



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 September 2016
EMA/PRAC/693633/2016
Inspections, Human Medicines Pharmacovigilance & Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes from the meeting on 30 August – 02 September 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 scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the PRAC meeting highlights once the procedures are finalised.

Of note, the minutes are a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).



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1. Introduction

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

The Chairperson opened the 30 August-2 September 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 advice were agreed unanimously, unless otherwise specified.

The PRAC Chair welcomed Helga Haugom Olsen, replacing Ingebjørg Buajordet, as the new member for Norway. The Committee thanked Ingebjørg Buajordet for her dedicated service over many years.

The PRAC noted that the European Commission (EC) adopted a report on 'Pharmacovigilance related activities of Member States and the European Medicines Agency concerning medicinal products for human use (2012-2014)' on 8 August 2016 ([COM\(2016\) 498 final](#)). The PRAC Members were thanked by the EC services for their contributions to the report which concludes that the European pharmacovigilance network is an example of successful cooperation at EU level which directly benefits patients.

1.2. Adoption of agenda of the meeting of 30 August-02 September 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 04-08 July 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 4-8 July 2016 were published on the EMA website on 23 September 2016 ([EMA/PRAC/632773/2016](#)).

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

None

3.2. Ongoing procedures

3.2.1. 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 oral and topical retinoid-containing medicines (acitretin; adapalene; alitretinoin; bexarotene; isotretinoin; tazarotene; tretinoin), indicated for the treatment of several conditions

mainly affecting the skin such as acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders¹, to evaluate measures currently in place for pregnancy prevention and for minimising the possible risk of neuropsychiatric disorders. For further background, see [PRAC minutes July 2016](#).

The PRAC was informed that further to the list of questions to MAHs adopted during last PRAC meeting in July 2016, GSK requested an extension of the deadline for providing a response to the list of questions (LoQ).

Moreover, the PRAC was informed of the UK's request to consider whether a public hearing should be held in context of this procedure.

Summary of recommendation(s)/conclusions

- In relation to the request to extend the deadline for providing a response to the LoQ, the PRAC considered that it was important to proceed as per already established timelines and supported maintaining the agreed timetable.
- With regard to the UK's request, the PRAC will further discuss the option of conducting a public hearing in the context of the procedure on retinoid-containing medicinal products at its October 2016 PRAC meeting (scheduled on 26-29 September).

3.3. Procedures for finalisation

None

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

None

3.5. Others

None

4. Signals assessment and prioritisation²

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I. 14.1.

4.1.1. Esomeprazole – NEXIUM CONTROL (CAP), NAP

Applicants: Pfizer Consumer Healthcare Ltd (Nexium Control), various

¹ Tretinoin may also be used to treat promyelocytic leukaemia

² 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

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of gastric polyps

EPITT 18725 – New signal

Lead Member States: LT, SE

Background

Esomeprazole is a proton pump inhibitor (PPI) indicated for the short-term treatment of gastro-oesophageal reflux disease (GORD) and erosive reflux oesophagitis and as a prolonged treatment after intravenous (i.v.) induced prevention of rebleeding of peptic ulcers. Esomeprazole is also used in the treatment of Zollinger Ellison syndrome in some Member States.

The exposure for esomeprazole (as oral formulation) has been estimated by MAH AstraZeneca to be approximately 116 million patient-years worldwide, in the period from March 2011 to March 2016.

During routine signal detection activities, a signal of gastric polyps was identified by the EMA, based on eight cases from EudraVigilance, including five available in the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the cases of gastric polyps and concurred that a plausible pathophysiologic mechanism could not be excluded. In addition, a positive dechallenge was observed in three cases of fundic gland polyps (FGP). The PRAC agreed to assess further the potential risk of gastric polyps associated with the prolonged use of esomeprazole and other proton pump inhibitors (PPI). Further data from EudraVigilance and relevant literature as well as available clinical guidance, will be assessed within a 60 day timetable.

The PRAC appointed Qun-Ying Yue as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed that the Rapporteur shall assess further data from EudraVigilance and relevant literature as well as available clinical guidance regarding the potential risk of gastric polyps associated with the prolonged use of esomeprazole and other proton pump inhibitors (PPI).
- 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 also Annex I. 14.2.

