from the available information with a main focus on discontinuation due to psychiatric adverse events, and a detailed analysis of neuropsychiatric adverse events captured during the completed PASS EURAS-IUD[13] and the ongoing PASS EURAS-LCS12[14] with a main focus on anxiety, panic attacks, sleep disorders, and restlessness.
- The MAHs of levonorgestrel IUDs, Allergan and Bayer, should in addition submit to EMA, within 60 days, a detailed analysis of post-marketing cases where concomitant use of psychoactive medicinal products was reported in women with a levonorgestrel IUD in connection to any of the topics under review – anxiety, panic attacks, sleep disorders, and restlessness including a discussion for each relevant case on whether there is a possibility that the concomitant psychoactive medicinal product(s) has/have been prescribed as a corrective treatment for psychiatric events induced by their levonorgestrel IUD. In addition, the MAHs should provide a discussion on the need for additional risk minimisation measures to improve communication to women receiving a levonorgestrel IUD, taking into account the national situation in the different EU Member States.

4.3.7. Tick-borne encephalitis vaccine[15] (NAP)

Applicant(s): various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of potential vaccination failure in children

EPITT 18825 – Follow-up to February 2017

Background

The MAH replied to the request for information on the signal of potential vaccination failure in children and the responses were assessed by the Rapporteur. For background information, see PRAC minutes February 2017.

Discussion

Having considered the available evidence from the cumulative review provided by the MAHs for the tick-borne encephalitis vaccines and additional clarifications, as well as the CHMP Vaccines Working Party (VWP) expert opinion on this matter, the PRAC agreed that the number of confirmed cases of vaccination failure with a temporal relationship to the specific

[13] European active surveillance study for intrauterine devices (NCT00461175)
[14] European active surveillance study of LCS12 (new intrauterine system) (NCT02146950)
[15] Inactivated

tick-borne encephalitis (TBE) vaccine was very low and that there was no evidence to conclude that a safety signal of reduced effectiveness of TBE vaccines in children was present. The likelihood of a causal relationship between treatment with the TBE vaccine and reduced effectiveness was not considered as sufficiently robust to warrant any further regulatory action at this stage.

Summary of recommendation(s)

- The MAHs for the tick-borne encephalitis vaccines should continue to monitor the potential reduced effectiveness events as part of routine safety surveillance.
- Additionally, it is recommended that ongoing surveillance in Austria may consider brand specific effectiveness and take into account potential changes in TBE virus epidemiology over time. Additionally, as soon as the updated results of the Austrian effectiveness surveillance present in the product information of FSME–IMMUN Junior (TBE vaccine, suspension for injection in pre-filled syringe) are available, the MAH (Pfizer) should submit a variation to amend the product information accordingly.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Avelumab - EMEA/H/C/004338, Orphan

Applicant: Merck Serono Europe Limited

Scope: Treatment of Merkel cell carcinoma (MCC)

5.1.2. Niraparib - EMEA/H/C/004249, Orphan

Applicant: Tesaro UK Limited

Scope: Treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer

5.1.3. Sirukumab - EMEA/H/C/004165

Scope: Treatment of rheumatoid arthritis (RA)

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0062

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC to update the safety information and reflect the possible occurrence of multiple vertebral fractures (MVF) particularly in patients with a history of vertebral fracture following discontinuation of Prolia treatment. This results from an analysis of osteoporosis-related fracture data in subjects who discontinued investigational product and remained on study in either the Prolia phase III pivotal fracture study (study 20030216: evaluation of denosumab in the treatment of postmenopausal osteoporosis FREEDOM (fracture reduction evaluation of denosumab in osteoporosis every 6 months)) or its study extension (study 20060289: open label, single arm, extension study to evaluate the long term safety and sustained efficacy of denosumab in the treatment of postmenopausal osteoporosis) to better understand the incidence of fracture following treatment discontinuation. The Package Leaflet is updated accordingly. The RMP (version 16.0) is also updated to reflect MVF as a new important risk. In addition, the product information is updated in line with the QRD template latest version and corrected to remove typographical errors and implement minor changes in the list of local representatives

Background

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

The CHMP is evaluating a type II variation for Prolia, a centrally authorised medicine containing denosumab, assessing the MAH's proposal to update the safety information and reflect the possible occurrence of multiple vertebral fractures (MVF) particularly in patients with a history of vertebral fracture following discontinuation of Prolia treatment. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes December 2016 and PRAC minutes April 2017.

Summary of advice

- The RMP version 16.0 for Prolia (denosumab) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC did not support the MAH's proposal to reflect in the RMP the increased risk for 'multiple vertebral fractures following discontinuation of denosumab treatment' as an important identified risk. The reason was that the data came from post–hoc subgroup analyses and that subjects who discontinued were older and had more baseline and on-treatment fractures than subjects who completed treatment. In addition, the PRAC noted that only multiple fractures were increased but not single ones. The PRAC did not consider that there was a rationale why only multiple fractures would increase. Therefore, the PRAC did not support the proposed change to the RMP.

See also under 10.1.1.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Autologous CD34$^+$ enriched cell fraction that contains CD34$^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - PSUSA/00010505/201611

Applicant: GlaxoSmithKline Trading Services; ATMP[16]

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Autologous CD34$^+$ enriched cell fraction that contains CD34$^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence is an immunostimulant indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Strimvelis, a centrally authorised medicine containing autologous CD34$^+$ enriched cell fraction that contains CD34$^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence, 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 benefit-risk balance of Strimvelis (autologous CD34$^+$ enriched cell fraction that contains CD34$^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence) in the approved indication(s) remains unchanged.
- The PRAC was informed of the recent advice issued by the Committee of Advanced Therapies (CAT) on the 'late event of insertional oncogenesis in a gene therapy trial involving a retroviral vector transduced into progenitor cells for the treatment of severe combined immunodeficiency (SCID)-X disease' reported by France. In light of the CAT advice and considering that no cases of malignancies such as leukaemia have been reported with Strimvelis, the PRAC did not consider that any amendment of the product information was warranted in relation to recommended duration of patient follow-up.

[16] Advanced therapy medicinal product

Overall, the risk minimisation measures and pharmacovigilance activities included in the RMP are considered sufficient to detect and monitor the risk of late malignancy events.

- The current terms of the marketing authorisation(s) should be maintained.

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

6.1.2. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/201610

Applicant: Pharming Group N.V

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Conestat alfa is a recombinant human complement component 1 (C1) esterase inhibitor (rhC1INH) indicated for the treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ruconest, a centrally authorised medicine containing conestat alfa, 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 benefit-risk balance of Ruconest (conestat alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to remove the existing advice on performing skin prick tests for cross-reactivity with cow's milk as results for study C1 1113[17] showed that the likelihood of cross-reactivity to host-related impurities appears to be low. Therefore the current terms of the marketing authorisation(s) should be varied[18].
- The MAH is requested to delete 'allergic reaction due to cross reaction with immunoglobulin E (IgE) antibodies against cow milk' in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP.

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

6.1.3. Daclizumab - ZINBRYTA (CAP) - PSUSA/00010518/201611

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

[17] Post-authorisation study on the development of a skin prick test to evaluate putative cross-reactive hypersensitivity in patients with an established cow's milk allergy to trace amounts of rabbit milk proteins in conestat alfa (requested as an additional risk minimisation measure)
[18] Update of SmPC section 4.4 and Annex II-D. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Scope: Evaluation of a PSUSA procedure

Background

Daclizumab is a humanised immunoglobulin G (IgG) 1 monoclonal antibody that binds to CD25 (interleukin (IL)-2Rα) prevent IL-2 binding to CD25 and is indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zinbryta, a centrally authorised medicine containing daclizumab, 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 benefit-risk balance of Zinbryta (daclizumab) in the approved indication(s) remains unchanged.
- The PRAC noted a fatal case of fulminant liver failure reported in an ongoing observational study after the data lock point (DLP) for the PSUR under evaluation. Taking into consideration four cases of serious liver injury reported from clinical trials during the period under evaluation of the PSUR and together with the seriousness of the reactions including the fatal case reported above, despite the monitoring of the patient's liver function as currently recommended in the product information, the PRAC considered that further investigation of this risk was warranted, including an assessment of its impact on the benefit-risk balance of the medicinal product and the need to consider the options to further minimise the risk of liver toxicity. As a consequence, the European Commission (EC) initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the Agency to assess the above concerns and their impact on the benefit-risk balance for daclizumab. See under 3.1.1.
- The current terms of the marketing authorisation(s) should be maintained. This recommendation is without prejudice to potential provisional measures and/or the final conclusions of the newly initiated referral procedure under Article 20 of Regulation (EC) No 726/2004 for Zinbryta (daclizumab) (EMEA/H/A-20/1456).
- In the next PSUR, the MAH should provide a detailed review of urinary tract infection cases from all sources and closely monitor cases of seizures.

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

6.1.4. Deferasirox - EXJADE (CAP) - PSUSA/00000939/201610

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

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

chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Exjade, a centrally authorised medicine containing deferasirox, 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 benefit-risk balance of Exjade (deferasirox) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the current warning on skin disorders in order to include severe cutaneous adverse reactions (SCARs) and drug reaction with eosinophilia and systemic symptoms (DRESS), and to ensure that patients are advised, at the time of prescription, of the possible occurrence of signs and symptoms of severe skin reactions that need to be closely monitored. In addition, 'DRESS' should be added as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide a comprehensive safety review of several musculoskeletal disorders as well as a discussion on the available literature review and possible mechanisms leading to such adverse events. In addition, the MAH should continue to closely monitor the risk of medication errors and propose any additional risk minimisation measures as necessary. Finally, the MAH should provide a comprehensive safety review of fixed drug eruption and should propose to update the product information accordingly as applicable.

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

6.1.5. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/201611 (with RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) as well as for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. Alone or in combination with bendamustine and rituximab (BR), ibrutinib is also indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

[19] 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 assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Imbruvica, a centrally authorised medicine containing ibrutinib, 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 benefit-risk balance of Imbruvica (ibrutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on 'hepatitis B reactivation' in order to ensure that hepatitis B virus (HBV) status is established before initiating treatment with ibrutinib and to provide advice on medical consultation for patients who tested positive for HBV infection. In addition, hepatitis B reactivation should be added as an undesirable effect with an uncommon frequency. Furthermore, the product information should be updated to expand the existing warning on atrial fibrillation/flutter to a warning on 'cardiac arrhythmia', including ventricular tachyarrhythmia as well as atrial fibrillation/flutter. In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, treatment with ibrutinib should be temporarily discontinued and a thorough clinical benefit/risk assessment performed before possibly restarting the therapy. Therefore the current terms of the marketing authorisation(s) should be varied[20].
- The PRAC recommended the distribution of a direct healthcare professional communication (DHPC) to prescribers to inform them on the risk of hepatitis B reactivation. The PRAC agreed the content of the DHPC and discussed the communication plan.
- The MAH should update the RMP by reflecting the MAH's proposal for a follow-up questionnaire for cardiac arrhythmias, which should be submitted at the next available opportunity or 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.

6.1.6. Ketoconazole[21] - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201611

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

Background

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

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

[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] Centrally authorised product only

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ketoconazole HRA (ketoconazole) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add information regarding interaction between edoxaban and isavuconazole and provide recommendation when the two substances are co-administered in order to reduce doses of edoxaban and to specify that it is not recommended to administer isavuconazole with ketoconazole due to an increased risk of isavuconazole related adverse reactions. Therefore the current terms of the marketing authorisation(s) should be varied[22].

