12 January 2017
EMA/PRAC/237221/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 28 November-01 December 2016

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 28 November – 1 December 2016 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 advices were agreed unanimously, unless otherwise specified.

The PRAC Chairperson announced that Margarida Guimarães and Leonor Chambel were to step down as PRAC member and alternate respectively for Portugal after the current PRAC plenary meeting. The PRAC thanked them for their important contribution to the work of the PRAC.

1.2. Adoption of agenda of the meeting on 28 November–01 December 2016

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

1.3. Adoption of the minutes of the previous meeting on 24–27 October 2016

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 24-27 October 2016 were published on the EMA website on 22 February 2017 (EMA/PRAC/127425/2017).

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. Lactose of bovine origin-containing medicinal products[1]: 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

The Croatian Medicines Agency (HALMED) sent a letter of notification dated 21 November 2016 of a referral under Article 31 of Directive 2001/83/EC for the review of medicinal products for intravenous (IV)/intramuscular (IM) use indicated for the treatment of allergic reactions containing lactose of bovine origin, following cases of hypersensitivity reactions, including life-threatening anaphylactic reactions, in patients allergic to cow's milk proteins administered a methylprednisolone-containing product[2]. Given the seriousness of the reactions, and considering that this risk may apply to other medicinal products containing lactose of bovine origin as an excipient and indicated for IV/ IM use in the treatment of acute allergy and anaphylactic shock, HALMED considered in the interest of the European Union to conduct a thorough assessment of this safety issue.

Discussion

The PRAC noted the notification letter from HALMED requesting a review of this safety issue as regards to its impact on the benefit-risk balance of medicinal products for IV/IM administration containing lactose derived from bovine milk used in the treatment of acute allergy and anaphylactic shock, and in particular, the need for risk minimisation measures. The PRAC also noted that medicinal products in the scope of this review are limited to certain strengths of IV/IM methylprednisolone-containing products. The PRAC discussed a list of questions to be addressed by the relevant MAHs as well as a timetable for conducting the review.

[1] For intravenous (IV) or intramuscular (IM) use indicated for the treatment of acute allergic reactions only
[2] Solu-Medrol 40 mg powder and solvent for solution for injection

The PRAC appointed Jan Neuhauser as Rapporteur and Nikica Mirošević Skvrce as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions to the MAHs (EMA/PRAC/787822/2016) and a timetable for the procedure (EMA/PRAC/787809/2016).

The PRAC discussed the option to conduct a public hearing in the context of the Article 31 procedure on medicinal products containing lactose of bovine origin for IV/IM use for the treatment of acute allergic reactions, according to the pre-defined criteria set out in the rules of procedure[3] (EMA/363479/2015). It was agreed by the Committee that at this stage in the assessment, 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.

3.2. Ongoing procedures

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

Applicant: Mallinckrodt Deutschland GmbH (Optimark); various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Doris Stenver

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

Background

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

Summary of recommendation(s)/conclusions

Four oral explanations took place at the meeting. In light of these oral explanations and the joint assessment report of the Rapporteurs, the PRAC adopted a third list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/195601/2016 Rev.3).

The EMA Secretariat informed the PRAC about a letter received from a MAH whose marketing authorisation is subject to the referral procedure raising alleged conflicts of interest of an expert who attended the ad-hoc expert group meeting held on 5 September 2016. Based on the expert's declaration of interest, in light of all the information available and in line with the 'EMA policy on the handling of competing interests of committee members and experts' (EMA/626261/2014,Rev. 1), the EMA Secretariat concluded that there were no interests which should have been declared by the expert or could have

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

resulted in the exclusion of the expert in the involvement in the ad-hoc expert group. The PRAC noted the above.

Post-meeting note: On 16/12/2016, the PRAC adopted a further revised timetable (EMA/PRAC/195601/2016 - Rev.4) for the procedure via written procedure.

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

Applicant: Eisai Ltd. (Panretin, Targretin), various

PRAC Rapporteur: Leonor Chambel; PRAC Co-rapporteur: Julie Williams

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for retinoid-containing medicines (acitretin; adapalene; alitretinoin; bexarotene; isotretinoin; tazarotene; tretinoin) indicated for the treatment of several conditions mainly affecting the skin such as acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders[4] to evaluate measures currently in place for pregnancy prevention and the possible risk of neuropsychiatric disorders for oral and topical retinoids. For further background, see PRAC minutes July 2016, PRAC minutes September 2016 and PRAC Minutes October 2016.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusion reached by the Rapporteurs and adopted a list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for conducting the review (EMA/PRAC/461927/2016 Rev 1). In addition, the PRAC concurred on the need to engage with patients and healthcare professionals and agreed with the organisation of a targeted meeting with patients and HCPs scheduled on 3 March 2017.

3.3. Procedures for finalisation

3.3.1. Direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free): daclatasvir – DAKLINZA (CAP); dasabuvir – EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/A-20/1438

Applicant: Bristol-Myers Squibb Pharma EEIG (Daklinza); AbbVie Ltd. (Exviera, Viekirax); Janssen-Cilag International N.V. (Olysio); Gilead Sciences International Ltd. (Harvoni, Sovaldi)

PRAC Rapporteur: Margarida Guimarães; PRAC Co-rapporteur: Dolores Montero Corominas

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

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

pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is to be concluded for direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free) (daclatasvir (Daklinza), dasabuvir (Exviera), ombitasvir/paritaprevir/ritonavir (Viekirax), simeprevir (Olysio), sofosbuvir (Sovaldi), sofosbuvir/ledipasvir (Harvoni)) to assess the risk of hepatitis B virus (HBV) reactivation as well as the risk of unexpected early hepatocellular carcinoma (HCC) recurrence in patients treated with a DAAV and to establish whether any measures are necessary to minimise these risks. For further background, see PRAC minutes March 2016, PRAC minutes April 2016, PRAC minutes July 2016 and PRAC minutes November 2016.

Discussion

The PRAC reviewed the totality of the data submitted by the MAHs, taking into consideration the information presented by the MAHs as part of a joint oral explanation during the meeting, the views expressed by the Scientific Advisory Group (SAG) HIV/Viral Diseases and the responses from the ANRS[5] collaborative group (French cohorts) to the PRAC list of questions (LoQ) on HCC.

Although the frequency of hepatitis B virus (HBV) re-activation appears low[6], the PRAC concluded that the available data provide evidence of a risk of HBV reactivation in patients co-infected with HBV/hepatitis C virus (HCV) treated for chronic hepatitis C with a DAAV. The PRAC was of the view that all patients should be screened for HBV infection before initiation of treatment with DAAV. Patients with HBV/HCV co-infection should be monitored during and after treatment according to current clinical guidelines. Therefore, the PRAC recommended the inclusion of a warning in the product information of these medicinal products to inform about the risk of hepatitis B reactivation and reflect these recommendations.

The PRAC also reviewed the available data on HCC in patients treated with a DAAV. The PRAC considered that further data were required on the impact of DAAV treatment on the risk of HCC recurrence before drawing firm conclusions. As a consequence, the PRAC considered that the MAHs shall conduct a prospective safety study in a well-defined group of patients based on an agreed protocol setting out criteria for entry and follow-up. Furthermore, the PRAC was of the opinion that the impact of DAAV treatment on the incidence and type of *de novo* HCC should be further investigated though a prospective cohort study in HCV infected patients with cirrhosis. The PRAC encouraged the MAHs to conduct joint studies for both issues.

Overall, the PRAC concluded that the benefit-risk balance of DAAV remains favourable subject to the agreed amendments to the product information[7].

Summary of recommendation(s)/conclusions

The PRAC adopted a recommendation to vary the terms of the marketing authorisations for direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free)

[5] Agence nationale de recherche sur le sida et les hépatites virales (French National Agency for Research on acquired immunodeficiency syndrome (AIDS) and viral hepatitis)
[6] Around 30 cases of hepatitis B re-activation have been reported to date amongst the many thousands of patients treated
[7] Update of sections 4.4 of the SmPC and Annex II. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

(daclatasvir (Daklinza), dasabuvir (Exviera), ombitasvir/paritaprevir/ritonavir (Viekirax), simeprevir (Olysio), sofosbuvir (Sovaldi), sofosbuvir/ledipasvir (Harvoni)) and adopted a recommendation to be considered by CHMP for an opinion. See EMA Press Release (EMA/795452/2016) entitled 'PRAC warns of risk of hepatitis B re-activation with direct-acting antivirals for hepatitis C. Review of liver cancer risk not conclusive and further studies are needed'.

Post-meeting note: The press release 'Direct-acting antivirals for hepatitis C: EMA confirms recommendation to screen for hepatitis B. Further studies needed to assess risk of liver cancer with these medicines' (EMA/824717/2016) representing the opinion adopted by the CHMP was published on the EMA website on 16 December 2016.

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

None

3.5. Others

None

4. Signals assessment and prioritisation[8]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I.14.1.

4.1.1. Meropenem (NAP); ciprofloxacin (NAP)

Applicant: various

PRAC Rapporteur: Jan Neuhauser

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

EPITT 18790 – New signal

Lead Member State: AT

Background

Meropenem is a carbapenem antibiotic, belonging to the β-lactam family of antibiotics with a broad-spectrum *in-vitro* activity against multiple aerobic and anaerobic Gram-positive and Gram-negative bacteria, but no activity against Methicillin-resistant *Staphylococcus aureus* (MRSA). It is indicated for the treatment of serious infections caused by single or multiple susceptible bacteria in adults and children over 3 months of age, and used as empiric therapy prior to the identification of the causative organisms.

Ciprofloxacin is a fluoroquinolone broad-spectrum antibiotic indicated for a variety of

[8] 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

infections including serious bacterial infections, especially hospital-acquired infections, and others caused by susceptible micro-organisms.

During the evaluation of a variation for Meropenem Noridem (meropenem) (UK/H/4931/001-002/II/006), two cases of incompatibility between meropenem and ciprofloxacin were described in the literature leading to possible precipitation when co-administered intravenously. Additionally, a case of serious adverse reactions (sudden chest pain radiating into arm, back and neck, and dyspnoea with wheezing) was reported to EudraVigilance following co-administration of meropenem and ciprofloxacin via a common intravenous line. Taking into account the current RMP, the literature review and evidence from EudraVigilance, Poland identified a signal. Austria confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the literature including the results from the study by *Chen LY et al.*[9] and the evidence from EudraVigilance of incompatibility and drug interaction after concomitant use of meropenem and ciprofloxacin and agreed on the need to gather further data before drawing any conclusion. To this end, the PRAC agreed a list of questions (LoQ) to the CHMP Quality Working Party (QWP).

The PRAC appointed Jan Neuhauser as Rapporteur for the signal.

Summary of recommendation(s)

- Based on the responses from the QWP, the Rapporteur should perform a further analysis of the signal. Further discussion is planned at the March 2017 PRAC meeting.

4.1.2. Pirfenidone – ESBRIET (CAP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Signal of colitis

EPITT 18793 – New signal

Lead Member State: UK

Background

Pirfenidone is an anti-fibrotic and anti-inflammatory agent indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

The exposure for Esbriet, a centrally authorised medicine containing pirfenidone, is estimated to have been more than 30,400 patient-years worldwide, in the period since first authorisation in 2011.

During routine signal detection activities, a signal of colitis was identified by the EMA based on a literature article by *Fiddler C et al.*[10] describing severe colitis associated with pirfenidone

[9] Chen LY, Chen J, Waters V, Boodhan S. Incompatibility of ciprofloxacin and meropenem injections, Am J Health-Syst Pharm. 2013 Nov 15;70(22):1966, 1970 (please delete this after reading: - between Health and Syst see here http://www.ashpfoundation.org/ajhpresearchseries.aspx)
[10] Fiddler C, Simler N, Parfrey H, Miremadi A and Chilvers E. Severe colitis associated with pirfenidone use in idiopathic pulmonary fibrosis. Annals of the American Thoracic Society. 2016 Aug;13 (8):1430-1432

in two cases and a further thirteen cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the literature and cases from Eudravigilance that included four cases with a positive dechallenge after treatment interruption, including one case with positive rechallenge that occurred within one month after reintroduction of pirfenidone treatment with a further round of positive dechallenge and positive rechallenge. Considering the evidence, and the seriousness of the reaction including several hospitalisations and/or treatment discontinuation, the PRAC agreed to request the MAH to perform a cumulative review of the MedDRA HLT[11] term 'colitis' (excluding infective). Depending on the outcome of the review, the MAH should discuss the need to amend the product information.