4.2.1. Propofol (NAP); valproate (NAP)

Applicant: various

PRAC Rapporteur: Helga Haugom Olsen

Scope: Signal of pharmacokinetic drug interaction leading to an increased propofol

exposure

EPITT 18696 – New signal

Lead Member State: NO

Background

Propofol is a short-acting anaesthetic agent with a rapid onset of action indicated for induction and maintenance of general anaesthesia, for sedation for diagnostic and surgical procedures and for sedation of ventilated patients (> 16 years) in the intensive care unit (ICU).

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

As part of a variation procedure³ submitted by MAH Sanofi-aventis in order to amend the product information of its valproate-containing medicinal products with new information on interaction with propofol based on a literature article by *Sayar et al.*⁴, also based on further two studies by *Ethell BT et al.*⁵ and *Ishii M et al.*⁶, Germany raised a signal of pharmacokinetic drug interaction leading to a decrease in the dose of propofol required during anaesthetised electroconvulsive therapy (ECT).

Norway confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the literature on the influence of valproate on the required dose of propofol and requested a cumulative review of all cases of suspected interaction between valproate and propofol with a view to amending the product information for propofol-containing medicines.

The PRAC appointed Helga Haugom Olsen as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for the originator-product containing propofol (Diprivan) should submit to the EMA, within 60 days, a cumulative review of all cases of suspected interaction between propofol and valproate, including a review of the published literature, clinical trials and post-marketing experience, and provide an analysis on possible mechanisms for the interaction as well as a proposal for amending the product information and/or RMP as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

³ Assessed at national level

⁴ Hızlı Sayar G, Eryılmaz G, Semieoğlu S, Ozten E, Göğceğöz Gül. Influence of valproate on the required dose of propofol for anesthesia during electroconvulsive therapy of bipolar affective disorder patients. *Neuropsychiatr Dis treat.* 2014; 10: 433-8

⁵ Ethell BT, Anderson GD, Burchell B. The effect of valproic acid on drug and steroid glucuronidation by expressed human Uridine 5'-diphospho (UDP)-glucuronosyltransferases. *Biochem Pharmacol.* 2003; 65: 1441-9

⁶ Ishii M, Higuchi H, Maeda S, Tomoyasu Y, Egusa M, Miyawaki T. The influence of oral valproate (VPA) on the required dose of propofol for sedation during dental treatment in patients with mental retardation: a prospective observer-blinded cohort study. *Epilepsia.* 2012; 53: e13-e6

4.2.2. 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: Rafe Suvarna

Scope: Signal of incident chronic kidney disease (CKD) and progression to end stage renal disease (ESRD)

EPITT 18698 – New signal

Lead Member State: UK

Background

Proton pump inhibitors (PPIs) are indicated for the treatment of gastroesophageal reflux disease, gastric and duodenal ulcer, Zollinger-Ellison syndrome, and in combination with antibiotics for the eradication of *Helicobacter pylori*.

Following a recent publication by Xie Y *et al.*⁷ in the Journal of American Society of Nephrology, a signal of incident chronic kidney disease (CKD) and progression to end stage renal disease (ESRD) was identified by Belgium suggesting that the use of proton pump inhibitors (PPI) is associated with increased risks for incident CKD, CKD progression and ESRD. The United Kingdom confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the results from three large observational studies (*Lazarus et al.*⁸, *Xie et al.*⁷, *Arora et al.*⁹) on the risk of incident CKD and progression to ESRD and agreed to request the MAHs for PPIs to provide a cumulative review of all events of CKD, events of terms from MedDRA SOC¹⁰ 'investigations' relevant for kidney function and data on kidney function measurements from all clinical trials in which estimated glomerular filtration rate (eGFR) or alternatives measurements have been captured, including clinical trial meta-analyses where available, regarding PPI versus comparator. The MAHs should provide a proposal for amending their product information and/or RMP as applicable.

The PRAC appointed Rafe Suvarna as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for pantoprazole-, lansoprazole-, dexlansoprazole-, rabeprazole-, omeprazole- and esomeprazole-containing products (Takeda, Janssen-Cilag, Eisai, AstraZeneca) should submit to the EMA, within 60 days, a cumulative review of all cases of CKD and progression to ESRD, including all MedDRA SOC investigations, related terms relevant to kidney function and data on kidney function measurements

⁷ Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J Am Soc Nephrol. Published online April 14, 2016.