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

6.1.7. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/201611 (with RMP)

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Lumacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) corrector and ivacaftor a CFTR potentiator. In combination, lumacaftor/ivacaftor is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the *F508del* mutation in the CFTR gene.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Orkambi, a centrally authorised medicine containing lumacaftor/ivacaftor, 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 benefit-risk balance of Orkambi (lumacaftor/ivacaftor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the warning for respiratory events in order to state that these can be serious and can lead to treatment discontinuation, particularly in patients with the percentage of predicted forced expiratory volume in one second ($ppFEV_1$) less than 40%. Moreover, the warning and the undesirable events for patients with advanced liver disease should be updated to warn that liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension. Finally, the warning on cataracts should be revised to reflect that cases of cataracts have been reported in lumacaftor/ivacaftor treated patients. Therefore the current terms of the marketing authorisation(s) should be varied[23].

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

- In the next PSUR, the MAH should provide a further analysis of respiratory events as well as discuss whether 'pulmonary function test decreased' or 'FEV_1 decreased' should be added to the description of respiratory events which may be experienced upon lumacaftor/ivacaftor treatment initiation. In addition, if follow up information from the literature becomes available, the MAH should provide updated information regarding patient discontinuation and serious undesirable effects. Furthermore, the MAH should continue to closely monitor cases for which treatment was discontinued in an effort to further identify possible risk factors for discontinuation and provide recommendations which may mitigate against respiratory events and hence decrease discontinuation rates. Finally, regarding the use of lumacaftor/ivacaftor in patients with liver disease, the MAH should provide the data on Child Pugh class and dose, if available, in order to assess if other changes in the product information are required.

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

6.1.8. Nintedanib[24] - VARGATEF (CAP) - PSUSA/00010318/201611

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: Evaluation of a PSUSA procedure

Background

Nintedanib is an angiokinase inhibitor indicated[25] in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma histology after first-line chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vargatef, a centrally authorised medicine containing nintedanib, 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 benefit-risk balance of Vargatef (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the current warning on diarrhoea in order to add that this can lead to dehydration and electrolyte disturbances, as well as to amend the current warning on haemorrhage to include information on reported events and information on action to be taken in case of bleeding. Moreover, the description of the adverse event 'bleeding' should be updated. Therefore the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, the MAH should provide detailed analyses of cases reporting interstitial lung disease (ILD)/pneumonitis and of cases of (acute) renal failure and propose an update on the product information as applicable. In addition, the MAH should

[24] Oncology indication(s) only
[25] Oncology indication(s)
[26] 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

closely monitor cases of dysphonia. The MAH should also provide a detailed analysis on gastrointestinal perforation based on the latest update of the product information for the authorised nintedanib-containing medicinal product with a respiratory indication (see PSUSA/00010319/201610, PRAC minutes May 2017).

- The MAH should submit to EMA, within 60 days, a variation to reflect information on drug induced liver injury (DILI) and subgroups and exposure (pharmacokinetic changes).

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. Radium (^{223}Ra) dichloride - XOFIGO (CAP) - PSUSA/00010132/201611

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Radium (^{223}Ra) dichloride is a therapeutic alfa particle-emitting pharmaceutical indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xofigo, a centrally authorised medicine containing radium (^{223}Ra) dichloride, 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 Xofigo (radium (^{223}Ra) dichloride) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on gastrointestinal toxicity leading to a risk of dehydration and to advise patients to seek medical advice if they experience severe or persistent diarrhoea, or nausea and vomiting. Patients who display signs or symptoms of dehydration or hypovolemia should be promptly treated. Therefore the current terms of the marketing authorisation(s) should be varied[27].

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. Rituximab - MABTHERA (CAP) - PSUSA/00002652/201611

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

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

Scope: Evaluation of a PSUSA procedure

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 (RA) as well as for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of MabThera, a centrally authorised medicine containing rituximab, 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 benefit-risk balance of MabThera (rituximab) 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 perform a review of the risk of thrombocytopenia in the RA indication with a discussion on whether the warnings given for granulomatosis for the GPA/MPA and RA indications should be brought together to reflect an overall safety profile. In addition, the MAH should comment on the risk of urothelial cancers in all rituximab indications and compare it with the risk in rituximab/intravenous immunoglobulin (IVIg) kidney transplants. The MAH should also report on CD4[28] count when available, with all future cases of progressive multifocal leukoencephalopathy (PML), as well as report on opportunistic infections including, but not limited to cytomegalovirus (CMV), varicella zoster, herpes simplex and John Cunningham viruses (JCV), fungi (Pneumocystis pneumoniae/jiroveci, aspergillosis, some Candida infections, cryptococcal and coccidioido-mycosis), bacteria [Mycobacterium avium complex and Mycobacterium tuberculosis] and protozoa (cryptosporidium and toxoplasma)], divided by indication. Furthermore, the MAH should provide a cumulative review of drug reaction with eosinophilia and systemic symptoms (DRESS) cases with rituximab, including spontaneous reports, reports from clinical trials and a literature review and present a suggestion of improvement regarding safety information in the paediatric population in the product information. Finally, the MAH should provide a discussion on the need to update the product information to reflect the risk of foetal harm in the off-label subcutaneous rituximab treatments, and perform a review of all patients included in trials using subcutaneous rituximab outside of the NHL and CLL indications.
- The MAH should submit to EMA, within 90 days, a cumulative review of T lymphocyte decrease overall as well as CD4+ and CD8+ lymphocyte decrease, addressing all relevant data (spontaneous reports, clinical trials, literature) split by indication with a focus on data in which rituximab was used as monotherapy, and include a discussion on biological plausibility together with a discussion on the impact of this review on the benefit-risk balance of the medicinal product and any relevant proposals to update the product information accordingly. The MAH should in addition submit a review of the incidence of PML in rituximab treated patients stratified by indication and clinical setting (e.g. backbone, pre-treatment or not), using all available information including literature

[28] cluster of differentiation (CD)

data. Based on the outcome of this review, the MAH should discuss the need to amend the product information accordingly. Moreover, the MAH should provide an in-depth review of all risk factors for PML in rituximab treated patients and discuss the need for PML risk stratification strategies with a proposal for a risk stratification algorithm. In particular, the MAH should provide a discussion on the usefulness of JCV diagnostic assays, duration of treatment, and prior immunosuppressant use as part of risk stratification. Of note, the discussion on JCV diagnostic assays should include analysis of the positive predictive value, sensitivity, specificity and any other information relevant to the clinical utility of the assays as a risk stratification tool. Finally, the MAH should propose accordingly risk proportionate measures to minimise the risk.

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

Post-meeting note: At its July 2017 meeting, the PRAC discussed the possibility of consulting external experts, including academic experts, patients and healthcare professionals to support the assessment of the above requested data. It was agreed that advice from an ad-hoc expert group should be sought in the context of the procedure as appropriate.

6.1.11. Rotavirus vaccine pentavalent (live, oral) - ROTATEQ (CAP) - PSUSA/00002666/201611

Applicant: MSD Vaccins

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Rotavirus vaccine pentavalent (live, oral) is indicated for the active immunisation of infants from the age of 6 weeks to 32 weeks for prevention of gastroenteritis due to rotavirus infection.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of RotaTeq, a centrally authorised rotavirus vaccine pentavalent (live, oral), 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 benefit-risk balance of RotaTeq (rotavirus vaccine pentavalent (live, oral)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to accurately reflect the known risk of intussusception following results of a European study by *Stowe et al.*[29]. Therefore the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH should provide an update regarding the reports of incorrect product storage. In addition, the MAH should continue to closely monitor cases of

[29] Stowe J et al. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine. 2016;34(32):3684-9
[30] 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

intussusception and provide a discussion of intussusception cases which occurred during the reporting period. Finally, the MAH should provide an updated cumulative review of thrombocytopenia, thrombocytopenic purpura, and idiopathic thrombocytopenic purpura (ITP) and propose an update to the product information if deemed necessary.

- The MAH should collaborate with National Competent Authorities, upon their request, to communicate a reminder about the risk of intussusception, which is very rare but merits healthcare professionals' (HCPs) awareness of presenting symptoms in the infant. The PRAC agreed some key messages for such communications.

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

6.1.12. Trametinib - MEKINIST (CAP) - PSUSA/00010262/201611

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Trametinib is an inhibitor of the mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase and is indicated as monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation as well as in combination with dabrafenib for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mekinist, a centrally authorised medicine containing trametinib, 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 benefit-risk balance of Mekinist (trametinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'photosensitivity reaction' for the trametinib/dabrafenib combination therapy as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the MAH should provide a detailed review of cases with serious clinical hepatic events.
- The MAH should delete the important potential risk of 'off label use' based on a review the MAH performed of adverse events reported in relation to this concern. This change should be made in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP.

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

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

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

See also Annex I 16.2.

6.2.1. Interferon alfa-2b - INTRONA (CAP), NAP - PSUSA/00001758/201609

Applicants: Merck Sharp & Dohme Limited (IntronA), various

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Interferon alfa-2b is a water-soluble protein indicated[32] for the treatment of chronic hepatitis B, chronic hepatitis C, hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour and malignant melanoma under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of IntronA, a centrally authorised medicine containing interferon alfa-2b, and nationally authorised medicines containing interferon alfa-2b, 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 benefit-risk balance of interferon alfa-2b-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'tongue pigmentation' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[33].

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. Irbesartan, hydrochlorothiazide - COAPROVEL (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), KARVEZIDE (CAP), NAP - PSUSA/00001653/201609

Applicants: Sanofi Clir SNC (CoAprovel), Sanofi-aventis groupe (Irbesartan

[32] As recombinant interferon alfa-2b
[33] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Hydrochlorothiazide Zentiva, Karvezide), various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Irbesartan/hydrochlorothiazide is an oral fixed-dose combination antihypertensive agent combining irbesartan, a nonpeptide angiotensin II receptor antagonist, and hydrochlorothiazide, a thiazide diuretic. The combination is indicated for the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of CoAprovel, Irbesartan Hydrochlorothiazide Zentiva and Karvezide, centrally authorised medicines containing irbesartan/hydrochlorothiazide, and nationally authorised medicines containing irbesartan/hydrochlorothiazide, 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 benefit-risk balance of irbesartan/hydrochlorothiazide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include thrombocytopenia as an undesirable effect with an unknown frequency for irbesartan alone. Therefore the current terms of the marketing authorisations should be varied[34].

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

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

See also Annex I 16.3.

6.3.1. Baclofen[35] (NAP) - PSUSA/00000294/201609

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Baclofen is an antispastic agent acting at the spinal level indicated for the treatment of adults with spasticity of the skeletal muscles in multiple sclerosis, spastic conditions occurring in

[34] 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
[35] Oral route of administration only

spinal-cord diseases of certain origins, muscle spasm of cerebral origin, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease. It is also indicated in the paediatric population for the symptomatic treatment of spasticity of cerebral origin, muscle spasms occurring in spinal cord diseases of certain origins, and compression of the spinal cord.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing baclofen, 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 benefit-risk balance of baclofen-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'sleep apnoea syndrome' as an undesirable effect with an unknown frequency and 'rhabdomyolysis' as a possible consequence of abrupt baclofen withdrawal and baclofen overdose. In addition, the warning on renal impairment should be revised. Therefore the current terms of the marketing authorisation(s) should be varied[36].
- In the next PSUR, the MAHs should provide a comprehensive critical evaluation of the safety profile of baclofen in off-label use in alcohol use disorders. This analysis should include data from the published literature and spontaneous reports and should be divided according to whether the dose of baclofen prescribed was in accordance or in excess of the recommended daily dose in authorised indications. Furthermore, the MAHs should also provide an updated critical analysis of all cases of completed suicide, attempted suicide, suicidal ideation and all related events in off-label use of baclofen in alcohol use disorders and propose an update of the product information if deemed necessary.

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

6.3.2. Carbidopa, levodopa[37] (NAP) - PSUSA/00000548/201610

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Carbidopa/levodopa is a drug combination of an immediate precursor of dopamine and a peripheral dopa-decarboxylase inhibitor, indicated for the treatment of Parkinson's disease.

[36] Update of SmPC sections 4.4, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[37] Except centrally authorised product(s)

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing carbidopa/levodopa, 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 benefit-risk balance of carbidopa/levodopa-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'dopamine dysregulation syndrome' as a warning and as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[38].