Summary of recommendation(s)

- The MAH for Esbriet (pirfenidone) should submit to EMA, within 60 days, a cumulative review of cases of colitis including discussion of the types of colitis, severity of the reported cases, possible mechanisms and appropriate risk minimisation measures. In addition, the MAH should submit a proposal for amending the product information as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

See Annex I.14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Acenocoumarol (NAP), fluindione (NAP), phenindione (NAP), phenprocoumon (NAP)

Applicant: various

PRAC Rapporteur: Martin Huber

Scope: Signal of calciphylaxis

EPITT 18710 – Follow-up to July 2016

Background

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

Discussion

Having considered the available evidence from EudraVigilance, the literature, the evaluation of the data submitted by the MAHs, as well as the existence of a plausible biological mechanism, the PRAC concluded that there is a reasonable possibility of a causal

[11] Medical dictionary for regulatory activities – high level terms

relationship between the use of vitamin K antagonists and calciphylaxis. As a consequence, the MAHs for acenocoumarol-, phenprocoumon-, fluindione- and phenindione-containing medicinal products should submit a variation to amend the product information to include a warning on calciphylaxis to ensure that appropriate treatment is started and to consider stopping treatment with any of these vitamin K antagonists. Calciphylaxis should also be included as an undesirable effect for acenocoumarol and phenprocoumon with an unknown frequency.

Summary of recommendation(s)

- The MAHs for acenocoumarol-, phenprocoumon-, fluindione- and phenindione-containing medicinal products should submit to the national competent authorities of the Member States, within 90 days, a variation for amending the product information[12].

For the full PRAC recommendation, see EMA/PRAC/740369/2016 published on 03/01/2017 on the EMA website.

4.3.2. Methylphenidate (NAP)

Applicant: various

PRAC Rapporteur: Julie Williams

Scope: Signal of priapism

EPITT 18719 – Follow-up to July 2016

Background

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

Discussion

Considering the assessment of the MAHs' responses including data from the MAHs' own safety database and from the literature, the PRAC concurred there was sufficient evidence to amend the product information of methylphenidate-containing products to include a warning on priapism to ensure that patients who developed abnormally sustained or frequent and painful erections should seek immediate medical attention. Priapism should be also added as an undesirable effect with an unknown frequency.

Summary of recommendation(s)

- The MAHs for methylphenidate-containing medicinal products should submit to the national competent authorities of the Member States, within 60 days, a variation for amending the product information[13].

For the full PRAC recommendation, see EMA/PRAC/740369/2016 published on 03/01/2017 on the EMA website.

[12] Update of SmPC sections 4.4 and 4.8 for acenocoumarol- and phenprocoumon-containing medicinal products. The package leaflet to be updated accordingly. Update of SmPC section 4.4 for fluindione- and phenindione-containing medicinal products only

[13] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

4.3.3. Proton pump inhibitors (PPIs): dexlansoprazole (NAP); esomeprazole – NEXIUM CONTROL (CAP), NAP; lansoprazole (NAP);omeprazole (NAP); pantoprazole – CONTROLOC CONTROL (CAP), PANTECTA CONTROL (CAP), PANTOLOC CONTROL (CAP), PANTOZOL CONTROL (CAP), SOMAC CONTROL (CAP), NAP; rabeprazole (NAP)

Applicants: Pfizer Consumer Healthcare Ltd. (Nexium Control), Takeda GmbH (Controloc Control, Pantecta Control, Pantoloc Control, Pantozol Control, Somac Control), various

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of gastric polyps

EPITT 18725 – Follow-up to September 2016

Background

The MAHs replied to the request for information on the signal of gastric polyps and the responses were assessed by the Rapporteur. For background information, see PRAC minutes September 2016.

Discussion

The PRAC considered the available evidence from the evaluation of the data submitted by the MAHs, data from EudraVigilance and the literature including cases with a positive dechallenge as well as the results from two systematic reviews with meta-analyses by *Tran-Duy A et al.*[14] and *Martin FC et al.*[15] published in 2016. Taking into account the pathophysiologic mechanism of the class of proton pump inhibitors (PPIs) when used for long treatment periods, the PRAC recommended that the product information of PPIs should be amended to include fundic gland polyps (benign) as an undesirable effect with a common frequency.

Summary of recommendation(s)

- The MAHs of PPIs (i.e. dexlansoprazole-,esomeprazole-, lansoprazole-, omeprazole-, pantoprazole-, rabeprazole-containing products) should submit to EMA or to the national competent authorities of the Member States as applicable, within 90 days, a variation for amending the product information[16].

For the full PRAC recommendation, see EMA/PRAC/740369/2016 published on 03/01/2017 on the EMA website.

4.3.4. Vildagliptin - GALVUS (CAP) - EMEA/H/C/000771/SDA/043; JALRA (CAP) - EMEA/H/C/001048/SDA/027; XILIARX (CAP) - EMEA/H/C/001051/SDA/027 vildagliptin, metformin hydrochloride - EUCREAS (CAP) - EMEA/H/C/000807/SDA/025; ICANDRA (CAP) - EMEA/H/C/001050/SDA/023; ZOMARIST (CAP) - EMEA/H/C/001049/SDA/023

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Qun-Ying Yue

[14] Tran-Duy A, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD. Use of proton pump inhibitors and risks of fundic gland polyps and gastric cancer: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016 May 19. pii: S1542-3565(16)30205-1. doi: 10.1016/j.cgh.2016.05.018. [Epub ahead of print]
[15] Martin FC, Chenevix-Trench G, Yeomans ND. Systematic review with meta-analysis: fundic gland polyps and proton pump inhibitors. Aliment Pharmacol Ther. 2016 Nov;44(9):915-925
[16] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

Scope: Signal of pemphigoid

EPITT 18692 – Follow-up to July 2016

Background

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

Discussion

Having considered the available evidence from case reports in EudraVigilance and in the literature, the PRAC recommended that the product information for vildagliptin-containing products is amended to include bullous pemphigoid as part of the undesirable effect exfoliative and bullous skin lesions with an unknown frequency.

Summary of recommendation(s)

- The MAH for vildagliptin-containing products should submit to EMA, within 60 days, a variation for amending the product information[17].

For the full PRAC recommendation, see EMA/PRAC/740369/2016 published on 03/01/2017 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I.15.1.

5.1.1. Abaloparatide – EMEA/H/C/004157

Scope: Treatment of osteoporosis

5.1.2. Baricitinib - EMEA/H/C/004085

Scope: Treatment of moderate to severe active rheumatoid arthritis (RA)

5.1.3. Cerliponase alfa - EMEA/H/C/004065, Orphan

Applicant: BioMarin International Limited

Scope accelerated assessment: Treatment of neuronal ceroid lipofuscinosis type 2

[17] Update of SmPC section 4.8. The package leaflet remains unchanged

5.1.4. Fluciclovine (^{18}F) - EMEA/H/C/004197

Scope: Diagnostic agent for positron emission tomography (PET) of adult men with suspected recurrence of prostate cancer

5.1.5. Midostaurin - EMEA/H/C/004095, Orphan

Applicant: Novartis Europharm Ltd.

Scope accelerated assessment: Treatment of mastocytosis and acute myeloid leukaemia

5.1.6. Padeliporfin - EMEA/H/C/004182

Scope: Treatment of prostate cancer

5.1.7. Rurioctocog alfa pegol - EMEA/H/C/004195

Scope: Treatment of haemophilia A

5.1.8. Tofacitinib - EMEA/H/C/004214

Scope: Treatment of active rheumatoid arthritis (RA)

5.1.9. Vosaroxin - EMEA/H/C/004118, Orphan

Applicant: Sunesis Europe Ltd.

Scope: Treatment of acute myeloid leukaemia

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 Annex I.15.3.

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. Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP); DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201605

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Aclidinium bromide is a selective muscarinic receptor antagonist and formoterol fumarate is a selective β_2-adrenoceptor agonist indicated in combination as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brimica Genuair and Duaklir Genuair, centrally authorised medicines containing aclidinium bromide and formoterol fumarate dihydrate, 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 Brimica Genuair and Duaklir Genuair (aclidinium bromide/formoterol fumarate dihydrate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include angina as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisations should be varied[18].
- In the next PSUR, the MAH should provide a detailed review of cases of medication/use of device errors and associated adverse events including a discussion on the impact of the education and awareness initiatives and proposal for updates as applicable. In addition, the MAH should provide a review of any cases of hallucination.

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. Anakinra - KINERET (CAP) - PSUSA/00000209/201605 (with RMP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

Anakinra is an interleukin-1α (IL-1α) and interleukin-1β (IL-1β) inhibitor indicated for the treatment of the signs and symptoms of rheumatoid arthritis (RA) in combination with methotrexate, in adults with an inadequate response to methotrexate alone. Anakinra is also indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of cryopyrin-associated periodic syndromes (CAPS), including neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological, cutaneous, articular syndrome (CINCA), Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS).

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Kineret (anakinra) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide reviews on hepatic toxicity and possible correlation with age as suggested in the study on off-label use by *Rossi-Semerano L et al.*[19] and on macrophage activation syndrome (MAS). In addition, the MAH should provide a review relating to the risk of congestive heart failure (CHF) and should reconsider the inclusion of heart failure as missing information in the safety concerns.
- The MAH should submit to EMA, within 90 days, a discussion on the feasibility of conducting a post-authorisation study (PASS) to evaluate the risk of adverse cardiovascular events associated with long-term use of anakinra in patients with rheumatoid arthritis based on data retrieved from electronic healthcare databases.

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. Apixaban - ELIQUIS (CAP) - PSUSA/00000226/201605

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Apixaban is a factor Xa inhibitor indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery as well as for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA[20] class ≥ II). Apixaban is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Eliquis (apixaban) in the approved indication(s) remains unchanged.

[19] Rossi-Semerano L,Fautrel B, Wendling D, Hachulla E, Galeotti C, Semerano L, Touitou I, Koné-Paut I and the MAIL1 (maladies auto-inflammatoires et anti-IL-1) study group on the behalf of CRI (Club Rhumatisme et Inflammation). Tolerance and efficacy of off-label anti-interleukin-1 treatment in France: a nationwide survey. Orphanet J Rare Dis. 2015 Feb 15;10(1):19

[20] New York Heart Association

- Nevertheless, the product information should be updated to clarify the wording with regard to the posology in patients with renal impairment. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should submit detailed reviews of cases of liver injury and cases of interstitial pneumonia and other interstitial lung 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.

6.1.4. Decitabine - DACOGEN (CAP) - PSUSA/00009118/201605

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Decitabine is a cytidine deoxynucleoside analogue indicated for the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Dacogen (decitabine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on interstitial lung disease (ILD) to prompt a careful assessment of patients with an acute onset or unexplained worsening of pulmonary symptoms. If ILD is confirmed, appropriate treatment should be initiated. ILD should be also added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should provide reviews of cases of hepatic failure and hepatotoxicity, cases of inflammatory pulmonary reactions including pulmonary fibrosis, interstitial lung disease, organising pneumonia and non-infectious pulmonary infiltrates. In addition, reviews on cases of atrial fibrillation, myocardial infarction and cardiomyopathy, and cases of haemorrhagic cystitis, extravasation, tumour lysis syndrome and renal and urinary disorders should also be provided.

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

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

6.1.5. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/201605

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

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.

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 include a warning on the possibility of progressive multifocal leukoencephalopathy (PML) occurring in the context of ibrutinib treatment and that appropriate diagnostic evaluations should be undertaken if PML is suspected and if confirmed treatment should be suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML and repeat neurological assessments should be considered. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In addition, the MAH should update the RMP to include PML as an important potential risk and propose appropriate risk minimisation measures at the next regulatory opportunity.
- In the next PSUR, the MAH should provide detailed reviews of cases under PT[24] 'pericardial effusion', 'cardiac tamponade' and 'pericardial haemorrhage' as well as a full clinical narrative of cases of the PT 'panniculitis' and 'erythema nodosum'. The MAH should propose to update the product information and the RMP as applicable. In addition, the MAH should provide an estimate of the frequency of 'cellulitis' and consider including it as an adverse drug reaction. Furthermore, the MAH should comment on the study by *Vitale C et al.*[25]. Finally, the MAH should include 'tumour lysis syndrome preventability' as an important identified risk and provide a cumulative review of cases of hepatitis due to viral reactivation.

[23] 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
[24] Medical dictionary for regulatory activities – preferred term
[25] Vitale C, Ahn E, I, Sivina M, Ferrajoli A, Wierda G. W, Estrov Z, Konoplev N. S, Jain N, O'Brien S, Farooqui M, Keating J. M, Wiestner A, Burger A. J. Autoimmune cytopenias in patients with chronic lymphocytic leukemia treated with ibrutinib, Haematologica, June 2016 101: e254-e258

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[26] - KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201605

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).

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 include new information related to the potent inhibition by ketoconazole of several transporters. In addition, information on ketoconazole inhibition of breast cancer resistant protein (BCRP) is updated to indicate that risk of interaction with BCRP substrates cannot be excluded at systemic level with very high doses of ketoconazole. Finally, information related to interaction with naloxegol is updated. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide detailed analyses of any data relating to new drug-drug interactions (DDIs) proposed to be included in the product information.