⁸ Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016 Feb 1; 176(2):238-46

⁹ Arora P, Gupta A, Golzy M, Patel N, Carter RL, Jalal K, Lohr JW. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. BMC Nephrol. 2016 Aug 3; 17(1): 112

¹⁰ Medical dictionary for regulatory activities - System organ class

from all clinical trials that have measured the eGFR (or creatinine clearance or other measures of renal function). In addition, the MAHs should submit a proposal for amending the product information and/or the RMP as applicable.

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

4.3. Signals follow-up and prioritisation

4.3.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/SDA/028; VALDOXAN (CAP) - EMEA/H/C/000915/SDA/028

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

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Signal of urinary retention

EPITT 18637 – Follow-up to April 2016

Background

For background information, see [PRAC minutes April 2016](#).

The MAH for agomelatine-containing products replied to the request for information on the signal of urinary retention and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, and the data submitted by the MAH, the PRAC agreed that the product information should be amended with respect to this signal of urinary retention.

Summary of recommendation(s)

- The MAH for Thymanax and Valdoxan (agomelatine) should submit to the EMA, within 60 days, a variation to amend the product information to add 'urinary retention' as an undesirable effect with a rare frequency.

For the full PRAC recommendation, see [EMA/PRAC/551805/2016](#) published on 26/09/2016 on the EMA website.

4.3.2. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/SDA/029; VALDOXAN (CAP) - EMEA/H/C/000915/SDA/029

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

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Signal of leukopenia

EPITT 18638 – Follow-up to April 2016

Background

For background information, see [PRAC minutes April 2016](#).

The MAH for agomelatine-containing products replied to the request for information on the signal of leukopenia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from clinical trials, non-clinical studies, case reports in EudraVigilance as well as data submitted by the MAH, the PRAC agreed that a causal association between agomelatine and leukopenia/neutropenia or thrombocytopenia could not be established. Therefore, the PRAC concluded that no update of the product information was warranted at present. Nevertheless, the PRAC concurred that it was not possible either to exclude a causal relationship with agomelatine. Thus, the PRAC recommended close monitoring of leukopenia/neutropenia for agomelatine-containing products and any new cases should be presented in future PSURs. Moreover, thrombocytopenia should be monitored as part of routine safety surveillance.

Summary of recommendation(s)

- The MAH for Thymanax and Valdoxan (agomelatine) should submit to the EMA any new cases of leukopenia/neutropenia in next PSURs and should continue to monitor thrombocytopenia as part of routine safety surveillance.

4.3.3. Boceprevir – VICTRELIS (CAP); daclatasvir – DAKLINZA (CAP); dasabuvir – EXVIERA (CAP); elbasvir, grazoprevir – ZEPATIER (CAP); ledipasvir, sofosbuvir – HARVONI (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatavir – EPCLUSA (CAP)

Applicants: AbbVie Ltd (Exviera, Viekirax), Bristol-Myers Squibb Pharma EEIG (Daklinza), Gilead Sciences International Ltd (Epclusa, Harvoni, Sovaldi), Janssen-Cilag International N.V. (Olysio), Merck Sharp & Dohme Limited (VICTRELIS, Zepatier)

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of drug interaction between direct-acting antivirals (DAAV) and vitamin K antagonists leading to a reduced international normalised ratio (INR)

EPITT 18654 – Follow-up to June 2016

Background

For background information, see [PRAC minutes June 2016](#).

The MAHs provided comments on the wording proposed by PRAC for the product information and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from case reports and the biological plausibility of changes in international normalised ratio (INR) in patients treated with direct-acting antivirals (DAAV) against hepatitis C and vitamin K antagonists due to changes in liver function, and taking into consideration the responses from MAHs, the PRAC considered that the product information of DAAV against hepatitis C (Daklinza, Exviera, Harvoni, Olysio, Sovaldi, Victrelis, Viekirax, Epclusa, Zepatier) should be updated to recommend that close monitoring of INR values is conducted when DAAV are administered with vitamin K antagonists.

Summary of recommendation(s)

- The MAHs for direct-acting antivirals against hepatitis C (Daklinza (daclatasvir),

Epclusa (sofosbuvir/velpatasir), Exviera (dasabuvir), Harvoni (ledipasvir/sofosbuvir), Olysio (simeprevir), Sovaldi (sofosbuvir), Victrelis (boceprevir), Viekirax (ombitasvir/paritaprevir/ritonavir) and Zepatier (elbasvir/grazoprevir)) should submit to the EMA, within 60 days, a variation to amend their product information to recommend close monitoring of international normalised ratio (INR) values in patients treated with vitamin K antagonists.