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. Felbamate (NAP) - PSUSA/00010155/201609

Applicant(s): various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Felbamate is an antiepileptic indicated for use as adjunctive therapy in patients with Lennox-Gastaut syndrome (LGS) who are 4 years of age or older, and who are refractory to all relevant available antiepileptic drugs.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing felbamate, 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 benefit-risk balance of felbamate-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include recommendations to ensure that women of childbearing potential use an effective contraception during felbamate treatment and up to one month after end of treatment, and to stress the need to reassess any antiepileptic treatment for women of childbearing potential who are pregnant or plan to become pregnant. Finally, recommendations are added to the product information to strengthen the section describing the risks related to felbamate intake for foetuses and for infants in case of breastfeeding. Therefore the current terms of the marketing authorisation(s) should be varied[39].

[38] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[39] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- In the next PSUR, the MAH should provide detailed discussions on the following important identified risks: hepatic failure, hepatotoxicity, severe hypersensitivity reactions, aplastic anaemia, other blood dyscrasias, drug interactions with carbamazepine, phenytoin, phenobarbital, valproate, oral contraceptives and increased seizure frequency. Furthermore, the MAH should discuss the following important potential risks: impairment of driving ability and use of machinery, suicidal ideation and behaviour, onset of new types of seizures. Moreover, the MAH should closely monitor sudden death or sudden unexplained death in epilepsy, purpura and psychotic disorders.

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

6.3.4. Letrozole (NAP) - PSUSA/00001842/201610

Applicant(s): various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Letrozole is a non-steroidal aromatase inhibitor (AI) indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer, and the extended adjuvant treatment of invasive early breast cancer in post-menopausal women who have received prior standard adjuvant tamoxifen therapy for five years. It is also indicated for the treatment of advanced breast cancer in postmenopausal women under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of letrozole-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'hyperbilirubinemia' and 'jaundice' as undesirable effects with an uncommon frequency, and 'chest pain' as an undesirable effect with a common frequency. In addition, the frequency of the undesirable effects 'arthritis' and 'palpitations' should be updated to common. Therefore the current terms of the marketing authorisation(s) should be varied[40].
- In the next PSUR, the MAH should continue to closely monitor cases of interstitial lung disease (ILD)/pneumonitis, cases of off-label use in paediatric patients, in male patients and in non-oncology indications, cases reporting a fatal outcome, cognitive disorders and auto-immune disorders. In addition, the MAH should discuss new cases of age-related macular degeneration/macular degeneration.

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

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

6.3.5. Methylphenidate (NAP) - PSUSA/00002024/201610

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Methylphenidate is a central nervous system stimulant drug indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and in children aged 6 to 18 years.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing methylphenidate, 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 benefit-risk balance of methylphenidate-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a comprehensive and cumulative review on myocardial infarction and cardiomyopathy and propose to update the product information and/or RMP as appropriate.

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

6.3.6. Rabeprazole (NAP) - PSUSA/00002601/201610

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Rabeprazole is a proton-pump inhibitor (PPI) indicated for the treatment of gastroesophageal reflux disease (GERD), gastric and duodenal ulcer, Zollinger-Ellison syndrome, and in combination with antibiotics for the eradication of *Helicobacter pylori*.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing rabeprazole, 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 benefit-risk balance of rabeprazole-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include microscopic colitis as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[41].
- In the next PSUR, the MAH(s) should closely monitor reduced efficacy of clopidogrel when co-administered with rabeprazole, food intolerance in the context of rabeprazole use, hypertension, drug interactions, unlisted blood dyscrasia cases with positive de-challenge and/or re-challenge, information on new cases of rhabdomyolysis with positive de-challenge and/or re-challenge and hypokalaemia.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Mycophenolate mofetil - CELLCEPT (CAP) - EMEA/H/C/000082/LEG 039

Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of a justification on the need for two forms of contraception and any evidence for non-compliance with these requirements leading to unintended pregnancy; a detailed review of all known clinical data of reported congenital malformations from paternal exposure cases; a review of available non-clinical data relating to the potential for male-mediated developmental toxicity as requested in the conclusions of EMEA/H/C/PSUSA/00002099/201605 adopted by PRAC in December 2016

Background

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an inosine monophosphate dehydrogenase inhibitor, indicated as CellCept in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants under certain conditions.

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

Summary of advice/conclusion(s)

[41] 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

- In their next PSUR[42], MAHs of mycophenolate mofetil- and mycophenolic acid-containing medicinal products should provide a review of the recommendations for pregnancy testing before treatment is started and discuss how practical this testing is for transplant patients. The MAHs should also include a review of the recommendation for contraception before use and consideration of this in relation to off-label use. In addition, as part of the review of spontaneous abortion and congenital malformations, MAHs should comment on the latest data and consider updating the product information regarding the risk of congenital malformations or their frequencies as warranted. Furthermore, MAHs should implement the changes to the product information, the patient and healthcare professional (HCP) guides with regard to contraception and pregnancy as advised by PRAC, and submit proposals for the revision of the product information as appropriate. Finally, MAHs should discuss the need to communicate the amendments to the product information to HCPs, and the appropriate method for any communication.

6.4.2. Orlistat - ALLI (CAP) - EMEA/H/C/000854/LEG 027

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of a detailed cumulative safety review on all case reports of nephrotoxicity for both orlistat 60 mg and orlistat 120 mg as requested in the conclusions of EMEA/H/C/PSUSA/00002220/201602 adopted by PRAC in September 2016

Background

Orlistat is a gastrointestinal lipases inhibitor indicated as Alli (orlistat 60 mg) for weight loss in adults who are overweight (body mass index (BMI) ≥28 kg/m^2) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.

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

Summary of advice/conclusion(s)

- Taking into account the evaluation of the cumulative review of nephrotoxicity cases and considering the existing information and measures for patients with existing kidney disease included in the SmPC section on 'special warnings and precautions for use', for both orlistat products as well as current medical practice, for patients at increased risk of kidney disease monitoring of renal function their renal function as part of the patients' general medical supervision, the PRAC concluded that the product information for Alli is adequate based on the current level of evidence. Therefore, the PRAC considered that there was no need for further regulatory action in light of the current knowledge.

6.4.3. Orlistat - XENICAL (CAP) - EMEA/H/C/000154/LEG 026

Applicant: Cheplapharm Arzneimittel GmbH

[42] Procedure: PSUSA/00010550/201705, data lock pointDLP: 02/05/2017; submission date: 11/07/2017

PRAC Rapporteur: Caroline Laborde

Scope: Submission of a detailed cumulative safety review on all case reports of nephrotoxicity for both orlistat 60 mg and orlistat 120 mg as requested in the conclusions of EMEA/H/C/PSUSA/00002220/201602 adopted by PRAC in September 2016

Background

Orlistat is a gastrointestinal lipases inhibitor indicated as Xenical (orlistat 120 mg) in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m², or overweight patients (BMI > 28 kg/m²) with associated risk factors.

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

Summary of advice/conclusion(s)

- Taking into account the evaluation of the cumulative review of nephrotoxicity cases and considering the existing information and measures for patients with existing kidney disease included in the SmPC Section on 'special warnings and precautions for use', for both orlistat products as well as current medical practice, for patients at increased risk of kidney disease, monitoring their renal function as part of the patients' general medical supervision, the PRAC concluded that the product information for Xenical is adequate based on the current level of evidence. Therefore, the PRAC considered that there was no need for further regulatory action in light of the current knowledge.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[43]

See also Annex I 17.1.

7.1.1. Aclidinium bromide – EKLIRA GENUAIR (CAP), BRETARIS GENUAIR (CAP); aclidinium bromide, formoterol – DUAKLIR GENUAIR (CAP), BRIMICA GENUAIR (CAP) - EMEA/H/C/PSA/S/0017

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Submission of a substantial amendment to the protocol for the aclidinium bromide PASS evaluating the potential for cardiovascular safety concerns and all-cause mortality described in the RMP, through sequential, nested case-control studies for each endpoint of interest

Background

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

Aclidinium bromide is a long-acting muscarinic receptor antagonist (also known as an anticholinergic) and formoterol a long-acting β2-adrenergic agonist. Aclidinium bromide alone as Eklira Genuair and Bretaris Genuair or in combination with formoterol as Duaklir Genuair and Brimica Genuair is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

In July 2013, the PRAC adopted a protocol for a non-interventional PASS (study ENCEPP/SDPP/6559) designed to evaluate the potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for aclidinium bromide, through sequential, nested case-control studies for each endpoint of interest. For further background, see PRAC minutes July 2013.

Further to the MAH submission of a substantial protocol amendment (version 3.0) to update the post authorisation safety study (PASS) milestones, as the number of aclidinium users in Clinical Practice Research Datalink (CPRD) was now considered lower than expected, to amend the original study milestones in order to continue with the plan to conduct the study in CPRD given its several advantages, the amended protocol (version 3.0) was reviewed by the PRAC.

Endorsement / Refusal of the protocol

- The PRAC, having considered the amended protocol version 3.0, dated 18 May 2017, in accordance with Article 107o of Directive 2001/83/EC, as set out in the appended assessment report, endorsed by consensus the protocol for the above listed medicinal product(s).

7.1.2. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS (CAP) - EMEA/H/C/PSP/S/0055

Applicant: MolMed SpA; ATMP[44]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of a protocol for study TK011: a prospective, non-interventional PASS on long-term safety and effectiveness in patients undergoing haploidentical hematopoietic stem cell transplantation for high-risk haematological malignancies

Background

Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) is constituted of donor's T lymphocytes genetically modified to express the HSV-TK Mut2, as suicide gene. Zalmoxis, is a centrally authorised medicine containing allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2), and is indicated as adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies.

[44] Advanced therapy medicinal product

To investigate the safety and effectiveness in real clinical practice as well as long-term safety and effectiveness in all patients treated with Zalmoxis, the MAH was requested to implement a PASS using the European Society for Blood and Marrow Transplantation (EBMT) registry including all patients treated with Zalmoxis. Further to the MAH submission of the protocol (IPR/29.F, version 1.0) for this prospective, non-interventional, post-authorisation safety study (PASS) of Zalmoxis prescribed in patients undergoing haploidentical hematopoietic stem cell transplantation for high-risk haematological malignancies (TK011 study), the protocol was reviewed by the PRAC.

Endorsement / Refusal of the protocol

- The PRAC, having considered the protocol version IPR/29.F of the TK011 PASS (version 1.0) in accordance with Article 107n of Directive 2001/83/EC, as set out in the appended assessment report, endorsed by consensus the protocol for the above listed medicinal product(s).

7.1.3. Pomalidomide – IMNOVID (CAP) - EMEA/H/C/PSA/S/0012.1

Applicant: Celgene Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Submission of a revised protocol for a non-interventional post authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy

Background

Pomalidomide has direct anti-myeloma tumoricidal activity, immunomodulatory activities and inhibits stromal cell support for multiple myeloma (MM) tumour cell growth. Imnovid is a centrally authorised medicine containing pomalidomide indicated in combination with dexamethasone in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. In order to characterise and determine the incidence of important identified and potential risks as outlined in the risk management plan (RMP) among previously treated MM patients who are currently being treated with Imnovid (pomalidomide) in a post-marketing setting, the MAH was requested to conduct and submit the results of a post-authorisation non-interventional registry according to an agreed protocol as a condition to the marketing authorisation. The initial PASS protocol was endorsed by PRAC in December 2013. For further background, see PRAC minutes December 2013.

In January 2017, the PRAC, having considered the amended PASS protocol version 3.0 to change the study milestones objected to the substantial amendments and recommended that key questions relating to study milestones should be addressed by the MAH. For further background, see PRAC minutes January 2017.

Endorsement / Refusal of the protocol

- The PRAC, having considered the amended protocol version 4.0, dated 9 March 2017, in accordance with Article 107o of Directive 2001/83/EC, endorsed by consensus the substantial amendments to the PASS protocol for the above listed medicinal product(s).