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

6.1.7. Mycophenolate mofetil - CELLCEPT (CAP) - PSUSA/00002099/201605

Applicant: Roche Registration Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Background

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an inosine monophosphate dehydrogenase inhibitor and is indicated in combination with ciclosporin and

[26] Centrally authorised product only
[27] Update of SmPC sections 4.5 and 5.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of CellCept, a centrally authorised medicine containing mycophenolate mofetil, 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 CellCept (mycophenolate mofetil) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 90 days, a discussion on the justification of the need for two forms of contraception and any evidence for non-compliance with these requirements leading to unintended pregnancy. In addition, the MAH should provide detailed reviews of cases of malformations following paternal exposure as well as the available non-clinical data relating to the potential for male-mediated developmental toxicity. Finally, the MAH should propose to update the product information and educational materials relating to paternal exposure as applicable. The MAH should also propose to update the product information and educational materials as necessary on the need for either male contraception or female contraception or both.
- In the next PSUR, the MAH should provide a full report of the ongoing analysis on the collection of pregnancies data in the US based mycophenolate pregnancy registry (study ML22679). In addition, the MAH should provide detailed reviews of medication errors and of rejection rates in black patients regardless of whether proton pump inhibitors (PPIs) are prescribed with a consideration on the appropriateness of the dosing for black patients. Moreover, the MAH should closely monitor the increased risk of gastro-intestinal disorders particularly in patients receiving concomitant tacrolimus, monitor any additional evidence to further characterise the risk of lymphoproliferative disorders as well as monitor any cases of kidney damage where mycophenolate and tacrolimus or sirolimus have been co-administered. Finally, with regard to pregnancy cases, the MAH should provide a detailed review of cases of malformation following maternal or paternal exposure.

The PRAC considered that mycophenolate mofetil- and mycophenolic acid-containing products should be assessed in the future within the same PSUSA procedure. The frequency of PSUR submission should be revised from two-yearly to yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. Therefore, the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly. The next PSURs should be submitted in accordance with the requirements set out in the EURD list.

6.1.8. Nintedanib[28] - VARGATEF (CAP) - PSUSA/00010318/201605

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Leonidas Klironomos

Scope: Evaluation of a PSUSA procedure

[28] Oncology indications only

Background

Nintedanib is an angiokinase inhibitor indicated[29] 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 include pancreatitis as an undesirable effect with an uncommon frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH should closely monitor cases of pneumonitis and interstitial lung disease (ILD), thrombocytopenia, and drug induced liver injury (DILI) and provide a detailed discussion should new information arise. In addition, the MAH should closely monitor cases of pulmonary embolism and discuss the potential for including this as a safety concern in the RMP. Moreover, the MAH should provide a detailed analysis of cases of bleeding and propose to update the product information as applicable.

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

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

See also Annex I.16.2.

6.2.1. Telmisartan - KINZALMONO (CAP); MICARDIS (CAP); PRITOR (CAP); telmisartan, hydrochlorothiazide - KINZALKOMB (CAP); MICARDISPLUS (CAP); PRITORPLUS (CAP); NAP - PSUSA/00002882/201604

Applicant: Boehringer Ingelheim International GmbH (Micardis, MicardisPlus), Bayer Pharma AG (Kinzalkomb, Kinzalmono, Pritor, PritorPlus), various

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Telmisartan is an angiotensin II receptor antagonist indicated for the treatment of essential hypertension, and the prevention of cardiovascular morbidity and mortality in patients 55 years or older at high risk of cardiovascular disease. Hydrochlorothiazide is a thiazide diuretic and used with telmisartan as a fixed combination for the treatment of essential hypertension

[29] Oncology indication(s)
[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

in patients whose blood pressure is not adequately controlled on telmisartan or hydrochlorothiazide alone.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Kinzalmono, Micardis and Pritor, centrally authorised medicines containing telmisartan, as well as Kinzalkomb, MicardisPlus, and PritorPlus, centrally authorised medicines containing telmisartan/hydrochlorothiazide, as well as nationally authorised medicine containing telmisartan 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 Kinzalmono, Micardis, Pritor (telmisartan) and of Kinzalkomb, MicardisPlus, PritorPlus (telmisartan/hydrochlorothiazide) and nationally authorised medicine containing telmisartan in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAH of Micardis (telmisartan) and MicardisPlus (telmisartan/hydrochlorothiazide) should provide detailed reviews of cases of hyponatremia and lichen planus, 'concomitant administration of co-trimoxazole and angiotensin II receptor blockers (ARBs)'. In addition, the MAH should further refine the monitoring on the risk of renal dysfunction as a consequence of dual renin-angiotensin-aldosterone system (RAAS) blockade, in particular on possible off-label use following the implementation of the updated safety information in the product information as an outcome of the referral procedure on renin-angiotensin-system (RAS)-acting agents dual blockade concluded in 2014 (EMEA/H/A-31/1370).
- In the next PSUR, the MAH Teva Group should provide further details relating to the design of the VATARO[31] non-interventional PASS (TV44801-CV-40058). In addition, the MAH should provide a detailed analysis of cases of foetotoxicity that occurred during pregnancy focussing on off-label use. Furthermore, the MAH should discuss any adverse drug reactions gathered following the monitoring of cases of renal dysfunction as a consequence of dual RAAS blockade, sepsis, hypoglycaemia in diabetic patients, rhabdomyolysis, hepatic function abnormal/liver disorder and malignancies.

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. Pramipexole - MIRAPEXIN (CAP); SIFROL (CAP); NAP - PSUSA/00002491/201604

Applicant: Boehringer Ingelheim International GmbH (Mirapexin, Sifrol), various

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

[31] Valsartan, telmisartan, amlodipine and rosuvastatin

Pramipexole is a dopamine agonist indicated in adults for the treatment of the signs and symptoms of idiopathic Parkinson's disease, alone or in combination with levodopa, and for symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS).

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Mirapexin and Sifrol, centrally authorised medicine containing pramipexole, as well as nationally authorised medicine containing pramipexole 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 Mirapexin and Sifrol (pramipexole) and nationally approved medicines containing pramipexole in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on dopamine agonist withdrawal syndrome (DAWS) and advice to discontinue treatment with pramipexole in patients with Parkinson's disease by tapering off the dopamine agonist. In addition, DAWS should be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[32].
- In the next PSUR, the MAHs should provide a detailed review of case(s) of punding where levodopa was also given to patients. In addition, based on evidence including relevant literature reviews, MAHs should propose to update the product information by including clarification on the compulsive elements of impulse control disorders (ICD) and known impulse control disorders as well as by including risk factors relating to DAWS and dopamine dysregulation syndrome (DDS).

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

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

See also Annex I.16.3.

6.3.1. Captopril, hydrochlorothiazide (NAP) - PSUSA/00000536/201604

Applicant: various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Captopril is an inhibitor of angiotensin-converting enzyme (ACE) and hydrochlorothiazide (HCTZ) is a thiazide diuretic antihypertensive. In combination, captopril/hydrochlorothiazide is indicated for the treatment of hypertension.

[32] 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(s), the PRAC reviewed the benefit-risk balance of centrally authorised medicine(s) containing captopril/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 captopril/hydrochlorothiazide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add warnings on the interaction with mTOR[33] inhibitors leading to an increased risk of angioedema as well as the interaction with co-trimoxazole leading to an increased risk of hyperkalaemia. Therefore the current terms of the marketing authorisations should be varied[34].
- In the next PSUR, the MAH should provide detailed cumulative reviews of cases of eczema and of cases of psoriasis, including aggravation of psoriasis.

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

6.3.2. Ethinylestradiol, levonorgestrel (NAP) - PSUSA/00001309/201604

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Ethinylestradiol/levonorgestrel is an oestrogen-progestin combined oral contraceptive (COC) indicated for the prevention of pregnancy under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ethinylestradiol/levonorgestrel, 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 ethinylestradiol/levonorgestrel-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should monitor the potential lack of efficacy observed in overweight women and propose to update the product information as applicable. With regard to the exacerbation of angioedema symptoms, the MAHs should propose to update the product information as applicable, consistent with the approach for other COC's product information.

[33] mechanistic target of rapamycin
[34] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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. Hydrochlorothiazide, quinapril (NAP) - PSUSA/00002592/201604

Applicant: various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Quinapril hydrochloride is an angiotensin-converting enzyme (ACE) inhibitor and hydrochlorothiazide (HCTZ) is a thiazide diuretic. In combination, HCTZ/quinapril is indicated for the treatment of hypertension in patients for whom combination therapy with quinapril and a diuretic is appropriate.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing HCTZ/quinapril, 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 HCTZ/quinapril-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should closely monitor cases of hallucination, renal failure, myocardial infarction and ischemic events, cerebrovascular accident and related events.

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

6.3.4. Ivermectin[35](NAP) - PSUSA/00010376/201604

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Ivermectin is a semi-synthetic derivative of macrocyclic lactones indicated, as topical formulation, for the treatment of inflammatory lesions of rosacea (papulopustular) in adult patients.

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

[35] For topical use only

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ivermectin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include dermatitis contact (allergic or irritant) as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[36].
- In the next PSUR, the MAH(s) should provide detailed reviews of cases of systemic allergic reaction, and on the monitoring of aggravation of rosacea with a mechanistic rationale regarding the physiological mechanism. In addition, the MAH(s) should propose to update the product information as applicable with regard to application site swelling, skin swelling and swelling face as undesirable effects.

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

6.3.5. Mycophenolic acid[37] (NAP) - PSUSA/00010243/201605

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Mycophenolate acid is an inosine monophosphate dehydrogenase inhibitor indicated in combination with cyclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal transplants.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing mycophenolate acid, 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 mycophenolate acid-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH(s) should submit to the National competent Authorities of the EU Member States, within 90 days, a discussion on the justification of the need for two forms of contraception and any evidence for non-compliance with these requirements leading to unintended pregnancy. In addition, the MAH(s) should provide detailed reviews of cases of malformations following paternal exposure as well as the available non-clinical data relating to the potential for male-mediated developmental toxicity. Finally, the MAH(s) should propose to update the product information and educational materials relating to

[36] 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
[37] Apart from mycophenolate mofetil

paternal exposure as applicable. The MAH(s) should also propose to update the product information and educational materials as necessary on the need for either male contraception or female contraception or both.

- In the next PSUR, the MAH(s) should provide a comprehensive review pertaining to off-label use with mycophenolic acid and proposal for additional preventive measures.

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. The PRAC also considered that mycophenolate mofetil- and mycophenolic acid-containing products should be assessed in the future within the same PSUSA procedure.

6.3.6. Paracetamol[38] (NAP) - PSUSA/00002311/201605

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Paracetamol is an aniline analgesic indicated for the short-term treatment of moderate pain as a solution for infusion.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of paracetamol solution for intravenous (IV) infusion in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should closely monitor cases of agranulocytosis in an overdose context, convulsion, metabolic acidosis, gastrointestinal haemorrhage, respiratory disorders. The MAH should also provide a discussion on the publication by *Fisher BG et al.*[39] in the context of the monitoring of 'drug exposure during pregnancy'. Furthermore, the MAHs should provide a detailed analysis of cases of hepatobiliary disorders and abnormal liver function with a distinction between the cases which occurred in a context of therapeutic dosage and those in a context of overdose. In addition, hypersensitivity reactions including severe cutaneous adverse reactions (SCARs) should be added as an important identified risk due to the severity of cases. Moreover, the MAHs should monitor any cases reporting a paracetamol IV overdose, in particular, those reporting rhabdomyolysis or pancreatitis. The MAHs should also present a detailed analysis of cases of medication error or risk of medication error including information on the implementation of risk minimisation measures in each

[38] Intravenous (IV) formulation only
[39] Fisher BG, Thankamony A, Hughes IA, Ong KK, Dunger DB, Acerini CL. Prenatal paracetamol exposure is associated with shorter anogenital distance in male infants, Hum Reprod (2016) 31 (11):2642-2650

country. Finally, the MAHs should review any new scientific evidence available on paracetamol, hepatocellular insufficiency and contributing risk factors.

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

6.3.7. Quinapril (NAP) - PSUSA/00002591/201604

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Quinapril is an angiotensin converting enzyme (ACE) inhibitor indicated for the treatment of hypertension alone or in combination with a thiazide diuretic or a beta-blocker. Quinapril is also indicated for the treatment of congestive heart failure when given concomitantly with a diuretic and/or a cardiac glycoside.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing quinapril, 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 quinapril-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should closely monitor cases of Kaposi's sarcoma.

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

6.3.8. Risedronate (NAP) - PSUSA/00002648/201603

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Risedronate is a bisphosphonate indicated for the treatment of Paget's disease of bone, for the treatment and prevention of post-menopausal (PMO) and corticosteroid-induced osteoporosis as well as in the reduction of hip fractures and osteoporosis in men.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing risedronate, 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 risedronate-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should closely monitor cases of 'gastrointestinal haemorrhage'.

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.