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[45]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[46]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[47]

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

[45] 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
[46] In accordance with Article 107p-q of Directive 2001/83/EC
[47] 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

8.2. Conditional renewals of the marketing authorisation

None

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

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

Scope: Pharmacovigilance inspection programme 2017-2020 (first revision for 2017)

The PRAC agreed the list of planned pharmacovigilance inspections for 2017-2020, the first revision having been agreed by the Pharmacovigilance Inspector Working Group (PhV IWG) and reviewed according to a risk based approach. This list is subsequently due for adoption at CHMP.

Post-meeting note: On 22 June 2017, the CHMP adopted by written procedure the pharmacovigilance inspection programme 2017-2020, first revision.

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0063

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: PRAC consultation on a type II variation to update section 5.1 of the SmPC in order to provide information on the clinical study data experience in patients in treatment transition from an oral bisphosphonate to denosumab, information resulting from the assessment of study report 20110153 and a discussion on the issue of long term antiresorptive treatment, in particular when long-term bisphosphonate treatment is followed by denosumab

Background

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

Following the conclusion of a PSUSA procedure (PSUSA/00000954/201509) for Prolia (denosumab) and its recommendation adopted at the April 2016 PRAC meeting (for further background, see PRAC minutes April 2016), the MAH submitted to EMA a type II variation to review long term antiresorptive treatment, in particular long term bisphosphonate (BP) treatment followed by denosumab treatment. The type II variation proposing to update the product information is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC supported the proposed changes to the product information that include a warning stating that long-term antiresorptive treatments (bisphosphonates, denosumab) may contribute to an increased risk for adverse outcomes such as osteonecrosis of the jaw (ONJ) and atypical femur fractures due to over-suppression of bone remodelling. In addition, the PRAC supported the inclusion of a statement, similar to that included in the product information of bisphosphonate-containing products, stipulating that the optimal total duration of antiresorptive treatment for osteoporosis has not yet been established, and that the need for continued treatment with denosumab should be re-evaluated periodically, particularly after five or more years of antiresorptive treatment. Furthermore, the PRAC acknowledged the need to revise the SmPC section on 'pharmacodynamic properties'[48] on the open-label extension study in the treatment of women with postmenopausal osteoporosis to reflect the additional long-term data reviewed in the current variation procedure, including fracture incidences over time.

  See also under 5.3.1.

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

None

10.3. Other requests

None

[48] SmPC section 5.1

10.4. 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.

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

12.1.1. PRAC Brexit ancillary working group

PRAC lead: Almath Spooner

At the organisational matters teleconference on 22 June 2017, as a follow-up to the May 2017 PRAC meeting (see PRAC minutes May 2017), Almath Spooner, the appointed Chair of the PRAC ancillary working group focussing on Brexit preparedness, reported to PRAC on the first group meeting that took place in the margins of the June 2017 PRAC plenary meeting. The group adopted its composition in terms of PRAC membership. The group also appointed alongside the Chairperson, Dolores Montero Corominas and Maia Uusküla to represent the PRAC and its Brexit ancillary group at the regular cross-Committee EMA 'Working Group on Committees' operational preparedness for human medicines'. Furthermore, the group reflected on its future mandate, governance and interaction with other groups and identified the areas where actions need to be put in place as priorities. A concept paper on Brexit preparedness is being prepared for discussion at the next group meeting scheduled on 30 June 2017 by teleconference. A further update will be given in July 2017.

12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of qualitative goals

PRAC lead: Martin Huber, Menno van der Elst, Tatiana Magalova, Albert van der Zeijden, Marianne Lunzer, Jan Neuhauser, Ulla Wändel Liminga

The topic was deferred to September 2017.

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Joint Paediatric Committee (PDCO)-PRAC Working Group - Guideline on conduct of pharmacovigilance for medicines used by the paediatric population – draft good pharmacovigilance practice (GVP) chapter for special populations

At the organisational matters teleconference on 22 June 2017, the PRAC was presented with a consolidated draft GVP chapter P. IV on the conduct of pharmacovigilance for medicines used by the paediatric population, following comments received from PRAC and PDCO at the strategic review and learning meeting (SRLM) held in April 2017 in Malta. The PRAC agreed with initiating the public consultation in Q3 2017 following consultation with the European Commission.

12.2.2. Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMP) – update

PRAC lead: Brigitte Keller-Stanislawski, Julie Williams

At the organisational matters teleconference on 22 June 2017, the PRAC endorsed the nomination of Sabine Straus, Dolores Montero Corominas and Ulla Wändel Liminga as additional PRAC members to participate in the cross-Committee working group dedicated to the ongoing revision of the 'guideline on safety and efficacy follow-up – RMP for ATMP' (EMEA/149995/2008) (for further background, see PRAC minutes April 2017) to ensure that the principles of GVP module V on 'risk management system' (EMA/838713/2011 Rev 2*) are applied to ATMPs and to develop a specific 'RMP template' for ATMPs. Follow-up discussion is planned at the October 2017 PRAC meeting (scheduled on 25-29 September 2017).

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

12.3.1. Blood Products Working Party (BPWP) - Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products – revision

PRAC lead: Brigitte Keller-Stanislawski

At the organisational matters teleconference on 22 June 2017, the EMA Secretariat together with the CHMP Blood Product Working Party (BPWP) Rapporteur (Anneliese Hilger) consulted the PRAC on the proposed revision of the existing 'guidelines on the clinical investigation and core SmPC of recombinant and human plasma-derived factor VIII products'. This revision follows the EMA workshop on haemophilia registries held in July 2015 and the concept paper (EMA/CHMP/BPWP/383118/2016) on the revision of the guideline prepared in 2016. The PRAC discussed the proposals and requested further clarification on the proposed approach in terms of the current clinical trials requirements and the registries for previously untreated patients (PUPs). An update will be given in September/October 2017.

12.3.2. Blood Products Working Party (BPWP) - Guideline on core SmPC for human plasma-derived and recombinant coagulation factor VIII products – revision

PRAC lead: Brigitte Keller-Stanislawski

At the organisational matters teleconference on 22 June 2017, the EMA Secretariat together with the CHMP Blood Product Working Party (BPWP) Rapporteur (Anneliese Hilger) consulted the PRAC on the proposed revision to the existing 'guidelines on the clinical investigation and core SmPC of recombinant and human plasma-derived factor VIII products'. This revision follows the EMA workshop on haemophilia registries held in July 2015 and the concept paper (EMA/CHMP/BPWP/383118/2016) on the revision of the guideline prepared in 2016. The PRAC discussed the proposals and requested further clarification on the proposed approach in terms of the current clinical trials requirements and the registries for previously untreated patients (PUPs). An update will be given in Sep tember/October 2017.

12.4. Cooperation within the EU regulatory network

12.4.1. European Network Training Centre (EU NTC) - operation of pharmacovigilance in the EU training needs and priorities

PRAC lead: Dolores Montero Corominas

At the organisational matters teleconference on 22 June 2017, the EMA Secretariat, on behalf of the Pharmacovigilance Training Curriculum Steering Group (EU PVOP-SG[49]) composed of EMA and NCA representatives, presented to PRAC the European Network Training Centre (EU NTC) operation of pharmacovigilance in the EU training needs and priorities. Following a PRAC survey on training needs and priorities in March 2017, seven topic areas were identified and priorities were given accordingly, with the highest priority given for training in the areas of risk management plans, signal management and post-authorisation studies. As next steps, based on the PRAC discussion, the EU PVOP-SG will work on elaborating a three year training delivery plan for priority areas and additional topics of interest, including the identification of training teams and leads. PRAC will receive regular updates on the progress made. The content will come from a variety of sources: e.g. Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action programme, other EU programmes or individual programmes run by NCAs, which are open for the network and curated sources of content recommended by the EU PVOP-SG.

12.5. Cooperation with International Regulators

None

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

None

[49] Steering group of the 'operation of pharmacovigilance in the EU'

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

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

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version June 2017 reflecting the PRAC's comments impacting on the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of June 2017, the updated EURD list was adopted by the CHMP and CMDh at their June 2017 meetings and published on the EMA website on 27/06/2017, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

At the organisational matters teleconference on 22 June 2017, the PRAC was updated on the outcome of the June 2017 SMART Working Group (SMART WG) work stream WS1. The WG WS1 discussed the frequency for EMA to provide NCAs with electronic reaction monitoring reports (eRMRs) as well as criteria for determining the frequency at NCA level for monitoring eRMRs. In addition, the PRAC was updated on SMART WS2-3 and its work programme on SMART methods focusing on eight areas (signal detection in paediatric population, unexpected increase in frequency (IUF), statistical correction of uncharacterised bias (SCRUB), MedDRA[50] synonyms, signals outcome and analysis project (SOAP), information on mechanism to help predict adverse drug reactions (ADR) and drug-drug interaction (DDI), reference dataset and ad hoc work on increasing signal detection (SD) efficiency). The PRAC welcomed this update and the important areas for progress, suggesting that some prioritisation of deliverables would be helpful.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Good Pharmacovigilance Practice (GVP) module VI on Management and reporting of adverse reactions to medicinal products - revision 2

The EMA Secretariat presented to PRAC draft revision 2 of GVP module VI on 'management and reporting of adverse reactions to medicinal products' with an overview of the aspects triggering this revision, mainly focussing on the simplification of submission of individual case safety reports (ICSR) by MAHs to EudraVigilance and the implementation of ICH-E2B(R3)[51] format. The EMA highlighted the process that followed the public consultation held in August-October 2016 and in particular the input provided by the EudraVigilance Expert Working Group (EV-EWG). Following consultation of the PRAC, CHMP, CMDh, CAT, PDCO, Pharmacovigilance Inspectors Working Group (PhV-IWG), the GVP module VI revision 2 will be scheduled for adoption at PRAC in July 2017.

[50] Medical Dictionary for Regulatory Activities
[51] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline on clinical safety data management :data elements for transmission of ICSRs

12.12.2. Management and reporting of adverse reactions to medicinal products

None

12.12.3. Additional monitoring

None

12.12.4. 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 28/06/2017 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

As agreed in May 2017 (see PRAC minutes May 2017), the EMA Secretariat provided PRAC with further details on the strategic development plan of operation of the new EudraVigilance (EV) system that comprises an EV technical support plan for NCAs and a checklist. The EMA Secretariat also presented the forward timetable in the form of a calendar for the final testing schedule at the level of NCAs, covering the testing of individual case safety reports (ICSR) and the acknowledgement message (ACK) in ICH[52]-E2B(R3) or ICH-E2B(R2) format generated by local pharmacovigilance databases of NCAs, testing of the new nullification process for nullifications sent by MAHs for ICSRs that were previously forwarded to EV by NCAs as well as other NCA testing activities. The EV external compliance testing environment (XCOMP) will be launched to all stakeholders on 26 June 2017. Further update will be given in July 2017.

Post-meeting note: On 26 June 2017, the launch of the XCOMP (test) environment was communicated to all registered users. In addition, an updated version of the change management plan was published on the EMA webpage on EudraVigilance change management on 23 June 2017, which reflects the launch of the XCOMP environment.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

[52] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline on clinical safety data management: data elements for transmission of ICSRs

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

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

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

12.20.2. Strategy on measuring the impact of pharmacovigilance - pilot report on prioritisation of collaborative impact research topics and criteria checklist

PRAC lead: Marieke de Bruin

At the organisational matters teleconference on 22 June 2017, and following previous PRAC discussions (for further background, see PRAC minutes April 2017), the PRAC endorsed the pilot report on prioritisation of collaborative impact research topics ,and supported the PRAC interest group's (PRAC IG) proposal to publish on the EMA website the criteria checklist for prioritising EU regulatory network collaborative impact research, taking into account the findings from the 6-month pilot.

Post-meeting note: The final 'checklist for prioritisation of EU regulatory network collaborative impact research' (EMA/318043/2017) was published on the EMA website following PRAC adoption.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[53]

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[54].