6.3.9. Thiopental (NAP) - PSUSA/00002929/201603

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Thiopental is a thiobarbiturate indicated as an anaesthetic agent.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing thiopental, 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 thiopental-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include anaphylaxis as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[40].
- In the next PSUR, the MAH should provide a review of any new evidence with regard to the risk of leukopenia, including events of agranulocytosis and neutropenia, associated with thiopental, and an evaluation of any relevant trends detected as regards significant patterns of drug misuse, if applicable.

The frequency of PSUR submission should be revised from five-yearly to fifteen-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.

[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

6.4.1. Ingenol mebutate - PICATO (CAP) - EMEA/H/C/002275/LEG 008.1

Applicant: Leo Pharma A/S

PRAC Rapporteur: Julie Williams

Scope: MAH's response to LEG 008 [submission of a review relating to study LP0105-1020[41] (efficacy and safety of ingenol mebutate gel 0.06% when applied once daily for 2, 3 or 4 consecutive days to a treatment area of approximately 250 cm^2 on trunk and extremities in subjects with actinic keratosis) as requested in the conclusions of PSUSA/00010035/201507] as per the request for supplementary information (RSI) adopted in July 2016

Background

Ingenol mebutate induces local lesion cell death and promotes an inflammatory response characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. It is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

Following the evaluation of a post-authorisation measure submitted based on the conclusions of the PSUR single assessment (PSUSA/00010035/201507) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see PRAC minutes July 2016). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 60 days, a variation[42] to update the product information with available data relating to keratoacanthoma in light of the results of study LP105-1020[43]. This study examined treatment areas larger than 25 cm^2 and has shown a higher incidence of keratoacanthoma in ingenol treated group compared with the vehicle group.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[44]

See Annex I.17.1.

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

See also Annex I.17.2.

7.2.1. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/MEA 011.4

Applicant: AstraZeneca AB

[41] Efficacy and safety of ingenol mebutate gel 0.06% when applied once daily for 2, 3 or 4 consecutive days to a treatment area of approximately 250 cm^2 on trunk and extremities in subjects with actinic keratosis. NCT01998984
[42] Update of SmPC sections 4.4 and 5.1
[43] An international, phase 2, randomised, multicentre, double-blind, vehicle-controlled, 8-week trial: efficacy and safety of ingenol mebutate gel 0.06% when applied once daily for 2, 3 or 4 consecutive days to a treatment area of approximately 250 cm^2 on trunk and extremities in subjects with actinic keratosis
[44] In accordance with Article 107n of Directive 2001/83/EC
[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

PRAC Rapporteur: Carmela Macchiarulo

Scope: MAH's response to MEA 011.3 [revised protocol for a PASS to collect and/or retrieve prospective data from sizeable patient cohorts with ovarian cancer (study D0816R00008b)] as per request for supplementary information (RSI) adopted in July 2016

Background

Lynparza is a centrally authorised medicine containing olaparib, a human poly (ADP-ribose) polymerase enzymes inhibitor, indicated for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have responded to platinum-based chemotherapy.

As part of the RMP for Lynparza (olaparib), the MAH was required to conduct a category 3 study entitled 'a post-marketing observational prospective study to assess real world outcomes and the risk of myelodysplastic syndromes (MDS)/acute myeloid leukaemia (AML) in platinum sensitive relapsed breast cancer susceptibility gene (BRCA) mutated ovarian cancer patients treated with Lynparza (olaparib) (LOCALISE study or D0816R00008)'. The aim was to obtain real world evidence of safety and clinical effectiveness amongst patients treated with Lynparza (olapraib) and thus to evaluate the important potential risk of developing MDS/AML amongst mutated BRCA (BRCAm) platinum sensitive relapsed high grade serous epithelial ovarian cancer patients, who have responded to the most recent platinum-based chemotherapy, treated with Lynparza (olaparib) in real world conditions of clinical practice. Further to the previous advice adopted by PRAC in July 2016, the MAH submitted a revised protocol for the 'LOCALISE study', which was assessed by the Rapporteur. For further background, see PRAC minutes July 2016.

Summary of advice

- The PRAC considered that the design of the 'LOCALISE study' as described in the revised PASS protocol (version 1) does not fulfil the study objectives as important limitations have been identified in the registries presented by the MAH as an external cohort.
- The MAH should commit to collect data emerging from the ongoing clinical programmes in order to provide further information regarding the important potential risk of MDS/AML with Lynparza (olaparib) treatment, and provide the corresponding analysis in the upcoming PSUR. As a consequence, the MAH should submit to EMA, within 60 days, an updated RMP in order to update the design of the study.

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

7.3.1. Cyproterone, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0003.1

Applicant: Bayer Pharma AG, various

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study results on the drug utilisation study (DUS) (database) designed to characterize the prescribing behaviours for cyproterone acetate/ethinylestradiol (CPA/EE) in three European countries: the Netherlands, United

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

Kingdom and Italy

In line with the conclusions of a procedure under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for cyproterone/ethinylestradiol-containing medicines (EMEA/H/107i/1357), the MAHs were required to conduct a drug utilisation study (DUS) to characterise prescribing practices for these medicinal products during typical clinical use in representative groups of prescribers, and to assess the main reasons for prescription. The protocol for this study was assessed and endorsed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. Further to the request for supplementary information (RSI) adopted by PRAC in September 2016 and based on the Rapporteur's assessment, the PRAC reviewed the study results and issued a recommendation on the marketing authorisations. For background information, see PRAC minutes April 2014, PRAC minutes September 2014, PRAC minutes October 2014, PRAC minutes December 2014, PRAC minutes April 2015, PRAC minutes April 2016, PRAC minutes June 2016 and PRAC minutes September 2016.

Summary of advice

- Based on the review of the final report of the non-interventional PASS results (version 1.0), the MAHs' responses to the request for supplementary information and taking into account the joint survey drug utilisation final study report submitted as a separate procedure (EMEA/H/N/PSR/J/0005), the PRAC considered that the benefit-risk balance of medicinal products containing cyproterone/ethinylestradiol concerned by the joint database drug utilisation final study report remains unchanged.
- Nevertheless, the marketing authorisations should be amended to remove the condition that the MAHs should provide a final study report by 31 July 2015 of the imposed drug utilisation study to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription. Therefore, the current terms of the marketing authorisation(s) should be varied[47].

7.3.2. Cyproterone, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0005.1

Applicant: Bayer Pharma AG, various

PRAC Rapporteur: Menno van der Elst

Scope: Final study results on the drug utilisation study (DUS) (survey) designed to characterize the prescribing behaviours for cyproterone acetate/ethinylestradiol (CPA/EE) in five European countries: Austria, Czech Republic, France, the Netherlands and Spain

In line with the conclusions of a procedure under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for cyproterone/ethinylestradiol-containing medicines (EMEA/H/107i/1357), the MAHs were required to conduct a drug utilisation study (DUS) to characterise prescribing practices for these medicinal products during typical clinical use in representative groups of prescribers, and to assess the main reasons for prescription. The protocol for this study was assessed and endorsed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. Further to the request for supplementary information (RSI) adopted by PRAC in September 2016 and based on the Rapporteur's assessment, the PRAC reviewed the study results and issued a

[47] The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

recommendation on the marketing authorisations. For background information, see PRAC minutes April 2014, PRAC minutes September 2014, PRAC minutes October 2014, PRAC minutes December 2014, PRAC minutes April 2015, PRAC minutes April 2016, PRAC minutes June 2016 and PRAC minutes September 2016.

Summary of advice

- Based on the review of the results of the joint survey drug utilisation final study report (version 01), the MAHs' responses to the request for supplementary information and taking into account the joint database drug utilisation final study report submitted as a separate procedure (EMEA/H/N/PSR/J/0003), the PRAC considered that the benefit-risk balance of medicinal products containing the active substance cyproterone/ethinylestradiol concerned by the joint survey drug utilisation final study report remains unchanged.
- Nevertheless, the marketing authorisations should be amended to remove the condition that the MAHs should provide a final study report by 31 July 2015 of the imposed drug utilisation study to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription. Therefore, the current terms of the marketing authorisation(s) should be varied[48].

7.3.3. Cyproterone, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0006.1

Applicant: Bayer Pharma AG, various

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study results on the PASS to evaluate the effectiveness of the risk minimisation activities with the objective to measure physicians' knowledge of safety and safe use information for cyproterone acetate/ethinylestradiol (CPA/EE) in five European countries: Austria, Czech Republic, France, the Netherlands and Spain

Background

In line with the conclusions of a procedure under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for cyproterone/ethinylestradiol-containing medicines (EMEA/H/107i/1357), the MAHs were required to conduct a drug utilisation study (DUS) to characterise prescribing practices for these medicinal products during typical clinical use in representative groups of prescribers, and to assess the main reasons for prescription. The protocol for this study was assessed and endorsed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. Further to the request for supplementary information (RSI) adopted by PRAC in September 2016 and based on the Rapporteur's assessment, the PRAC reviewed the study results and issued a recommendation on the marketing authorisations. For background information, see PRAC minutes April 2014, PRAC minutes September 2014, PRAC minutes October 2014, PRAC minutes December 2014, PRAC minutes April 2015, PRAC minutes April 2016, PRAC minutes June 2016 and PRAC minutes September 2016.

Summary of advice

- Based on the review of the results of the joint PASS final study report (version 1.0) and the MAHs' responses to the request for supplementary information, the PRAC

[48] The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

considered that the benefit-risk balance of medicinal products containing the active substance cyproterone/ethinylestradiol concerned by the joint PASS final study report remains unchanged.

- Nevertheless, the marketing authorisations should be amended to remove the condition that the MAHs should provide a final study report by 31 July 2015 to evaluate the effectiveness of the risk minimisation activities. Therefore, the current terms of the marketing authorisation(s) should be varied[49].
- The PRAC supported the proposal from the MAH for the originator cyproterone/ethinylestradiol-containing medicine to liaise with the EU National Competent Authorities to further explore the feasibility and implementation of alternative communication methods, as applicable, and in accordance with available EU guidance (including GVP module XVI Addendum I – Educational materials).

7.4. Results of PASS non-imposed in the marketing authorisation(s)[50]

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.

[49] The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[50] 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

See Annex I.18.2.

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 2016-2019 (second revision for 2016)

The PRAC agreed the list of planned pharmacovigilance inspections 2016-2019, second revision 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.

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. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/II/0008

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: PRAC consultation on a variation to update sections 4.4 and 4.8 of the SmPC in order to reinforce the wording on the risk of anaphylaxis. The Package Leaflet is updated accordingly. The MAH took the opportunity to include the pharmacotherapeutic group in section 5.1

Background

Strensiq is a centrally authorised medicinal product containing asfotase alfa, a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein, and

is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease.

A type II variation proposing to update the product information and educational material of Strensiq (asfotase alfa) on the risk of anaphylaxis 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 and evidence, the PRAC supported the proposed changes to the product information including a revision to the contraindication to severe or life-threatening hypersensitivity to the active substance or to any of the excipients. The PRAC also supported the updates to the warning on the risk of hypersensitivity in patients treated with asfotase alfa in order to more fully reflect the nature of the reactions. In addition, the PRAC considered it important to include precautionary measures (i.e. pre-medications, patients monitoring) in case of re-challenge as this is likely to occur given the severity and limited treatment options of the disease.
- The PRAC considered the MAH's proposal for a proactive and timely distribution of the educational materials to HCPs acceptable, provided that it is supported by a cover letter including relevant key elements for appropriate risk management. The PRAC emphasised that this is contingent on prompt submission of the educational material within agreed timelines.

10.1.2. Ponatinib – ICLUSIG (CAP) - EMEA/H/C/002695/II/0032/G

Applicant: Incyte Biosciences UK Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: PRAC consultation on a variation to update sections 4.2, 4.4, 4.8, 5.1 of the SmPC based on data from ongoing study AP24534-07-101 with a median duration of follow-up of approximately 48 months for the CP-chronic myeloid leukaemia (CML) patients and 3.6 months for the advanced phase Ph+ leukemia patients, as well as 48-month follow-up data from the ongoing study AP24534-10-201 (PACE) (dose reduction advice as previously agreed by PRAC in the procedure under Article 20 of Regulation (EC) No 726/2004 finalised in 2014). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and to align the annexes with the latest QRD template (version 10)

Background

Iclusig is a centrally authorised medicinal product containing ponatinib, a tyrosine kinase inhibitor, indicated in adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation. Iclusig (ponatinib) is also indicated in adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

A grouped type II variation proposing to update the product information of Iclusig (ponatinib) on the dose reduction in chronic phase chronic myeloid leukaemia (CP-CML) patients who

have achieved a maintained major cytogenetic response (MCyR) 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 considered that the proposed update of the product information for Iclusig (ponatinib) on the dose reduction in CP-CML patients who have achieved MCyR is acceptable on the basis that additional data provide adequate reassurance that the dose reduction is not associated with a risk of loss of efficacy in these patients, and that there is adequate clinical and non-clinical data to conclude that the risk of occlusive events is dose-related.
- The PRAC advised that the educational materials should be updated to reflect the new recommendations, and a cover letter accompanying the educational materials should highlight the new recommendations. In addition, the PRAC also concluded that a direct healthcare professionals' communication (DHPC) was not warranted in light of the current evidence.

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

None

10.3. Other requests

None

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Chlormadinone, ethinyl estradiol (NAP)

Applicant: Gedeon Richter, various

PRAC Lead: Valerie Strassmann

Scope: PRAC consultation on the revised statistical analysis plan (SAP) for an imposed PASS comparing the risk of venous thromboembolism (VTE) with chlormadinone/ethinyestradiol (CMA/EE) versus levonorgestrel/ethinylestradiol (LVG/EE) following the PRAC endorsement in January 2016 of its protocol (EMEA/H/N/PSP/j/0012.3), as per the conclusions of the review under Article 31 of Directive 2001/83/EC on combined hormonal contraceptive (CHC) (EMA/607314/2013)

Background

Chlormadinone acetate (CMA), a steroidal synthetic progestin, in combination with ethinylestradiol, an oestrogen, is used as a combined oral contraceptive (COC). In January

2016, the PRAC endorsed a protocol (version 1.6) for an imposed post-authorisation safety study (EMEA/H/N/PSP/j/0012.3) to study the risk of venous thromboembolism (VTE) associated with chlormadinone/ethinylestradiol (CMA/EE)-containing products, which was submitted to the PRAC by a consortium of MAHs in accordance with the conditions to the marketing authorisation(s) included in the EC decision Annex IV for the referral under Article 31 of Directive 2001/83/EC (EMA/607314/2013) for combined hormonal contraceptives (CHCs) finalised in 2013. For further background, see PRAC minutes January 2016.

As the statistical analysis plan (SAP) for the PASS was not finalised and could not be fully assessed within procedure EMEA/H/N/PSP/j/0012.3, the Lead Member State (Germany) conducted a review at national level of the submitted SAP (versions 1.0 and 1.1) and requested PRAC advice on its assessment in September 2016. For further background, see PRAC minutes September 2016. As an outcome of the September 2016 PRAC advice, a revised SAP was requested to be submitted for assessment. Germany presented its conclusion of the assessment of the revised SAP at the current meeting and requested PRAC to give further advice.

Summary of advice

- Based on the review of the available information and the assessment performed by Germany, the PRAC considered that the revised SAP (version 1.2) was acceptable.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) steering group - nomination of PRAC representative for 2017-2019

The EMA Secretariat launched a call for PRAC nomination to the ENCePP Steering Group for a three-year term (2017 to 2019) in line with its mandate (EMA/333923/2009 Rev.2). The Committee/Working Party representatives will be appointed for the duration of the term of service of the Steering Group (three years), and may be renewed. PRAC members were invited to send their expression of interest for nomination to the ENCePP Secretariat by 9 December 2016.

Post-meeting note: Marieke de Bruin was nominated as PRAC representative at the ENCePP steering group for a three-year term from 2017 to 2019.

12.4.2. Pharmacovigilance operation - EU training curriculum design document

PRAC lead: Margarida Guimarães

The EMA Secretariat presented to PRAC an outline of the draft EU training curriculum design document developed following the approval in February 2016 by the Heads of Medicines Agencies (HMA) of setting up seven curricula for the European Network Training Centre (EU NTC). As the operation of pharmacovigilance in the EU was identified as one of these curricula, a sub-group composed of representatives from National Competent Authorities and EMA Secretariat was set up as the 'Curriculum Steering Group'. In September/October 2016, the 'Pharmacovigilance Business Team' and the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) work package leads provided input. Following consolidation and agreement by the Training Curriculum Steering Group and 'Pharmacovigilance Business Team', the draft outline of the curriculum framework for operating pharmacovigilance by the EU network was presented to PRAC with the view to adopt it in January 2017. The aim of this document is to provide an overview of the training areas related to the operation of pharmacovigilance and to drive training in key priority areas in a consistent way across the EU network and to support the objectives with a main focus on consistency of decision making in the EEA. A follow-up discussion is planned in January 2017.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

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

The EMA Secretariat presented to PRAC a draft revised 'GVP Module II – Pharmacovigilance system master file (PMSF)' implementing some administrative revisions following agreement at the Pharmacovigilance Inspectors' Working Group (PhV IWG) in light of recent regulatory changes and minor edits. PRAC members were invited to provide any further comments by 9 December 2016. The PRAC adoption of the revised GVP module II is scheduled in February-March 2017.

12.9.2. Pharmacovigilance systems and their quality systems

None

12.9.3. Pharmacovigilance inspections

None

12.9.4. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Margarida Guimarães

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

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version December 2016 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 December 2016 (held on 28 November-1 December 2016), the updated EURD list was adopted by the CHMP and CMDh at their December 2016 meetings and published on the EMA website on 21/12/2016, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the December 2016 SMART Working Group (SMART WG) work stream WS1. The WG WS1 held a follow-up discussion on signals recommendations affecting the outer packaging of medicinal products. In addition, as agreed at the last WG WS1 meeting (see PRAC minutes November 2016) the group

discussed aspects relating to spontaneously submitted Type II variations after a signal had been identified at PRAC. The SMART also discussed the pilot currently in place for adoption of PRAC recommendations for new signals without a plenary discussion. The main goal of the pilot is to evaluate if the risk-based criteria for adoption of recommendation with or without plenary discussion, implemented as of June 2016, has optimised the number of signal procedures discussed at PRAC plenary meetings or whether the criteria need amendments. The SMART agreed to collect first some metrics. Follow-up discussion is planned in February 2017.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on 19/12/2016 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

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Good Pharmacovigilance Practice (GVP) Module V on risk management systems – Revision 2

The topic was deferred to the January/February 2017 PRAC meeting.

12.14.2. Risk management systems

None

12.14.3. 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 hearings - procedural and best practice guidance for PRAC members

PRAC Lead: Albert van der Zeijden

As a follow-up to previous discussion (see PRAC minutes November 2016), the 'PRAC public hearing subgroup' together with the EMA Secretariat presented to PRAC a refined draft version of the 'Procedural and Best Practice Guidance for PRAC members on Public Hearings' for internal use. Following further clarification, PRAC members were invited to send any final comments by 5 January 2017.

Post-meeting note: The guidance was finalised on 5/01/2017 by written procedure.

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 2016/2017 - update on GVP status overview

The PRAC was provided in writing with an overview of the GVP 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. Emphasis was placed on the revision

of the GVP definitions Annex and revision of GVP module V on risk management systems.

12.20.2. Policy on handling competing interests for scientific committees' members and experts - update

The EMA secretariat presented to PRAC the updated 'EMA policy on the handling of competing interests of scientific committee members and experts' (EMA/626261/2014,Rev. 1) implemented as of 1 December 2016. The main change relates to additional restrictions for Committee and Working Party members declaring close family member interests.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[51]

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[52].

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Albiglutide – EPERZAN (CAP)

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Signal of acute kidney injury

EPITT 18778 – New signal

Lead Member State: UK

14.1.2. Brentuximab vedotin – ADCETRIS (CAP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Signal of cytomegalovirus (CMV) reactivation

EPITT 18789 – New signal

Lead Member State: NL

14.1.3. Daratumumab – DARZALEX (CAP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Leonor Chambel

Scope: Signal of tumour lysis syndrome (TLS)

EPITT 18777 – New signal

Lead Member State: PT

14.1.4. Dabrafenib – TAFINLAR (CAP); trametinib – MEKINIST (CAP)

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

[51] 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

[52] 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 sepsis

EPITT 18779 – New signal

Lead Member States: SE, UK

14.1.5. Temozolomide – TEMODAL (CAP), NAP

Applicant: Merck Sharp & Dohme Limited; various

PRAC Rapporteur: Martin Huber

Scope: Signal of meningoencephalitis herpetic

EPITT 18785 – New signal

Lead Member State: DE

14.2. New signals detected from other sources

14.2.1. Leflunomide – ARAVA (CAP); teriflunomide – AUBAGIO (CAP)

Applicant: Sanofi-aventis Deutschland GmbH (Arava), Sanofi-Aventis Groupe (Aubagio)

PRAC Rapporteur: Sabine Straus

Scope: Signal of falsely decreased ionised calcium levels

EPITT 18787 – New signal

Lead Member States: DE, NL

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. Human immunoglobulin (Ig)G1 monoclonal antibody specific for human interleukin-1 alpha - EMEA/H/C/004388

Scope: Treatment of metastatic colorectal cancer

15.1.2. Ivabradine - EMEA/H/C/004241, Generic

Scope: Treatment of angina pectoris

15.1.3. Pemetrexed - EMEA/H/C/004488, Generic

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

15.1.4. Simoctocog alfa - EMEA/H/C/00459

Scope: Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)

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/0028/G

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Grouped variations including: 1) update of the RMP in order to introduce additional risk minimisation measures addressing the important potential risk of medication errors. Annex II of the Product Information is updated accordingly; 2) update of the RMP to add a new category 3 study as an additional pharmacovigilance activity - study 204879: a randomized, open-label, active-controlled, parallel-group, exploratory study on the effects of repeated doses of albiglutide compared to exenatide on gastric myoelectrical activity and gastric emptying in subjects with type 2 diabetes mellitus; 3) update of the RMP to add a new category 3 study as an additional pharmacovigilance activity - study 201840: an exploratory randomized, 2-part, single-blind, 2-period crossover study comparing the effect of albiglutide with exenatide on regional brain activity related to nausea in healthy volunteers; 4) update of the RMP to add a new category 3 study as an additional pharmacovigilance activity: cross-sectional survey to assess the effectiveness of the proposed additional educational materials using patient connect

15.2.2. Antithrombin alfa - ATRYN (CAP) - EMEA/H/C/000587/II/0027

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Claire Ferard

Scope: Introduction of a RMP (version 1) as requested in the sixth annual re-assessment (EMEA/H/C/000587/S/0021) and second five-year renewal (EMEA/H/C/000587/R/0024)

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

Applicant: AbbVie Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update the RMP for Exviera and Viekirax to 1) add information on cases of hepatic decompensation observed in patients with Child-Pugh B hepatic impairment, and to the reflect the changes of the SmPC to change the dose recommendation of these patients to 'not recommended', as well as the addition of statements recommending the monitoring of hepatic function in these patients as approved on WS/0873; 2) add a reference to nine drug-drug interaction studies as approved in WS0896/G; 3) include a reference to the

completion of rat 2 year carcinogenicity studies as recently approved in variations II-06 (Exviera) and II-04 (Viekirax) respectively; 4) reflect the update of section 4.2 of SmPC for Viekirax to recommend a decrease in treatment duration of 12 weeks in genotype 4 (GT4) cirrhotic patients, with a consequential change to sections 4.4 and 5.1 as approved in II-22-G; 5) remove the non-clinical PAMS 1-3,(MEA/003, MEA/002, MEA/003)

15.2.4. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS0953/0019; empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS0953/0019

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the RMP in order to reflect the outcome of the recently finalised procedure under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) including the addition of atypical DKA as an important identified risk for all sodium-glucose cotransporter-2 (SGLT2) inhibitors. In addition, ongoing and planned activities are being included in the RMP

15.2.5. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/II/0033

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 4.2) to reflect the revised protocol for a post-authorisation study to capture data on the frequency of resolution and time to resolution of eribulin-induced or aggravated peripheral neuropathy from study E7389-A001-303 (ACCRU: a randomized phase III trial of eribulin compared to standard weekly paclitaxel as first- or second-line therapy for locally recurrent or metastatic breast cancer) to an observational post authorisation, single-arm, prospective multicentre cohort study E7389-M044-504 (IRENE). The submission of the corresponding study report to EMA remains unchanged and is planned in 2019

15.2.6. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0047

Applicant: Hospira UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of the RMP (version 7.0) to merge the RMPs for Remsima and Inflectra

15.2.7. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0039

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

Scope: Update of the RMP (version 7.0) to merge the RMPs for Remsima and Inflectra

15.2.8. Thyrotropin alfa - THYROGEN (CAP) - EMEA/H/C/000220/II/0088

Applicant: Genzyme Europe BV

PRAC Rapporteur: Almath Spooner

Scope: Update of the RMP to bring it in line with the latest RMP template. As a consequence, 'gastrointestinal symptoms', 'constitutional symptoms' and 'injection site reactions' are deleted resulting from their downgrade to identified risks as not categorized as important any longer. In addition, 'perceived lower thyroid-stimulating hormone (TSH) elevation after thyrotropin alfa administration' is deleted from the list of important potential risks as it does not correspond to a safety risk for patients treated with Thyrogen. Finally, the study results and completion date for the T4 study (collection of data about remnant ablation in patients originally diagnosed with T4 thyroid cancer) are added and as a consequence, use of Thyrogen for remnant ablation in patients originally diagnosed with T4N0-1M0-1 thyroid cancer' is removed as missing information. The RMP (version 9.0) is updated accordingly