14.1.1. Amitriptyline (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

[53] 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

[54] 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

Scope: Signal of risk of drug induced liver injury (DILI) and hepatocellular injury

EPITT 18890 – New signal

Lead Member State(s): EL

14.1.2. Ledipasvir, sofosbuvir – HARVONI (CAP)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of blood cholesterol increased, low density lipoprotein increased

EPITT 18903 – New signal

Lead Member State(s): PT

14.2. New signals detected from other sources

14.2.1. Dasatinib – SPRYCEL (CAP); warfarin (NAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG (Sprycel); various

PRAC Rapporteur: Doris Stenver

Scope: Signal of serious adverse drug reactions (ADRs) including bleeding events following potential drug interaction between dasatinib and warfarin

EPITT 18894 – New signal

Lead Member State(s): DK

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. Entecavir - EMEA/H/C/004458

Scope: Treatment of chronic hepatitis B virus (HBV) infection

15.1.2. Glibenclamide - EMEA/H/C/004379, Orphan

Applicant: Ammtek

Scope: Treatment of neonatal diabetes

15.1.3. Imatinib - EMEA/H/C/004748

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

15.1.4. Lacosamide - EMEA/H/C/004443

Scope: Treatment of epilepsy

15.1.5. Miglustat - EMEA/H/C/004366

Scope: Treatment of Gaucher disease

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. Albiglutide - EPERZAN (CAP) - EMEA/H/C/002735/II/0029/G

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Grouped variation to: 1) update the RMP to amend the category 3 study 201805: an observational study of the risk of common malignant neoplasms and malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide compared to those prescribed other antidiabetic agents, in order to use a different database to study the risk of neoplasms in association with albiglutide exposure; 2) update the RMP to add a new category 3 study as an additional pharmacovigilance activity study 207351: an observational study to assess maternal and foetal outcomes following exposure to albiglutide during pregnancy

15.2.2. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0095

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 28.0) in order to remove the post-authorisation measure (PAM) relating to the submission of an extension protocol to obtain additional long-term follow-up (LTFU) information from the paediatric population after patients complete a minimum of 5.5 year follow-up period as defined in the protocol of study BO20924 (BERNIE): an open-label, multicentre, randomized study of the safety and effect on event-free survival of bevacizumab in combination with standard chemotherapy in childhood and adolescent patients with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma, as well as to amend the submission date of its final report (addendum

clinical study report (CSR))

15.2.3. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0065

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 18) to update the 'important potential risk: hypercalcemia following treatment discontinuation in patients with growing skeletons' to 'important potential risk: hypercalcemia following treatment discontinuation in patients with growing skeletons and the adult population'. The RMP is updated based on the MAH's updated safety assessment conducted in 2016. The MAH also took the opportunity to request the removal of the important potential risk of fracture healing complications as recommended in April 2016 by PRAC in procedure EMEA/H/C/PSUSA/00000954/201509. Furthermore, addition of study 20090601: a post-marketing active safety surveillance programme for soliciting adverse events of special interest in the United States as a category 4 study pharmacovigilance activity

15.2.4. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0051

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 23) to update the 'important potential risk: hypercalcemia following treatment discontinuation in patients with growing skeletons' with the new important potential risk: hypercalcemia following treatment discontinuation in patients other than those with growing skeletons'. The MAH also took the opportunity to include minor changes for correction and/or to add clarification

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

15.2.6. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58) - EMEA/H/W/002300/II/0020

Applicant: GSK Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of the RMP (version 3.0) in order to 1) add cerebral malaria as an important

potential risk, 2) add mortality by gender as missing information, 3) add the WHO[55] pilot implementation programme as a category 3 study, 4) change the study dates for studies malaria-073 (200596, phase IIIb randomized, open, controlled study to evaluate the immunogenicity and safety of Mosquirix, when administered as primary vaccination at 6, 7.5 and 9 months of age with or without coadministration of measles and rubella and yellow fever vaccines to children living in sub-Saharan, Africa), EPI-MAL-002 (115055, an observational cohort study to estimate the incidence of adverse event of special interest (AESI), of meningitis and of other adverse events (AE) leading to hospitalisation or death, in children, prior to implementation of Mosquirix), EPI-MAL-003 (115056, a prospective surveillance study to evaluate the safety, the effectiveness and the impact of Mosquirix in infants and young children in sub-Saharan Africa), EPI-MAL-005 (116682, an epidemiology study to assess *Plasmodium falciparum* parasite prevalence and malaria control measures in catchment areas of two interventional studies pre- and post-Mosquirix introduction (EPI-MAL-002 and EPI-MAL-003) to assess, in field conditions, vaccine benefit-risk in children in sub-Saharan Africa), EPI-MAL-010 (205071, a longitudinal, cross-sectional ancillary study of the EPI-MAL-005 study to evaluate the genetic diversity in circumsporozoite sequences before and after the implementation of Mosquirix in malaria-positive subjects ranging from 6 months to less than 5 years of age), 5) amend the protocol of study EPI-MAL-002, 6) update the draft protocol of study EPI-MAL-003, 7) provide a new draft of the protocol of study EPI-MAL-010, 8) provide a new protocol for the pilot implementation programme

15.2.7. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0038, Orphan

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 17) in order to provide the statistical analysis plan (SAP) for study AP24534-14-401 (a post-marketing observational cohort study to evaluate the incidence of and risk factors for vascular occlusive events associated with Iclusig in routine clinical practice in the United States (US)), as per the PRAC request made in the framework of MEA 015

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/0105

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Extension of indication to include the treatment of psoriatic arthritis in adults. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 21) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

[55] World Health Organization

15.3.2. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0001

Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Extension of indication to 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, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 2.0) are updated accordingly

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

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

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

15.3.4. Atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/II/0111

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

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

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

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.6. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0011, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, and amend the safety information. The Labelling and the RMP (version 4.0) are updated accordingly

15.3.7. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0045, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.1 of the SmPC in order to add 5-year follow-up overall survival (OS) data from patients included in study SG035-0004, a phase 2 open-label study of brentuximab vedotin in the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL), in accordance with specific obligation SOB 028. Annex II of the product information and the RMP (version 9.0) are updated accordingly

15.3.8. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0015

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.2 of the SmPC in order to update the safety information based on the primary pharmacokinetic (PK) and preliminary safety results of food effect study CLDK378A2112: a multicentre, randomized open label study to assess the systemic exposure, efficacy, and safety of 450 mg ceritinib taken with a low-fat meal and 600 mg ceritinib taken with a low-fat meal as compared with that of 750 mg ceritinib taken in the fasted state in adult patients with anaplastic lymphoma kinase (ALK) rearranged (ALK-positive) metastatic non-small cell lung cancer (NSCLC). The Package Leaflet and the RMP (version 9.0) are updated accordingly

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

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

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

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) line extension to introduce a new pharmaceutical form associated with new strengths (1 mg, 2.5 mg and 5 mg hard capsules), 2) type II 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)

15.3.11. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/II/0007

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add 'autoimmune haemolytic anaemia' with a frequency uncommon and to include a warning concerning symptoms of this adverse drug reaction. The Package Leaflet and the RMP (version 5.0) are updated accordingly. In addition, the MAH took the opportunity to implement minor editorial amendments throughout the Product Information

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

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

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

15.3.13. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0068

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture as well as the prevention of osteoporosis in women and men at increased risk of fracture who are starting or have recently started long-term glucocorticoid therapy. As a consequence, sections 4.1 and 5.1 of the SmPC are updated to reflect the new indications based on the analysis of the data from the pivotal study glucocorticoid-induced osteoporosis (GIOP): study 20101217: a randomized, double-blind, active controlled study evaluating the efficacy and safety of denosumab compared with risedronate in glucocorticoid-treated individuals. The Package Leaflet and the RMP (version 19.0) are updated accordingly

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC in order to update the safety information as cataract is no longer considered to be a potential risk and/or adverse reaction associated with denosumab therapy following the completion of study 20080560 (a phase 3, multicentre, randomized, double-blind, placebo-controlled study in men to evaluate new or worsening lens opacifications in subjects with non-metastatic prostate cancer receiving denosumab for bone loss due to androgen deprivation therapy and progression study using a slit-lamp-based evaluation system (lens opacities classification system III (LOCS III)). The Package Leaflet is updated accordingly. In addition, the RMP (version 20.0) is updated to remove the important potential risk of 'cataract in men with prostate cancer receiving androgen deprivation therapy'

15.3.15. 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 adverse drug reaction frequencies. The RMP (version 14.0) is updated accordingly

15.3.16. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/II/0005/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of: 1) update of section 4.4. of the SmPC to add a warning on the risk of lower limb amputations to align the product information (PI) with the outcome of the completed referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1442) on the risk of lower limb amputation for sodium-glucose co-transporter-2 (SGLT2) inhibitors. The Package Leaflet is updated accordingly; 2) update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC to update the PI with data from study 1245.25 Emp-Reg: a phase III, multicentre, international, randomized, parallel group, double blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus (T2DM) patients with increased cardiovascular risk. The RMP (version 2.0) is updated accordingly

15.3.17. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0026

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final results of a non-clinical study on the effect of empagliflozin

on blood ketone level at refeeding after a fasting period, comparison between refeeding with glucose or fat in order to fulfil MEA 010. The RMP (version 11.0) is updated accordingly

15.3.18. 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

15.3.19. Fulvestrant - FASLODEX (CAP) - EMEA/H/C/000540/II/0057

Applicant: AstraZeneca UK Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of postmenopausal women with locally advanced or metastatic breast cancer who have not received prior endocrine therapy for Faslodex. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated in order to update the safety and pharmacodynamics information. The Package Leaflet and the RMP (version 10) are updated accordingly. In addition, the MAH took the opportunity to introduce clarifications in the SmPC

15.3.20. Fulvestrant - FASLODEX (CAP) - EMEA/H/C/000540/II/0059

Applicant: AstraZeneca UK Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the use of Faslodex in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy. In pre- or peri-menopausal women, the combination treatment with palbociclib should be combined with a luteinizing hormone releasing hormone (LHRH) agonist for Faslodex. As a consequence, sections 4.1, 4.2, 4.4, 5.1, 5.3 and 6.6 of the SmPC are updated to update the safety and efficacy information. The Package Leaflet and the RMP (version 11) are updated accordingly

15.3.21. 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 consisting of an 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

15.3.22. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0033/G, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 5.1 of the SmPC in order to update the safety information related to bleeding related events based on final results from study PCYC-1132-NT (RMP, category 3 (MEA 004.1) study): an in-vitro study to evaluate the effect of ibrutinib on platelet aggregation. The Package Leaflet is updated accordingly; 2) update of section 4.4 and 4.5 of the SmPC in order to update the safety information based on the final results from study LYM1003 (RMP, category 3 (MEA 009.1) study): a drug-drug interaction study to assess steady state pharmacokinetic (PK) of repeated oral doses of ibrutinib alone in patients with B-cell malignancies and when combined with a moderate and strong CYP3A[56] inhibitor. The Package Leaflet is updated accordingly; 3) update of section 4.5 of the SmPC in order to update the safety information based on the final results from study FK12024: a drug-drug interaction (DDI) study with CYP3A inhibitor posaconazole in simulated subjects. The Package Leaflet is updated accordingly; 4) update of section 4.4 of the SmPC in order to update the safety information on antimicrobial prophylaxis following routine pharmacovigilance activity; 5) update of the RMP in order to extend the closure date of study PCYC-1112-CA (ANX 003.2: a randomized, multicentre, open-label, phase 3 study of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma) to Q2 2019. Yearly updates will be submitted in Q2 2017 and Q2 2018. Annex II has been updated accordingly; 6) update of the RMP to include an additional action for study PCI-32765 CAN3001 (MEA017) to provide a 'further interim report in 5 years' from the time of the cut-off date of the current report (12 November 2015)' as agreed in the CHMP outcome for procedure EMA/H/C/003791/MEA 017. The RMP (version 6.8) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.23. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/II/0084