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. 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 (NYHA Class II - IV). The RMP (version 13) is updated accordingly

15.3.2. Atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/II/0105/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Claire Ferard

Scope: Grouped variations to: 1) update of section 4.6 of the SmPC in order to update the safety information on lactation to indicate that atazanavir has been detected in human milk. The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet; 2) update of the RMP in order to add 'immune reconstitution inflammatory syndrome (IRIS)' and 'angioedema' as important identified risks and to update the epidemiology/exposure sections. The MAH also took the opportunity to make some reformatting changes to align the RMP with the current approved EMA template

15.3.3. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0092

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the use of Avastin in combination with paclitaxel

and carboplatin for the treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated with efficacy and safety information from study GOG-0213 (a phase III randomized controlled clinical trial of carboplatin and paclitaxel (or gemcitabine) alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer. NCI-supplied agents: bevacizumab). The Package Leaflet and the RMP (version 27) are updated accordingly

15.3.4. C1-esterase inhibitor, human - CINRYZE (CAP) - EMEA/H/C/001207/II/0045

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include children with hereditary angioedema (HAE) in the treatment and pre-procedure prevention of angioedema attacks. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.5 of the SmPC are updated. The Package Leaflet and Labelling are updated accordingly. In addition, the MAH proposed to update regional information in module 3.2.R due to the proposed dose recommendation for children

15.3.5. Canakinumab - ILARIS (CAP) - EMEA/H/C/001109/X/0045/G

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped application comprising a line extension covering an additional formulation (150 mg/ml solution for injection) and a type II variation to add a new indication based on the results of the pivotal phase 3 study CACZ885N2301 on the treatment of adults and children of 2 years of age and older with one of the following periodic fever syndromes: tumour necrosis factor receptor associated periodic syndrome (TRAPS); hyperimmunoglobulin D syndrome (HIDS), mevalonate kinase deficiency (MKD); familial Mediterranean fever (FMF) in patients in whom colchicine is contraindicated, is not tolerated, or does not provide an adequate response. As a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 11) are updated accordingly. In addition, the annexes have been aligned with the latest QRD template (version 10)

15.3.6. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0054

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final clinical study report (CSR) for study AS001: a phase 3, multicentre, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of certolizumab pegol in subjects with active axial spondyloarthritis (axSpA). As a consequence, sections 4.8 and 5.1 of the SmPC are revised in order to update the efficacy and safety information (week 204) for study AS001. The RMP (version 11.0) is updated accordingly. The package leaflet remains unchanged

15.3.7. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0055

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final clinical study report (CSR) for study PsA001: a phase 3, multicentre, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with adult onset active and progressive psoriatic arthritis (PsA), in order to provide data on long-term use of Cimzia in psoriatic arthritis subjects up to 216 weeks of treatment. As a consequence, sections 4.8 and 5.1 of the SmPC are revised in order to update the efficacy and safety information (week 216) for study PsA001. The RMP (version 11) is updated accordingly. The package leaflet remains unchanged

15.3.8. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0002

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Leonor Chambel

Scope: Extension of indication in the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy. As a consequence, sections 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC are updated in order to update the information on posology, warnings, interactions, efficacy and pharmacokinetics. A new warning is introduced in section 4.4 regarding neutropenia/thrombocytopenia induced by background therapy. Annex II is updated to remove all the specific obligations following submissions of the final results of studies MMY3003 (a phase III randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma) and MMY3004 (a phase III randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma). The Package Leaflet and RMP (version 2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.9. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0057

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to delete references to the pregnancy and lactation surveillance programmes. The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial updates to the product information

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the 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 3 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 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

15.3.11. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0046

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to delete references to the pregnancy and lactation surveillance programmes. The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to make minor editorial updates to the product information

15.3.12. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0035

Applicant: Biogen Idec Ltd.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to include 'liver function abnormalities' as an adverse event observed in the post-marketing setting and to clarify events not observed in placebo-controlled studies. The Package Leaflet and the RMP (version 8) are updated accordingly. The MAH has also taken the opportunity to make minor administrative changes in the Package Leaflet

15.3.13. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/X/0018/G

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Grouped application comprising a line extension to add two new strengths (10 mg and 25 mg tablets) to support the extension of indication for the treatment of paediatric patients from 6 years of age infected with human immunodeficiency virus (HIV). Data from cohort I and II A of study ING112578 (a 48 week Phase 1/2 multicentre open-label non-comparative study to evaluate pharmacokinetic (PK), safety, tolerability and antiviral activity of dolutegravir in HIV-1 infected children and adolescents of 6 weeks to <18 years of age) are presented in support of the new therapeutic indication

15.3.14. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0086/G

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

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

15.3.15. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0014

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include the prevention of cardiovascular events, based on the final data of the cardiovascular safety clinical trial EMPA-REG OUTCOME (a phase 3, multicentre, international, randomised, parallel group, double blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk). As a consequence, section 4.1 of the SmPC is updated in order to add safety information on this study. The Package Leaflet is updated accordingly

15.3.16. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS0971/0022; empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS0971/0021

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final clinical report for study 1245.28 (4-year data) (a phase 3, randomised, double-blind, active controlled parallel group efficacy and safety study of empagliflozin compared to glimepiride administered orally during 104 weeks with a 104-week extension period in patients with type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment)

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

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the use of Zebinix as monotherapy in adults, in addition to the previously authorised indication as adjunctive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 15.0) are updated accordingly

15.3.18. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/X/0016

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Rafe Suvarna

Scope: Line extension to add a new strength of 25 mg solution for injection in pre-filled syringe

15.3.19. Everolimus - VOTUBIA (CAP) - EMEA/H/C/002311/II/0041

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the adjunctive treatment of patients aged 2 years and older with refractory seizures associated with tuberous sclerosis complex (TSC) for Votubia 2 mg, 3 mg and 5 mg dispersible tablets. Sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated based on the results from the pivotal study. In addition, sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 are also updated for the 2.5 mg, 5 mg and 10 mg tablets to reflect data relevant to these formulations. The Package Leaflet is updated accordingly. Furthermore, the Product Information is brought in line with the latest QRD template (version 10)

15.3.20. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/II/0004

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to include a warning and update the safety information as a result of a post-marketing case of hypertensive encephalopathy upon abrupt discontinuation of Intuniv (guanfacine hydrochloride). The Package Leaflet is updated accordingly

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

Applicant: GSK Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of study EPI-HPV-069, a meta-analysis assessing the risk of three autoimmune diseases following vaccination with Cervarix: autoimmune thyroiditis (AIT), Guillain-Barre syndrome (GBS) and inflammatory bowel disease (IBD). The RMP (version 18) is updated accordingly, and includes minor updates related to other studies

15.3.22. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0029

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.5 of the SmPC to remove the statement that an interaction with medicinal products increasing stomach pH may decrease ibrutinib exposure as well as section 5.2 to include the findings from study CLL1005: an open-label, sequential-design drug interaction study of the effect of omeprazole on the pharmacokinetics of ibrutinib in healthy adults. The RMP (version 6.3) is updated accordingly. The Package Leaflet remains unchanged

15.3.23. Icatibant - FIRAZYR (CAP) - EMEA/H/C/000899/II/0034/G

Applicant: Shire Orphan Therapies GmbH

PRAC Rapporteur: Qun-Ying Yue

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

15.3.24. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/II/0009

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final clinical study report (CSR) of study SB2-G31-RA: a randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of Flixabi compared to Remicade in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy. The RMP (version 4) is updated to reflects the results from the 78 weeks CSR, to exclude 2 of the 5 registries of the pharmacovigilance plan and update the due date for the prospective observational cohort study of Flixabi in ankylosing spondylitis (AS) and Crohn's disease (CD) patients

15.3.25. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/II/0061

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.3 and 4.8 of the SmPC to reflect that Fluenz Tetra is contraindicated only in children with severe hypersensitivity to eggs (instead of all children with egg allergy), and to update the safety information by implementing the number of children and adolescents in the safety database. The Package Leaflet is updated accordingly. In addition, the RMP is updated to implement administrative changes to the high level description on enhanced safety surveillance (ESS) and to change the milestones for study MA-VA-MEDI3250-1116 (a case control study of the effectiveness of Fluenz Tetra versus inactivated influenza vaccine and no vaccine in subjects 2-17 years of age)

15.3.26. Ferric maltol - FERACCRU (CAP) - EMEA/H/C/002733/II/000002/G

Applicant: Shield TX (UK) Ltd.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of two final study reports for in vitro studies conducted as part of post-authorisation measures MEA 001 and MEA 002: 1) drug-drug interaction study to

investigate drug interactions with Feraccru; 2) drug-drug interaction study to identify UGT isoenzyme(s) that are responsible for metabolism of ferric maltol. Consequential changes have been made to the RMP to reflect the completion of the studies

15.3.27. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/II/0162

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Update of section 4.8 of the SmPC in order to include acute kidney injury as an undesirable effect. The Package Leaflet is updated accordingly

15.3.28. Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/II/0020

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final clinical study report for study EFC12382, a randomized double-blind, placebo-controlled, 2 arm parallel group, multicentre study with a 24-week treatment period to assess the efficacy and safety of lixisenatide in patients with T2DM insufficiently controlled with basal insulin or without metformin, in order to fulfil MEA 004. In addition, the MAH took the opportunity to update the RMP (version 4.0) accordingly

15.3.29. Lopinavir, ritonavir - ALUVIA (Art 58[53]) - EMEA/H/W/000764/II/0100

Applicant: AbbVie Ltd.

PRAC Rapporteur: Claire Ferard

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to introduce the outcome from an analysis of the published 48-week study results PENTA 18/KONCERT: 'a Kaletra once daily randomised trial of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in human immunodeficiency virus (HIV)-1–infected children'. In addition, the RMP (version 8) is updated to remove the missing information safety concern of limited information of Aluvia 100 mg/25 mg film-coated tablets in the paediatric population

15.3.30. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/II/0160

Applicant: AbbVie Ltd.

PRAC Rapporteur: Claire Ferard

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to introduce the outcome from an analysis of the published 48-week study results PENTA 18/KONCERT: 'a Kaletra once daily randomised trial of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in human immunodeficiency virus (HIV)-1–infected children'. In addition, the RMP (version 8) is updated to remove the missing information safety concern of limited

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

information of Kaletra 100 mg/25 mg film-coated tablets in the paediatric population

15.3.31. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0087

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final clinical study report (CSR) from study CAMN107A2132: a phase I, single centre, two group, open-label, non-randomized, drug-drug interaction study to evaluate the effects of nilotinib on the pharmacokinetics (PK) of valsartan in healthy volunteers (HV). The RMP (version 17) is updated accordingly

15.3.32. Nitisinone - ORFADIN (CAP) - EMEA/H/C/000555/II/0057

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to amend the dosing frequency further to the results of a clinical pharmacology study NTBC-003: 'an open-label, non-randomized, sequential, multicentre study to evaluate the pharmacokinetics, efficacy and safety of once daily dosing compared to twice daily dosing of Orfadin in patients diagnosed with hereditary tyrosinemia type 1'. The Package Leaflet is updated accordingly

15.3.33. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0019

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy for Opdivo. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the proposed indication, add a warning about the patient populations excluded from the clinical trial and update the safety information. The Package Leaflet and the RMP (version 7.0) are updated accordingly

15.3.34. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0009/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 based on the results from study D5160C00003 (a phase 3, open label, randomized study of Tagrisso versus platinum-based doublet chemotherapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed with previous epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor therapy and whose tumours harbour a T790M mutation within the EGFR gene (AURA3)), the updated clinical study reports (CSR) for studies D5160C00001 (a phase 2, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and anti-tumour activity of ascending doses of Tagrisso in patients with advanced NSCLC who have progressed following prior therapy with an EGFR-tyrosine kinase inhibitor agent (AURAex)) and D5160C00002 (a phase 2, open-label,

single-arm study to assess the safety and efficacy of Tagrisso in patients with locally advanced/metastatic NSCLC whose disease has progressed with previous EGFR-tyrosine kinase inhibitor therapy and whose tumours are EGFR mutation and T790M mutation positive (AURA2)). The Package Leaflet and RMP (version 6.0) are updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet. The provision of the CSR from study AURA3 addresses the Specific Obligation (SO) and hence the MAH requests the conversion from a conditional marketing authorisation (CMA) to a full MA

15.3.35. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0031/G

Applicant: Biogen Idec Ltd.

PRAC Rapporteur: Julie Williams

Scope: Grouped variation to update section 4.8 of the SmPC with data on exposure and section 5.1 with information on maintenance of long-term efficacy based on clinical study data (study ATTAIN: a dose-frequency blinded, multicentre, extension study to determine the long-term safety and efficacy of pegylated interferon beta-1a (Plegridy) in subjects with relapsing multiple sclerosis). In addition, update of section 4.8 of the SmPC in order to add information concerning the onset and duration of flu-like symptoms based on clinical study data (study ALLOW: an open-label, two-arm randomized study to characterize flu-like symptoms in relapsing multiple sclerosis patients transitioning from current interferon beta therapies to Plegridy). The Package Leaflet and the RMP (version 3) are updated accordingly

15.3.36. Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/X/0035/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Grouped application including a line extension to introduce a new pharmaceutical form associated with 3 new strengths (267mg, 534mg and 801mg film-coated tablets). In addition, manufacturing sites are also introduced for the currently approved 267mg hard capsules presentations (EU/1/11/667/001-003)

15.3.37. Rufinamide - INOVELON (CAP) - EMEA/H/C/000660/II/0037

Applicant: Eisai Ltd.

PRAC Rapporteur: Claire Ferard

Scope: Extension of indication to include the treatment of seizures associated with Lennox-Gastaut syndrome in paediatric patients of 1 year of age and older, based on the results of study E2080-G000-303 (study 303): a randomized, controlled, open-label study to evaluate the cognitive development effects and safety, and pharmacokinetics of adjunctive rufinamide treatment in paediatric subjects 1 to less than 4 years of age with inadequately controlled Lennox-Gastaut syndrome. This study was conducted to fulfil the long-term (2 years) safety and efficacy objectives required as part of the paediatric investigation plan (PIP) EMEA-000709-PIP01-09. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 9.0) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial

changes in the annexes, to implement changes in line with the latest QRD template and to combine the SmPCs, labelling and Package Leaflets for the three authorised strengths of the tablet formulation in line with the current version of the QRD template

15.3.38. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0031

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information for melofibrosis following the completion of two 5-year follow up studies: INCB 18424-351 (randomized, double-blind, placebo-controlled study of the ruxolitinib tablets administered orally to subjects with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis) and INC424A2352 (randomized study of ruxolitinib tablets compared to best available therapy in subjects with primary myelofibrosis, post-polycythemia vera-myelofibrosis or post-essential thrombocythemia myelofibrosis). Annex II is updated accordingly

15.3.39. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/II/0003

Applicant: Gilead Sciences International Ltd.

PRAC Rapporteur: Margarida Guimarães

Scope: Update of sections 4.4, 4.5 and 5.1 of the SmPC in order to reflect on emerging clinical data from study GS-US-342-1202 (a phase 3, open-label study to investigate the efficacy and safety of sofosbuvir/velpatasvir fixed dose combination for 12 weeks in subjects with chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV)-1 coinfection). The RMP (version 1.0) is updated accordingly. In addition, minor administrative changes are implemented throughout the Product Information

15.3.40. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/II/0027/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations including: 1) submission of the final clinical study report (CSR) for study TDM4997g/BO25734 (TH3RESA study: a phase 3, randomized, multicentre, two arm, open-label trial to evaluate the efficacy of trastuzumab emtansine compared with treatment of physician's choice in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer who have received at least two prior regimens of HER2 directed therapy) to address the safety concerns of left ventricular dysfunction and safety in elderly patients. The RMP (version 6.0) and Annex II.D are updated accordingly; 2) update of the RMP following the submission of the third annual report of study H4621g (an observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with Herceptin, Perjeta in combination with Herceptin, or Kadcyla during pregnancy or within 7 months prior to conception). The MAH took the opportunity to implement the following administrative changes to the RMP: inclusion of standard post-authorisation data based on PSUR#4; change of Herceptin picture in the Kadcyla educational material to align the picture with the recently approved version of the Herceptin vial label and carton

15.3.41. Travoprost - IZBA (CAP) - EMEA/H/C/002738/II/0005

Applicant: Alcon Laboratories (UK) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Extension of indication to include treatment of paediatric patients aged 2 months to <18 years with ocular hypertension or paediatric glaucoma in order to decrease of elevated intraocular pressure (IOP). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet and the RMP (version 9.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor corrections in the SmPC and to update the list of local representatives in the Package Leaflet

15.3.42. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/II/0037

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.5 of the SmPC in order to include information on drug-drug interaction with rifampicin. In addition, the MAH took the opportunity to update the RMP and to request modification of MEA 011 part 2 'study GO29475: a two-part steady-state interaction study with and rifampin (3YP3A4 inducer). Furthermore the MAH is requesting change of due dates for category 3 final study reports for studies GO29475 (MEA011), MO25515 (MEA006) and GP28492 (MEA010). The MAH is also including request for deletion from the RMP of the study 'phase I dose-escalation with efficacy tail extension study of vemurafenib in pediatric patients with surgically incurable and unresectable stage IIIC or stage IV melanoma harboring BRAFV600 mutations (MEA 005)' to reflect the paediatric product specific waiver for treatment of melanoma as agreed with the PDCO on 24 April 2016

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. Abiraterone - ZYTIGA (CAP) - PSUSA/00000015/201604

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.2. Alipogene tiparvovec - GLYBERA (CAP) - PSUSA/00010056/201604

Applicant: UniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.3. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201605

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Mladá

Scope: Evaluation of a PSUSA procedure

16.1.4. Bortezomib - VELCADE (CAP) - PSUSA/00000424/201604

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.5. Brinzolamide, timolol - AZARGA (CAP) - PSUSA/00000433/201604

Applicant: Alcon Laboratories (UK) Ltd.

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.6. Budesonide, formoterol - BIRESP SPIROMAX (CAP); BUDESONIDE/FORMOTEROL TEVA (CAP); BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP); DUORESP SPIROMAX (CAP); VYLAER SPIROMAX (CAP) - PSUSA/00010202/201604

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.7. Carbidopa, levodopa[54] - NUMIENT (CAP) - PSUSA/00010479/201605

Applicant: Impax Laboratories Netherlands BV

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.8. Ceritinib - ZYKADIA (CAP) - PSUSA/00010372/201604

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

[54] Centrally authorised product only

Scope: Evaluation of a PSUSA procedure

16.1.9. Cetrorelix - CETROTIDE (CAP) - PSUSA/00000633/201604

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.10. Cobicistat, darunavir - REZOLSTA (CAP) - PSUSA/00010315/201605

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.11. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/201605

Applicant: Gilead Sciences International Ltd.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.12. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/201605

Applicant: Durata Therapeutics International B.V.

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.13. Delamanid - DELTYBA (CAP) - PSUSA/00010213/201604

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.14. Dihydroartemisinin, piperaquine tetraphosphate - EURARTESIM (CAP) - PSUSA/00001069/201604

Applicant: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.15. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/201605

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.16. Fentanyl[55] - IONSYS (CAP) - PSUSA/00010453/201605

Applicant: Incline Therapeutics Europe Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.17. Flutemetamol (^{18}F) - VIZAMYL (CAP) - PSUSA/00010293/201604

Applicant: GE Healthcare Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.18. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP); REVINTY ELLIPTA (CAP) - PSUSA/00010099/201605

Applicant: Glaxo Group Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.19. Hemoprostol - MISOPROSTOL (Art 58[56]) – EMEA/H/W/002652/PSUV/0005

Applicant: Linepharma International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.20. Ivabradine - CORLENTOR (CAP); IVABRADINE ANPHARM (CAP); PROCORALAN (CAP) - PSUSA/00001799/201604

Applicant: Anpharm Przedsiębiorstwo (Ivabradine Anpharm), Les Laboratoires Servier (Corlentor, Procorolan)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.21. Lidocaine, prilocaine[57] - FORTACIN (CAP) - PSUSA/00010110/201605

Applicant: Plethora Solutions Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

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

16.1.22. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/201605

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.23. Methylthioninium chloride - METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP) - PSUSA/00002029/201605

Applicant: Provepharm SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.24. Necitumumab - PORTRAZZA (CAP) - PSUSA/00010471/201605

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.25. Obinutuzumab - GAZYVARO (CAP) - PSUSA/00010279/201604

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.26. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/201605

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.27. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP); prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - PREPANDRIX (CAP) - PSUSA/00002281/201605

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.28. Pixantrone - PIXUVRI (CAP) - PSUSA/00009261/201605

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.29. Propranolol[58] - HEMANGIOL (CAP) - PSUSA/00010250/201604

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.30. Radium (Ra^{223}) dichloride - XOFIGO (CAP) - PSUSA/00010132/201605

Applicant: Bayer Pharma AG

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.31. Ramucirumab - CYRAMZA (CAP) - PSUSA/00010323/201604

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.32. Retapamulin - ALTARGO (CAP) - PSUSA/00002622/201604

Applicant: Glaxo Group Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.33. Shingles (herpes zoster) vaccine (live) - ZOSTAVAX (CAP) - PSUSA/00009289/201605

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.34. Siltuximab - SYLVANT (CAP) - PSUSA/00010254/201604

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.35. Simeprevir - OLYSIO (CAP) - PSUSA/00010255/201605

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

[58] Centrally authorised product only

16.1.36. Sunitinib - SUTENT (CAP) - PSUSA/00002833/201604

Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.37. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/201605

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.38. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/201605

Applicant: Pfizer Limited

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.39. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/201604

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.40. Tilmanocept - LYMPHOSEEK (CAP) - PSUSA/00010313/201605

Applicant: Navidea Biopharmaceuticals Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.41. Tolvaptan[59] - SAMSCA (CAP) - PSUSA/00002994/201605

Applicant: Otsuka Pharmaceutical Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.42. Turoctocog alfa - NOVOEIGHT (CAP) - PSUSA/00010138/201604

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[59] Indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)

16.1.43. Ulipristal[60] - ELLAONE (CAP) - PSUSA/00003074/201605

Applicant: Laboratoire HRA Pharma, SA

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.44. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/201605

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Olanzapine - OLAZAX DISPERZI (CAP); ZALASTA (CAP); ZYPREXA (CAP); ZYPREXA VELOTAB (CAP); NAP - PSUSA/00002205/201603

Applicant: Glenmark Pharmaceuticals s.r.o. (Olazax Disperzi), Krka, d.d., Novo mesto (Zalasta), Eli Lilly Nederland B.V. (Zyprexa, Zyprexa Velotab), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Bacterial lysate of haemophilus influenzae, klebsiella pneumoniae, moraxella catarrhalis, staphylococcus aureus, streptococcus mitis, streptococcus pneumoniae, streptococcus pyogenes; bacterial lysate of haemophilus influenzae, klebsiella pneumoniae, moraxella catarrhalis, staphylococcus aureus, streptococcus pneumoniae, streptococcus pyogenes (NAP) - PSUSA/00002786/201603

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.2. Ivabradine, metoprolol (NAP) - PSUSA/00010381/201604

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[60] Female emergency contraceptive

16.3.3. Ivermectin[61] (NAP) - PSUSA/00010377/201604

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.4. N(2)-L-alanyl-L-glutamine (NAP) - PSUSA/00003158/201603

Applicant: various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

16.3.5. Tobramycin[62] (NAP) - PSUSA/00009317/201603

Applicant: various

PRAC Lead: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

16.3.6. Valganciclovir (NAP) - PSUSA/00003089/201603

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Carglumic acid - CARBAGLU (CAP) - EMEA/H/C/000461/LEG 032

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

PRAC Rapporteur: Leonor Chambel

Scope: Cumulative review and analysis of cases of off-label use, lack of efficacy and medication errors as requested in the conclusions of procedure EMEA/H/C/PSUSA/00000564/201501 adopted by PRAC in September 2015

16.4.2. Eptotermin alfa – OPGENRA[63], OSIGRAFT[64]

Applicant: Olympus Biotech International Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Assessment of the final PSUR for eptotermin alfa following the conclusions of procedure PSUSA/00001247/201509 adopted by PRAC in May 2016 and following EC decisions of MA withdrawal

[61] For systemic use only
[62] For ophthalmic and otic use only
[63] EC decision of MA withdrawal dated 30/06/2016
[64] EC decision of MA withdrawal dated 16/12/2015

16.4.3. Colesevelam - CHOLESTAGEL (CAP) - EMEA/H/C/000512/LEG 031.1

Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Review on improving the ease of administration due to the increased number of cases reporting 'drug administration error' between the two most recent PSURs, in particular cases where tablets were either crushed or cut as requested in the conclusions of EMEA/H/C/PSUSA/00000864/201503 adopted by PRAC in October 2015

16.4.4. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/LEG 050.2

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Qun-Ying Yue

Scope: The MAH's response to LEG 050.1 [venous thromboembolism (VTE) cumulative review as requested in the conclusions of EMEA/H/C/PSUSA/00002214/201412 adopted by the PRAC in July 2015] as per the request for supplementary information (RSI) adopted in May 2016

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[65]

17.1.1. Brentuximab vedotin – ADCETRIS (CAP) - EMEA/H/C/PSA/0009

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Submission of an amended PASS protocol for study MA25101: an observational cohort study of the safety of brentuximab vedotin in the treatment of relapsed or refractory CD30+ Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) (study referenced in SOB 008 and SOB 009; initial protocol endorsed by PRAC in May 2014 (EMEA/H/C/002455/SOB 008))

17.1.2. Eliglustat – CERDELGA (CAP) - EMEA/H/C/PSP/S/0047.1

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised PASS protocol for registry study OBS14099: a prospective, multicentre, observational post authorisation safety sub-registry to characterize the long-term safety profile of eliglustat of adult patients with Gaucher disease as per the request for

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

supplementary information (RSI) adopted at PRAC in July 2016

17.1.3. Glycerol phenylbutyrate – RAVICTI (CAP) - EMEA/H/C/PSP/S/0048.1

Applicant: Horizon Pharma Ireland Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Revised PASS protocol for a multicentre prospective non-interventional registry in patients with urea cycle disorders on treatment with glycerol phenylbutyrate to characterise patients' demographics, and to document long-term safety and clinical outcomes as per the request for supplementary information (RSI) adopted at PRAC in July 2016

17.1.4. Levofloxacin – QUINSAIR (CAP) - EMEA/H/C/PSP/S/0049.1

Applicant: Raptor Pharmaceuticals Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised PASS protocol for an open-label, observational safety study of Quinsair (nebulised levofloxacin hemihydrate) in patients with cystic fibrosis and chronic *Pseudomonas Aeruginosa* infection, using data collected through European cystic fibrosis registries as per the request for supplementary information (RSI) adopted at PRAC in July 2016

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[66]

17.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.1

Applicant: Genzyme Therapeutics Ltd.