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Submission of the summary analysis report on the incidence of neoplasms with the combination of liraglutide and insulin detemir from the cardiovascular outcome trial for Victoza (liraglutide): study EX2211-3748 (LEADER: liraglutide effect and action in diabetes): a long-term, multicentre, international, randomized double-blind, placebo-controlled trial to

[56] Cytochrome P450, family 3, subfamily A

determine liraglutide effects on cardiovascular events. The RMP (version 18) is updated accordingly to delete the important potential risk of malignant neoplasms following combination treatment with insulin detemir, liraglutide and metformin

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

Applicant: Eli Lilly Regional Operations GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Submission of the final report from study I4L-MC-ABER (ABER): 'a prospective, randomized, open-label comparison of long-acting basal insulin analog Abasaglar (LY2963016) to the reference product (Lantus (insulin glargine)) in adult patients with type 2 diabetes mellitus (T2DM): the ELEMENT 5 study' conducted in non-European countries. This study replaces the cancelled studies initially planned to be conducted in China and other countries. The RMP (version 1.6) is updated accordingly

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

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

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

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in children and adolescents 12 years of age and older. As a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 15) are updated accordingly

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Grouped variations consisting of: 1) update of section 4.4 to revise the current warning on concurrent administration with vemurafenib to enhance awareness on the potential of hypersensitivity reactions when ipilimumab is used sequentially with

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

15.3.28. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/II/0011

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to reflect the clinical study results of the LEADER study (EX2211-3748, category 3 study): liraglutide effect on and action in diabetes - evaluation of cardiovascular outcome results to specifically address the important potential risk of cardiovascular disorders in patients with type 2 diabetes mellitus (T2DM)). The Package Leaflet, labelling and RMP (version 27) are updated accordingly. This variation application fulfils two post-approval commitments in relation to the cardiovascular outcomes trial (MEA 002), as well as providing additional information on the breast cancer cases reported in the LEADER study (MEA 005). Finally, the MAH took the opportunity to implement minor editorial changes throughout the product information

15.3.29. Liraglutide - VICTOZA (CAP) - EMEA/H/C/001026/II/0042

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the prevention of major adverse cardiovascular events (MACE) in adults with type 2 diabetes mellitus (T2DM) at high cardiovascular risk and as an adjunct to standard of care therapy in section 4.1 of the SmPC implementing the clinical study results of the LEADER study (EX2211-3748): liraglutide effect on and action in diabetes, evaluation of cardiovascular outcome results (category 3 study: to specifically address the important potential risk of cardiovascular disorders in patients with T2DM). As a consequence, sections 4.2, 4.4, 4.7, 4.8, 5.1 and 6.5 of the SmPC, the Package Leaflet, Labelling and RMP (version 27) are updated accordingly

15.3.30. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/II/0161/G

Applicant: AbbVie Ltd.

PRAC Rapporteur: Caroline Laborde

Scope: Grouped variation including: 1) extension of indication to include children aged 14 days and older in the treatment of human immunodeficiency virus (HIV)-1. As a consequence, sections 4.1, 4.2, 4.3, 4.8, 5.1 and 5.2 of the SmPC are updated. The studies provided in support of the paediatric indication are part of the agreed paediatric investigation plan (PIP) decision P/0144/2012. In addition, the MAH further updated section 4.4 to add information regarding the use of Kaletra oral solution with feeding tubes. The

Package Leaflet, Labelling and RMP (version 8) are updated accordingly; 2) addition of a new pack size of 120 mL in (2 x 60mL bottles) for Kaletra 80mg/ml and 20 mg/ml oral solution (EU/1/01/172/003); 3) addition of a new 2 mL oral dose syringe for the 120 mL presentation

15.3.31. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0021

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Update of section 4.8 of the SmPC in order to add information on respiratory events based on final results from study VX14-809-106 (study 106): a Phase 3b, open-label study to evaluate the safety and tolerability of lumacaftor/ivacaftor combination therapy in subjects aged 12 years and older with cystic fibrosis and advanced lung disease homozygous for the F508del-cystic fibrosis transmembrane conductance regulator (CFTR) mutation. This study report is submitted to fulfil MEA 002. The RMP (version 3.2) is updated accordingly

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

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

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

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

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

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

cardiovascular risk factors in overweight and obese subjects (the Ignite study)). The MAH also took the opportunity to update the RMP to include references to the PASS protocols currently under discussion at PRAC

15.3.34. 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

15.3.35. 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

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

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

15.3.37. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0027

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include first line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with platinum-pemetrexed

chemotherapy based on the results from study KEYNOTE-021 (cohort G): a Phase 1/2, open-label trial of pembrolizumab in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic NSCLC. 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 9.0) are updated accordingly

15.3.38. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0028

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.4 and 4.8 of the SmPC to include the risk of myocarditis reported in patients treated with pembrolizumab. The Package Leaflet and the RMP (version 10.0) are updated accordingly

15.3.39. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/II/0029

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 of the SmPC, Annex II and relevant sections of the Packet Leaflet in order to update information on cardiac safety and reflect the results from study BERENICE (WO29217) listed as a specific obligation in Annex II: an ongoing multicentre, multinational, phase II study to evaluate Perjeta in combination with trastuzumab and standard neoadjuvant anthracycline-based chemotherapy in patients with human epidermal growth factor receptor 2 (HER2)-positive, locally advanced, inflammatory, or early-stage breast cancer. The RMP (version 9) is updated accordingly

15.3.40. 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

15.3.41. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/II/0020

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with one systemic therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and RMP (version 5.0) are updated accordingly. Furthermore, the product information is brought in line with the latest QRD template (version 10)

15.3.42. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/II/0024

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4, 4.6, 5.1 and 5.2 of the SmPC in order to include information: use of rilpivirine in combination with a background regimen for the treatment of human immunodeficiency virus (HIV)-1 infection during pregnancy and postpartum, without dose adjustment following final results from study TMC114HIV3015 (a single arm, open-label trial to assess the pharmacokinetics of darunavir/ritonavir, etravirine, and rilpivirine in HIV-1-infected pregnant women) listed as a category 3 study in the RMP. The Package Leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to introduce the latest renewal date in section 9 of the SmPC and the physical address of the Netherlands local representative in the Package Leaflet

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

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variation consisting of: 1) update of sections 4.2, 4.8 and 5.1 of the SmPC to reflect available data from previously untreated patients (PUP) based on the interim report of interventional study GENA-05 (an immunogenicity, efficacy and safety of treatment with human cell line-derived recombinant factor VIII (human-cl-rhFVIII) in previously untreated patients with severe haemophilia A). The Package Leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the product information throughout to bring it in line with the core SmPC for human plasma-derived and recombinant coagulation factor VIII products (EMA/CHMP/BPWP/1619/1999 rev. 2) and with the latest QRD template (version 10). Moreover, the MAH proposed to combine the SmPC for all strengths and to update Annex A with detailed information on the packaging

15.3.44. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/WS1141/0056; RISTABEN (CAP) - EMEA/H/C/001234/WS1141/0048; TESAVEL (CAP) - EMEA/H/C/000910/WS1141/0056; XELEVIA (CAP) - EMEA/H/C/000762/WS1141/0060

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.4 of the SmPC in order to add ‘bullous pemphigoid’ as a warning following the PRAC outcome for EMEA/H/C/PSUSA/2711/201408 procedure completed in

2015. The Labelling and the RMP (version 7) are updated accordingly

15.3.45. Sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/WS1130/0081/G; JANUMET (CAP) - EMEA/H/C/000861/WS1130/0081/G; RISTFOR (CAP) - EMEA/H/C/001235/WS1130/0068/G; VELMETIA (CAP) - EMEA/H/C/000862/WS1130/0084/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variation consisting of: 1) update of section 4.4 of the SmPC in order to add 'bullous pemphigoid' as a warning following the PRAC outcome for EMEA/H/C/PSUSA/2711/201408 procedure. The Labelling and the RMP (version 7) are updated accordingly; 2) The RMP (version 7) is updated to add a targeted questionnaire related to lactic acidosis as part of the outcome of a referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1432) on metformin-containing medicines completed in 2016

15.3.46. Sulphur hexafluoride - SONOVUE (CAP) - EMEA/H/C/000303/X/0034/G

Applicant: Bracco International B.V.

PRAC Rapporteur: Claire Ferard

Scope: Grouped application consisting of: 1) line extension to introduce intravesical use as a new route of administration; 2) type II variation to add a new indication to include the use in ultrasonography of the excretory urinary tract in paediatric patients to detect or exclude vesicoureteral reflux. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6 of the SmPC are updated. The Package Leaflet and the RMP (version 9.1) are updated accordingly. In addition, the MAH took the opportunity to bring Annex IIIA in line with the latest QRD template (version 10)

15.3.47. 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

15.3.48. Varenicline - CHAMPIX (CAP) - EMEA/H/C/000699/II/0064

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.5 and 5.1 of the SmPC in order to update the safety information based on the final results from study A3051078: a varenicline pregnancy cohort

study (a prospective population-based cohort study to examine whether varenicline use during pregnancy is associated with an increased risk of major congenital malformations in infants above that associated with smoking during pregnancy). The Package Leaflet and the RMP (version 10.1) are updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10)

15.3.49. Varenicline - CHAMPIX (CAP) - EMEA/H/C/000699/II/0066

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of section 5.1 of the SmPC in order to update the safety information based on the final results from clinical study A3051148 (a phase 4, non-treatment follow-up for cardiac assessments following use of smoking cessation treatments in subjects with and without a history of psychiatric disorders), a non-treatment extension to study A3051123, to collect data on cardiovascular safety for all participants in study A3051123 (a phase 4, randomized, double-blind, active and placebo-controlled, multicentre study evaluating the neuropsychiatric safety and efficacy of 12 weeks varenicline tartrate 1mg twice a day (bid) and bupropion hydrochloride 150mg bid for smoking cessation in subjects with and without a history of psychiatric disorders) for an additional 28 weeks, allowing for a total of 52 weeks of cardiovascular safety data collection. The RMP (version 10.1) is updated accordingly

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. Aclidinium bromide, formoterol - BRIMICA GENUAIR (CAP), DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201611

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Aflibercept[57] - EYLEA (CAP) - PSUSA/00010020/201611

Applicant: Bayer AG

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.3. Albutrepenonacog alfa - IDELVION (CAP) - PSUSA/00010497/201611

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.4. Cabozantinib - CABOMETYX (CAP); COMETRIQ (CAP) - PSUSA/00010180/201611

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.5. Carbidopa, levodopa[58] - NUMIENT (CAP) - PSUSA/00010479/201611

Applicant: Impax Laboratories Ireland Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.6. Ceftaroline fosamil - ZINFORO (CAP) - PSUSA/00010013/201610

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.7. Ceritinib - ZYKADIA (CAP) - PSUSA/00010372/201610

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.8. Cobicistat, darunavir - REZOLSTA (CAP) - PSUSA/00010315/201611

Applicant: Janssen-Cilag International NV

[57] For wet macular degeneration and central retinal vein occlusion (CRVO) indications only
[58] Centrally authorised product only

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.9. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/201611

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.10. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/201611

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.11. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/201611

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.12. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/201611

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.13. Eribulin - HALAVEN (CAP) - PSUSA/00001254/201611

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.14. Fentanyl[59] - IONSYS (CAP) - PSUSA/00010453/201611

Applicant: Incline Therapeutics Europe Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

[59] Transdermal system - centrally authorised product

16.1.15. Flutemetamol (^{18}F) - VIZAMYL (CAP) - PSUSA/00010293/201610

Applicant: GE Healthcare Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.16. Glycerol phenylbutyrate - RAVICTI (CAP) - PSUSA/00010454/201611

Applicant: Horizon Pharma Ireland Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.17. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - PSUSA/00009175/201611