PRAC Rapporteur: Torbjorn Callreus

Scope: Revised PASS protocol for study OBS13434: a prospective, multicentre, observational, PASS to evaluate the long term safety profile of alemtuzumab treatment in patients with relapsing forms of multiple sclerosis (RMS) as per the request for supplementary information (RSI) adopted in May 2016

17.2.2. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 019.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 019 [Protocol for a drug utilisation study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low low-density lipoprotein (LDL)-C levels (study OBS14697)] as per the request for supplementary information (RSI) adopted in July 2016

17.2.3. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 007

Applicant: Janssen-Cilag International N.V.

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

PRAC Rapporteur: Valerie Strassmann

Scope: 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)

17.2.4. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 008

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Retrospective, observational cohort study protocol, using 4 administrative claims databases, to assess the incidence of diabetic ketoacidosis among patients with Type 2 diabetes mellitus treated with canagliflozin-containing medicines or other antihyperglycemic agents

17.2.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 006

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Non-clinical mechanistic study protocol in dogs to investigate the mechanism behind canagliflozin-containing medicines induced diabetic ketoacidosis occurrence, as an 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)

17.2.6. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 007

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Retrospective, observational cohort study protocol, using administrative claims databases, to assess the incidence of diabetic ketoacidosis among patients with type 2 Diabetes Mellitus treated with canagliflozin-containing medicines or other antihyperglycemic agents.

17.2.7. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/MEA 001

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Leonor Chambel

Scope: PASS protocol for study entitled 'survey of the effectiveness of Darzalex educational materials regarding the minimisation of risk of interference for blood typing with daratumumab'

17.2.8. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/MEA 067

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Claire Ferard

Scope: PASS protocol and questionnaire for a cross sectional physician survey (study N6987) to assess the impact of educational materials on prescribers' awareness of doses and biological monitoring recommendations and also to assess the awareness and appropriate use of both formulations (orodispersible tablets and film-coated tablets) as requested as part of X/43 (category 3 study in the RMP)

17.2.9. Migalastat - GALAFOLD (CAP) - EMEA/H/C/004059/MEA 001

Applicant: Amicus Therapeutics UK Ltd.

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol for a registry: prospective, multicentre, multinational, observational disease registry in Fabry disease patients treated with migalastat and untreated patients) to evaluate the long-term safety and effectiveness of migalastat in Fabry disease patients in real-world setting

17.2.10. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 003

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: PASS protocol for a study to evaluate risk minimisation measures for mEDication errors with Uptravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in Clinical prAcTicE (EDUCATE), protocol number: AC-065A403 version 1

17.2.11. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 025

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Valerie Strassmann

Scope: PASS protocol to evaluate the effectiveness of risk minimisation measures: a survey among healthcare professionals and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of velaglucerase alfa in 6 European countries as per the conclusions of variation EMEA/H/C/001249/II/0029 dated April 2016

17.3. Results of PASS imposed in the marketing authorisation(s)[67]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[68]

17.4.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/II/0031; VALDOXAN (CAP) - EMEA/H/C/000915/II/0033

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

[67] In accordance with Article 107p-q of Directive 2001/83/EC
[68] 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

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of the final study report for study CLE-20098-095: 'HLA alleles as genetic risk factors for elevation of aminotransferase levels in patients treated with agomelatine'. The product information and RMP remain unchanged

17.4.2. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/II/0093

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final clinical study report for PASS 1160.149: observational study to evaluate the effectiveness of the risk minimisation activities in the treatment of stroke prevention in atrial fibrillation (SPAF) in order to address part of follow-up measure MEA 026. The RMP (version 31.6) is updated accordingly

17.4.3. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS1028/0027; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS1028/0023

Applicant: Glaxo Group Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of study HZA107112 (a randomised, double-blind, two-way crossover study to investigate the effect of inhaled fluticasone furoate on short-term lower-leg growth in paediatric subjects with asthma) to investigate the important potential risk of growth retardation in children. This study was conducted as part of the paediatric investigational plan (EMEA-000431-PIP01-08). In addition, the RMP (version 8.2) is updated to amend the due date for drug utilisation study 205052

17.4.4. Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/II/0019

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final clinical study report (CSR) for a non-interventional PASS: a retrospective database study of glucagon-like peptide-1 (GLP-1) receptor agonists and risk of acute pancreatitis, pancreatic cancer and thyroid cancer in particular medullary thyroid cancer, a category 3 study in order to fulfil MEA 007.2

17.4.5. Olanzapine - ZYPADHERA (CAP) - EMEA/H/C/000890/II/0032

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final study report of the PASS: post-injection syndrome in patients with schizophrenia receiving olanzapine long-acting injection. The RMP (version 12) is updated accordingly

17.4.6. Regadenoson - RAPISCAN (CAP) - EMEA/H/C/001176/II/0023

Applicant: Rapidscan Pharma Solutions EU Ltd.

PRAC Rapporteur: Julie Williams

Scope: Submission of study report 01-1-401 to assess the safety profile of Rapiscan (regadenoson) in patients with liver impairment and to observe common adverse events reported in the post marketing setting

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[69]

17.5.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 046.6

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Seventh annual interim report of the registry in juvenile idiopathic arthritis (JIA) patients (P10-262: a long-term, multicentre, longitudinal post-marketing, observational study to assess long term safety and effectiveness of Humira (adalimumab) in children with moderately to severely active polyarticular or polyarticular-course JIA - STRIVE) (due date: final registry report 31 December 2021)

17.5.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 065.6

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

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

17.5.3. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 075.5

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth annual interim study report Humira ulcerative colitis registry (P11-282): a long-term non-interventional postmarketing study to assess safety and effectiveness of Humira (adalimumab) in patients with moderately to severely active ulcerative colitis (UC)

17.5.4. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 080.4

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second annual interim report (P11-292 registry) from 'a long-term non-interventional registry to assess safety and effectiveness of Humira (adalimumab) in

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

paediatric patients with moderately to severely active Crohn's disease (CD) CAPE'

17.5.5. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 056.1

Applicant: Genzyme Europe BV

PRAC Rapporteur: Claire Ferard

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

17.5.6. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.1

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 002 on the interim report for a long-term observational study of ataluren safety and effectiveness in usual care (protocol PTC124-GD-025o-DMD)] as per the request for supplementary information (RSI) adopted in July 2016

17.5.7. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/MEA 011.4

Applicant: Pfizer Limited

PRAC Rapporteur: Claire Ferard

Scope: Second interim report for study A8081038 to estimate the incidence rate and incidence proportion over a 3-year period of observation for hepatotoxicity, pneumonitis/interstitial lung disease (ILD), QTc prolongation related events, bradycardia, and visual disorder among lung cancer patients receiving crizotinib prescriptions as per the request for supplementary information (RSI) adopted by PRAC and CHMP in September 2015

17.5.8. Data collection on adverse events of anti-HIV[70] drugs (D:A:D) study - PRAC evaluation of D:A:D data merger results

Applicant: various

PRAC Representatives: Filip Josephson, Deborah Ashby

Scope: Evaluation of the sixteenth data merger

17.5.9. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/MEA 004

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Progress report for study GENA-99: prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice

[70] Human immunodeficiency virus

17.6. Other

17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 009

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Feasibility assessment to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in Type 1 Diabetes Mellitus, using 3 EU databases (United Kingdom, Spain and Italy)

17.6.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 008

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Feasibility assessment to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus, using 3 EU databases (United Kingdom, Spain and Italy)

17.6.3. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 008

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Feasibility assessment regarding prospective plasma hormone sampling (e.g. insulin, glucagon and incretin) in new or ongoing clinical trials, as an 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)

17.6.4. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 005

Applicant: Boehringer Ingelheim GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Feasibility assessment regarding prospective plasma hormone sampling (e.g. insulin, glucagon and incretin) in new or ongoing clinical trials, as an 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)

17.6.5. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 026

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Valerie Strassmann

Scope: Update of RMP Annex 7 (inclusion of the updated Laboratory test requisition form for antibody testing as per conclusions EMEA/H/C/001249/II/0029 dated 28 April 2016)

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. Antithrombin alfa - ATRYN (CAP) - EMEA/H/C/000587/S/0028 (without RMP)

Applicant: GTC Biotherapeutics UK Limited

PRAC Rapporteur: Claire Ferard

Scope: Annual reassessment of the marketing authorisation

18.1.2. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0011 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: Annual reassessment of the marketing authorisation

18.1.3. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0065 (without RMP)

Applicant: BioMarin Europe Ltd.

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/R/0023 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

18.2.2. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0023 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Docetaxel - DOCETAXEL ACCORD (CAP) - EMEA/H/C/002539/R/0030 (without RMP)

Applicant: Accord Healthcare Ltd.

PRAC Rapporteur: Claire Ferard

Scope: 5-year renewal of the marketing authorisation

18.3.2. Docetaxel - DOCETAXEL KABI (CAP) - EMEA/H/C/002325/R/0015 (with RMP)

Applicant: Fresenius Kabi Oncology Plc

PRAC Rapporteur: Claire Ferard

Scope: 5-year renewal of the marketing authorisation

18.3.3. Follitropin alfa, lutropin alfa - PERGOVERIS (CAP) - EMEA/H/C/000714/R/0050 (without RMP)

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

Action: For adoption of advice to CHMP

18.3.4. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/R/0091 (without RMP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: 5-year renewal of the marketing authorisation

18.3.5. Pioglitazone - PIOGLITAZONE TEVA (CAP) - EMEA/H/C/002297/R/0016 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.6. Pioglitazone - PIOGLITAZONE TEVA PHARMA (CAP) - EMEA/H/C/002410/R/0013 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Almath Spooner

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 28 November - 1 December 2016 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
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callréus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Claire Ferard	Member	France	No interests declared	Full involvement
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Leonidas Klironomos	Member	Greece	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Zane Stade	Alternate	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Alternate	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Helga Haugom Olsen	Member	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Leonor Chambel	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani	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
Flora Musuamba Tshinanu	Expert - via telephone*	Belgium	No interests declared	Full involvement
José Javier Sawchik Monegal	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Nathalie Morgensztejn	Expert - via telephone*	France	No interests declared	Full involvement
Simone Bergner	Expert - via telephone*	Germany	No interests declared	Full involvement
Thomas Grüger	Expert - via telephone*	Germany	No interests declared	Full involvement
Tania Meier	Expert - via telephone*	Germany	No interests declared	Full involvement
Niamh Buckley	Expert - in person*	Ireland	No interests declared	Full involvement
Anna Marie Coleman	Expert - via telephone*	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Else Carrière	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Quirine Fillekes	Expert - in person*	Netherlands	No interests declared	Full involvement
Reynold Francisca	Expert - in person*	Netherlands	No interests declared	Full involvement
Eirik Hagtvet	Expert - via telephone*	Norway	No interests declared	Full involvement
Anna-Lena Axelson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Bengt Ljungberg	Expert - via	Sweden	No interests	Full

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	involvement
Helena Möllby	Expert - via telephone*	Sweden	No interests declared	Full involvement
Janet Post	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Annika Ekbom Schnell	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Craig Allen	Expert - in person*	United Kingdom	No interests declared	Full involvement
Patrick Batty	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Philip Bryan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Claire Davies	Expert - in person*	United Kingdom	No interests declared	Full involvement
Katherine Donegan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Richard Gilson	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Anna Radecka	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

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, 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:

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/