Applicant: GSK Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.18. Hydrocortisone[60] - PLENADREN (CAP) - PSUSA/00009176/201611

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.19. Insulin detemir - LEVEMIR (CAP) - PSUSA/00001750/201610 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.20. Levofloxacin[61] - QUINSAIR (CAP) - PSUSA/00010429/201611

Applicant: Horizon Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

[60] Adrenal insufficiency, modified-release tablets only
[61] Centrally authorised product only

16.1.21. Lidocaine, prilocaine[62] - FORTACIN (CAP) - PSUSA/00010110/201611

Applicant: Plethora Solutions Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.22. Metformin, saxagliptin - KOMBOGLYZE (CAP) - PSUSA/00002686/201611

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.23. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/201611

Applicant: Amicus Therapeutics UK Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.24. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - PSUSA/00010296/201611

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.25. Necitumumab - PORTRAZZA (CAP) - PSUSA/00010471/201611

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.26. Obinutuzumab - GAZYVARO (CAP) - PSUSA/00010279/201610

Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.27. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/201611

Applicant: AstraZeneca AB

[62] Centrally authorised product only

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.28. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 MEDIMMUNE (CAP) - PSUSA/00010501/201611

Applicant: MedImmune LLC

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.29. Pixantrone - PIXUVRI (CAP) - PSUSA/00009261/201611

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.30. Sapropterin - KUVAN (CAP) - PSUSA/00002683/201612 (with RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.31. Simeprevir - OLYSIO (CAP) - PSUSA/00010255/201611

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.32. Stiripentol - DIACOMIT (CAP) - PSUSA/00002789/201611

Applicant: Biocodex

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.33. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/201611

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.34. Tadalafil - ADCIRCA (CAP), CIALIS (CAP), NAP - PSUSA/00002841/201610 (with RMP)

Applicant: Eli Lilly Nederland B.V. (Adcirca, Cialis)

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.35. Tilmanocept - LYMPHOSEEK (CAP) - PSUSA/00010313/201611

Applicant: Norgine BV

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.36. Tolvaptan[63] - JINARC (CAP) - PSUSA/00010395/201611

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.37. Turoctocog alfa - NOVOEIGHT (CAP) - PSUSA/00010138/201610

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.38. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/201611

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.39. Zinc acetate dihydrate - WILZIN (CAP) - PSUSA/00003145/201610

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

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

[63] Adults with autosomal dominant polycystic kidney disease (ADPKD) indication only

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

16.2.1. Sevelamer - RENAGEL (CAP); RENVELA (CAP), SEVELAMER CARBONATE ZENTIVA (CAP), TASERMITY (CAP), NAP - PSUSA/00002697/201610

Applicants: Genzyme Europe BV (Renagel, Renvela, Sevelamer carbonate Zentiva, Tasermity), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.2.2. Sodium oxybate - XYREM (CAP), NAP - PSUSA/00002757/201610

Applicants: UCB Pharma Ltd. (Xyrem), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acitretin (NAP) - PSUSA/00000051/201610

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.2. Ambroxol (NAP) - PSUSA/00000130/201609

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.3. Ambroxol, clenbuterol (NAP) - PSUSA/00000131/201609

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.4. Aminosalicylate sodium (NAP) - PSUSA/00000165/201610

Applicant(s): various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.5. Amlodipine, perindopril (NAP) - PSUSA/00000179/201610

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.6. Artemether, lumefantrin[64] (NAP) - PSUSA/00000236/201610

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.7. Brimonidine[65] (NAP) - PSUSA/00000430/201609

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.8. Brimonidine, timolol (NAP) - PSUSA/00000431/201609

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.9. Bromhexine (NAP) - PSUSA/00000437/201609

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.10. Dinoprostone (NAP) - PSUSA/00001104/201609

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

[64] All except dispersible tablet
[65] Except centrally authorised product(s)

16.3.11. Erythromycin, tretinoin (NAP) - PSUSA/00001259/201610

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.3.12. Ivermectin[66] (NAP) - PSUSA/00010376/201610

Applicant(s): various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.13. Levosimendan (NAP) - PSUSA/00001858/201609

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.14. Olmesartan (NAP) - PSUSA/00002207/201610

Applicant(s): various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.3.15. Olmesartan, hydrochlorothiazide (NAP) - PSUSA/00000179/201610

Applicant(s): various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.3.16. Technetium (^{99m}Tc) bicisate (NAP) - PSUSA/00002856/201610

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.17. Tetrabenazine (NAP) - PSUSA/00002911/201610

Applicant(s): various

PRAC Lead: Almath Spooner

[66] For topical use only

Scope: Evaluation of a PSUSA procedure

16.3.18. Timolol[67] (NAP) - PSUSA/00010432/201610

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.19. Tiotropium (NAP) - PSUSA/00002972/201610

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/LEG 028

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of a review on the feasibility of conducting a PASS in order to evaluate the risk of adverse cardiovascular events associated with long-term use of anakinra in patients with rheumatoid arthritis (RA) as requested in the conclusions of EMEA/H/C/PSUSA/00000209/201605 adopted by PRAC in December 2016

16.4.2. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/LEG 005

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of a detailed review on suicidal ideation and behaviour providing preclinical, clinical, epidemiology and post-marketing data as requested in the conclusions of EMEA/H/C/PSUSA/00010341/201606 adopted by PRAC in January 2017

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.

[67] For systemic use only

17.1. Protocols of PASS imposed in the marketing authorisation(s)[68]

17.1.1. Ketoconazole – KETOCONAZOLE HRA (CAP) - EMEA/H/C/PSP/S/0040.3

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Submission of a revised PASS protocol for a prospective, multinational, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole (using the existing European Registry on Cushing's syndrome (ERCUSYN)), to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

17.1.2. Lesinurad - ZURAMPIC (CAP) - EMEA/H/C/PSP/S/0050.2

Applicant: Grunenthal GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of a revised PASS protocol for an observational post-authorisation study of lesinurad patients (SATURATES), to investigate cardiovascular risk in association with lesinurad exposure, mainly in patients with a history of cardiovascular disorders

17.1.3. Thiocolchicoside (NAP) - EMEA/H/N/PSA/J/0010.1

Applicant: Sanofi

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of a revised PASS protocol for a drug utilisation study (DUS) for thiocolchicoside (TCC)-containing medicinal products for systemic use in France and Italy: an electronic medical records database study

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[69]

17.2.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/MEA 050

Applicant: Teva B.V.

PRAC Rapporteur: Claire Ferard

Scope: Submission of a protocol for a post-authorisation long term safety cohort study in acute promyelocytic leukaemia (APL) patients treated with Trisenox to assess the long-term safety of all-trans retinoic acid (ATRA) + arsenic trioxide (ATO) in newly diagnosed low to intermediate risk APL patients in a real-world clinical practice setting as requested in the conclusions of variation II/0058 finalised in October 2016

[68] In accordance with Article 107n of Directive 2001/83/EC
[69] 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

17.2.2. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/MEA 026.2

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of substantial amendments to the protocol for cross sectional study CLE-20098-96-096: a non-interventional PASS: drug utilisation study (DUS) in selected European countries: a multinational, observational study to assess the effectiveness of risk-minimisation measures

17.2.3. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/MEA 026.2

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of substantial amendments to the protocol for cross sectional study CLE-20098-96-096: a non-interventional PASS: drug utilisation study (DUS) in selected European countries: a multinational, observational study to assess the effectiveness of risk-minimisation measures

17.2.4. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 007.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of the MAH's response to MEA 007 [submission of a non-clinical mechanistic study protocol in dogs to investigate the mechanism behind canagliflozin-containing medicines induced diabetic ketoacidosis occurrence, as per the outcome of the recently finalised procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA)] as per the request for supplementary information (RSI) adopted in December 2016

17.2.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 006.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of the MAH's response to MEA 006 [submission of a non-clinical mechanistic study protocol in dogs to investigate the mechanism behind canagliflozin-containing medicines induced diabetic ketoacidosis occurrence, as per the outcome of the recently finalised procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA)] as per the request for supplementary information (RSI) adopted in December 2016

17.2.6. Collagenase clostridium histolyticum - XIAPEX (CAP) - EMEA/H/C/002048/MEA 030.1

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of the MAH's response to MEA 030 relating to protocol amendments [protocol for study Sobi.Xiapex-PASS02: a non-interventional PASS measuring the effectiveness of Xiapex educational material for healthcare professional in the treatment of Dupuytren's contracture (as per the conclusions of variation II/59)] as per the request for supplementary information (RSI) adopted in January 2017

17.2.7. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/MEA 002.1

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of the MAH's response to MEA 002 relating to an updated pregnancy registry protocol [submission of a PASS protocol for the category 3 Biogen multiple sclerosis (MS) pregnancy exposure registry 109MS402 (PASS category 3) to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product] as per the request for supplementary information (RSI) adopted in January 2017

17.2.8. Emtricitabine, rilpivirine, tenofovir disoproxil - EVIPLERA (CAP) - EMEA/H/C/002312/MEA 011.4

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for study EDMS-ERI-139775027: an ongoing healthcare professionals (HCP) survey: observational cohort study to assess rilpivirine (RPV) utilisation according to the EU product information

17.2.9. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/MEA 167.2

Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of the MAH's response to MEA 167.1 relating to a revised PASS protocol [submission of a revised PASS protocol for study B1801396: an observational cohort study to evaluate the risk of adverse pregnancy outcomes in patients treated with etanercept compared to those not treated with etanercept or other biologics using merged data from Sweden, Denmark and Finland (as per the conclusions of variation II/184)] as per the request for supplementary information (RSI) adopted in January 2017

17.2.10. Florbetapir (^{18}F) - AMYVID (CAP) - EMEA/H/C/002422/MEA 001.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Amendment to the protocol of study I6E-AV-AVBE: a non-interventional PASS evaluating the effectiveness of Amyvid reader training programme, initially endorsed by PRAC/CHMP in December 2013, amended following the conclusions of variation II/22 finalised at CHMP in December 2016 to allow the optional use of quantitative reading as an

adjunct to visual reading leading resulting in changes in the reader training programme

17.2.11. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.1

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of the MAH's response to MEA 046 [submission of a PASS protocol to further investigate and characterise the associations of lenalidomide and tumour flare reaction (TFR)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL) (as per the conclusions of variation II/79) (final study report planned in December 2022)] as per the request for supplementary information (RSI) adopted in January 2017

17.2.12. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/MEA 001.2

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Sabine Straus

Scope: Revised protocols for: 1) study AMDC-204-401 (PASS): a post-authorisation observational study to evaluate the safety of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care and study; 2) study 204-403 (drug utilisation study (DUS)): a multinational retrospective medical record to evaluate utilisation patterns of Adasuve-(oxapine for inhalation) in agitated persons in routine clinical care

17.2.13. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/MEA 011.4

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for study EDMS-ERI-139775027: an ongoing healthcare professionals (HCP) survey: observational cohort study to assess rilpivirine (RPV) utilisation according to the EU product information

17.3. Results of PASS imposed in the marketing authorisation(s)[70]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[71]

17.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0062

Applicant: Genzyme Europe BV

PRAC Rapporteur: Caroline Laborde

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

Scope: Submission of the final study report for ALGMYC08432: a non-interventional, non-imposed PASS entitled: 'Myozyme (alglucosidase alfa) safety information packet (SIP) effectiveness evaluation: a healthcare professional (HCP) survey' (Myozyme SIP EU HCP survey). The RMP (version 8.0) is updated accordingly

17.4.2. Collagenase clostridium histolyticum - XIAPEX (CAP) - EMEA/H/C/002048/II/0089

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for B1531005: a non-interventional study to evaluate the outcomes (clinical treatment success measured by goniometry assessment, recurrence rate measured by goniometry assessment, subject and physician global assessment of treatment satisfaction, complications resulting from the procedure based on the adverse event/serious adverse event (AE/SAE)) of 3 various treatment options for Dupuytren's contracture, listed as a category 3 study in the RMP. The RMP (version 13.0) is updated accordingly

17.4.3. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0025

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final results for a non-interventional study 1245.122 exploring the characteristics of patients initiating empagliflozin or other noninsulin glucose lowering drugs in the United Kingdom in order to fulfil MEA 009. The RMP (version 11.0) is updated accordingly

17.4.4. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0088

Applicant: GSK Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final study report for study EPI-HPV-067: a PASS pregnancy registry. Data and information related to the use of Cervarix during pregnancy was identified as important missing information in the RMP

17.4.5. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0201/G

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variation consisting of: 1) submission of the clinical study reports (CSR) for studies C0168T45 (safety under long term study: multicentre international observational study of the long-term safety of infliximab) and C0168T62 (safety under long-term study in ulcerative colitis (UC): multicentre international study of the long-term safety of infliximab in UC) together with an overall summary and evaluation of the complete long term safety follow-up programmes for Remicade (as per MEA 79). The RMP (version 14.0) is updated

accordingly

17.4.6. 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 Finnish medical birth registers and an evaluation of pregnancy data from multiple sources. As a consequence, section 4.6 of the SmPC is updated. The Package Leaflet and the RMP (version 13.2) are updated accordingly. In addition, the MAH took the opportunity to bring the product in line with the latest QRD template and update the local representative section of the Package Leaflet

17.4.7. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/II/0002

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report from a pharmacoepidemiology study listed as a category 3 study in the RMP: a retrospective database study on glucagon-like peptide-1 (GLP-1) receptor agonists and risk of acute pancreatitis, pancreatic cancer and thyroid cancer, in particular medullary thyroid cancer, for which the primary objective was to estimate the incidence rates of acute pancreatitis, pancreatic and thyroid cancer amongst adult patients with type 2 diabetes mellitus (T2DM) treated with GLP-1 receptor agonists versus patients treated with other antidiabetics. The RMP (version 2.0) is updated accordingly

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

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final study report for a PASS using European Union databases to assess the risk of cardiovascular and cerebrovascular adverse events in elderly patients treated with paliperidone palmitate, paliperidone prolonged-release, and other antipsychotics

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

Applicant: UCB Pharma Ltd.

PRAC Rapporteur: Ana Sofia Diniz Martins

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

17.4.10. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0011

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final results from study CLDE225C2301: a phase 2, multicentre, open-label, single-arm study of the efficacy and safety of oral LDE225 in patients with Hegehog (Hh)-signalling pathway activated relapsed medulloblastoma, and study LDE225X2104. a phase 1/2 study of sonidegib (LDE225) in paediatric patients with recurrent or refractory medulloblastoma or other tumours potentially dependent on the Hh-signalling pathway and adult patients with recurrent or refractory medulloblastoma. The RMP (version 6.0) is updated accordingly

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[72]

17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 046.4

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Ninth and last annual update of the rheumatoid arthritis registries: interim post-marketing epidemiology assessment report from the abatacept post-marketing epidemiology programme that includes studies whose primary focus is to evaluate the safety of abatacept for the treatment of rheumatoid arthritis (RA) (RMP category 3 - due date: final report in 2018)

17.5.2. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.5

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Annual report for study IM101240: observational registry of abatacept in patients with juvenile idiopathic arthritis (JIA registry) to explore the long-term safety of abatacept treatment for JIA in routine clinical practice (due date: final registry report by 2029)

17.5.3. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 065.7

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eighth interim report for the psoriasis patient registry (study P10-023: a 10-year, post-marketing, observational study to assess the long term safety of Humira (adalimumab) in adult patients with chronic plaque psoriasis (PS)) (due date: final registry report planned in February 2023)

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

17.5.4. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 066.6

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report from the RABBIT registry (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie) for cohort 2: evaluation of safety data through 31 October 2016 from the clinical use of adalimumab

17.5.5. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.11

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth interim report for study BEL116543/HGS1006-C1124: a long-term controlled safety registry evaluating the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus followed for a minimum of 5 years

17.5.6. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.5

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.4: first interim analysis report for a US category 3, PASS (B2311060 study): active surveillance of conjugated estrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data as per the request for supplementary information (RSI) adopted in December 2016

17.5.7. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 010

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: First monitoring interim report for PASS study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study

17.5.8. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 006

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: First monitoring interim report for PASS study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study

17.5.9. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 002

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: First monitoring interim report for PASS study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study

17.5.10. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 002

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Patrick Batty

Scope: Annual interim report from an established nationwide register (British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR-RA) for patients with rheumatological disorders treated with biologic agents, designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice

17.5.11. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 003

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Patrick Batty

Scope: Annual interim report for study from RABBIT-RA (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie): a prospective, observational cohort study evaluating the long-term effectiveness, safety, and costs associated with tumour necrosis factor (TNF)-inhibitor therapies in the treatment of rheumatoid arthritis (RA) and comparing it to a cohort of RA patients treated with non-biologic disease-modifying anti-rheumatic drugs (DMARDs)

17.5.12. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 004

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Patrick Batty

Scope: Annual interim report for study from ARTIS register (Anti-Rheumatic Treatment in Sweden): a national prospective, observational, uncontrolled cohort study evaluating the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept

17.5.13. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 005

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Patrick Batty

Scope: Annual interim report for study from BADBIR (British Association of Dermatologists Biologic Interventions Register): a nationwide registry assessing the long-term safety of

biologic treatments for psoriasis

17.5.14. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 008.4

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of MAH's responses to MEA 008.3 regarding the annual interim report on an i3 drug safety epidemiology study CNTO148ART4002: golimumab safety and surveillance programme using the Optum research database

17.5.15. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/MEA 028.4

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Fourth interim report of a PASS study (RMP category 3): a post-approval safety surveillance for monthly lot-specific adverse event review and analysis to evaluate any potential change in the frequency of hypersensitivity and immunogenicity events with the altered manufacturing process (sKPB) of Humalog and Liprolog. This fourth interim report covers the batches released to the market between 15 October 2013 and 31 January 2017

17.5.16. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/MEA 021.4

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Fourth interim report of a PASS study (RMP category 3): a post-approval safety surveillance for monthly lot-specific adverse event review and analysis to evaluate any potential change in the frequency of hypersensitivity and immunogenicity events with the altered manufacturing process (sKPB) of Humalog and Liprolog. This fourth interim report covers the batches released to the market between 15 October 2013 and 31 January 2017

17.5.17. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/MEA 036.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Annual interim report (covering the period 1 February 2016 to 31 January 2017) on the effectiveness of risk minimisation measures for multiple patch use with copies of Council for International Organizations of Medical Sciences (CIOMS) reports of medication errors and misuse

17.5.18. Rivastigmine - PROMETAX (CAP) - EMEA/H/C/000255/MEA 037.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Annual interim report (covering the period 1 February 2016 to 31 January 2017) on

the effectiveness of risk minimisation measures for multiple patch use with copies of Council for International Organizations of Medical Sciences (CIOMS) reports of medication errors and misuse

17.5.19. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First yearly progress report (22 December 2015-27 January 2017) for study PGL14-001: a prospective, multinational, multicentre, non-interventional study to evaluate the long-term safety of Esmya in particular the endometrial safety and the current prescription and management patterns of Esmya in a long-term treatment setting

17.6. Others

17.6.1. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/MEA 093.5

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of the MAH's response to MEA 093.4 on the statistical analysis plan (SAP) for the RIVAS study [PASS registry protocol for a long-term surveillance study of rituximab (Mabthera)-treated patients with granulomatosis, with polyangiitis (GPA) or microscopic polyangiitis (MPA) (RIVAS)] as per request for supplementary information (RSI) adopted in April 2017

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.

17.8. Ongoing Scientific Advice

None

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

None

18. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no

amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

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

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

None

18.3. Renewals of the marketing authorisation

18.3.1. Anidulafungin - ECALTA (CAP) - EMEA/H/C/000788/R/0033 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

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

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Valerie Strassmann

Scope: 5-year renewal of the marketing authorisation

18.3.3. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/R/0035 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

18.3.4. Linaclotide – CONSTELLA (CAP) - EMEA/H/C/002490/R/0032

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Valerie Strassmann

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.6. Zoledronic acid - ZOLEDRONIC ACID HOSPIRA (CAP) - EMEA/H/C/002365/R/0026 (without RMP)

Applicant: Hospira UK Limited

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 June 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
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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Member	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
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
David Benee Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	3.2.3. Valproate and related substances; 3.4.1. Gadolinium contrast agents; 3.5.1. Human coagulation (plasma - derived) factor VIII, Recombinant

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				factor VIII; 4.1.4. Telmisartan; telmisartan, hydrochlorothiazide; telmisartan, amlodipine; 4.2.2. Prednisolone; 4.3.6. Levonorgestrel (intrauterine device); 5.3.42. Regorafenib; 6.1.2. Aflibercept; 6.1.38. Radium (223Ra) dichloride; 6.2.2. Irbesartan, hydrochlorothiazide; 7.1.6. Thiocolchicoside; 7.4.7. Insulin glargine, lixisenatide
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Sanches de Castro Lopes Silva	Alternate - via telephone*	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
Peter Koren	Alternate	Slovakia	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
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
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Marianne Depreter	Expert - via telephone*	Belgium	No interests declared	Full involvement
Sophie Goethals	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani	Expert - via telephone*	Belgium	No interests declared	Full involvement
Fabrice Moore	Expert - via telephone*	Belgium	No interests declared	Full involvement
Anne-Catherine Thomas	Expert - via telephone*	Belgium	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
Veerle Verlinden	Expert - via telephone*	Belgium	No interests declared	Full involvement
Adriana Andrić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Petar Mas	Expert - via telephone*	Croatia	No interests declared	Full involvement
Maja Tabak Slošić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Jana Lukacisinova	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Torben Laursen	Expert - in person*	Denmark	No interests declared	Full involvement
Céline Chartier	Expert - via telephone*	France	No interests declared	Full involvement
Ghania Chamouni	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Pauline Dayani	Expert - via telephone*	France	No participation in discussion, final deliberations and voting on:	3.2.3. Valproate and related substances; 6.2.2. Irbesartan, hydrochlorothiazide; 7.1.6. Thiocolchicoside; 7.4.7. Insulin glargine, lixisenatide
Catherine Deguines	Expert - via telephone*	France	No interests declared	Full involvement
Vincent Gazin	Expert - in person*	France	No interests declared	Full involvement
Marc Martin	Expert - via telephone*	France	No interests declared	Full involvement
Cyndie Picot	Expert - via telephone*	France	No interests declared	Full involvement
Fanny Raguideau	Expert - via telephone*	France	No participation in discussion, final deliberations and voting on:	5.3.37. Pegfilgrastim
Véronique Tonnay	Expert - via telephone*	France	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Cathrin Bruederle	Expert - via telephone*	Germany	No interests declared	Full involvement
Anneliese Hilger	Expert - via telephone*	Germany	No interests declared	Full involvement
Johannes Pohly	Expert - via telephone*	Germany	No interests declared	Full involvement
Sofia Trantza	Expert - in person*	Greece	No restrictions applicable to this meeting	Full involvement
Niamh Buckley	Expert - in person*	Ireland	No interests declared	Full involvement
Emma Lawless	Expert - via telephone*	Ireland	No interests declared	Full involvement
Lourens Bloem	Expert - via telephone*	Netherlands	No participation in discussion, final deliberations and voting on:	5.3.38. Pembrolizumab; 5.3.39. Pembrolizumab
Marcel Kwa	Expert - in person*	Netherlands	No interests declared	Full involvement
Inge Zomerdijk	Expert - in person*	Netherlands	No interests declared	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Miriam Verčinská	Expert - via telephone*	Slovakia	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Karin Bolin	Expert - in person*	Sweden	No interests declared	Full involvement
Elina Rönnemaa	Expert - in person*	Sweden	No interests declared	Full involvement
Emma Cornforth	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
Vicky O'Keefe	Expert - via telephone*	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: www.ema.europa.eu/