For the full PRAC recommendation, see [EMA/PRAC/551805/2016](https://www.ema.europa.eu/en/press-room/2016/09/W161600001) published on 26/09/2016 on the EMA website.

4.3.4. Cobicistat-containing products:
cobicistat – TYBOST (CAP); cobicistat, atazanavir sulfate – EVOTAZ (CAP); cobicistat, darunavir – REZOLSTA (CAP); cobicistat elvitegravir, emtricitabine, tenofovir alafenamide – GENVOYA (CAP); cobicistat elvitegravir, emtricitabine, tenofovir disoproxil fumarate – STRIBILD (CAP); NAP

Applicants: Gilead Sciences International Ltd (Genvoya, Stribild, Tybost), Bristol-Myers Squibb Pharma EEIG (Evotaz), Janssen-Cilag International N.V. (Rezolsta)

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of drug interaction with corticosteroids leading to adrenal suppression

EPITT 18647 – Follow-up to April 2016

Background

For background information, see [PRAC minutes April 2016](#).

The MAHs replied to the request for information on the signal of drug interaction with corticosteroids leading to adrenal suppression and the responses were assessed by the Rapporteur.

Discussion

Having considered the recommendations for risk minimisation provided by the MAHs Bristol-Myers Squibb and Janssen-Cilag as well as the data provided by the MAH Gilead that indicated a low reporting rate for events of adrenal suppression/insufficiency and Cushing's syndrome occurring in relation to co-administration of corticosteroids with cobicistat-containing products, the PRAC concurred that the addition of a warning is not warranted in light of the current knowledge and evidence. Nevertheless, the PRAC agreed that the wording of section 4.5 on 'interaction with other medicinal products and other forms of interaction' of the product information of cobicistat-containing products should be strengthened to indicate that cases of adrenal suppression and Cushing's syndrome have been identified following interaction with concomitant administration of corticosteroids. In addition, the PRAC considered that the product information of all corticosteroids-containing products (excluding cutaneous formulations) should be updated to reflect this interaction accordingly.

Summary of recommendation(s)

- The MAHs for cobicistat-containing products (Evotaz, Rezolsta, Genvoya, Stribild, Tybost) should submit to the EMA, within 60 days, a variation to amend their product information to indicate that cases of adrenal suppression and Cushing's syndrome have been identified following interaction between corticosteroids and cobicistat.

- The MAHs of corticosteroid-containing medicines (excluding cutaneous formulations) should submit, within 90 days, to the EMA or to national competent authorities of the Member States as applicable, a variation to update the product information to reflect that co-treatment with CYP3A¹¹ inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The concomitant administration of cobicistat with a corticosteroid should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

For the full PRAC recommendation, see [EMA/PRAC/551805/2016](#) published on 26/09/2016 on the EMA website.

Post-meeting note: The amendments of the product information for corticosteroids will be further reviewed by PRAC at its November 2016 meeting (scheduled on 24-27 October). A further PRAC recommendation will be adopted.

4.3.5. Iomeprol (NAP)

Applicant: various

PRAC Rapporteur: Helga Haugom Olsen

Scope: Signal of haemolysis

EPITT 18625 – Follow-up to April 2016

Background

For background information, see [PRAC minutes April 2016](#).

The MAH replied to the request for information on the signal of haemolysis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, the literature and the data submitted by the MAH(s), the PRAC agreed that the product information of iomeprol-containing products should be amended to include haemolytic anaemia as an undesirable effect.

Summary of recommendation(s)

- The MAHs for iomeprol-containing products should submit to national competent authorities of the Member States, within 60 days, a variation amending the product information to add haemolytic anaemia as an undesirable effect with an unknown frequency.

For the full PRAC recommendation, see [EMA/PRAC/551805/2016](#) published on 26/09/2016 on the EMA website.

4.3.6. Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); mirtazapine (NAP); paroxetine (NAP); sertraline (NAP) Serotonin–noradrenaline reuptake inhibitors (SNRIs): duloxetine - ARICLAIM

¹¹ Cytochrome P450 3A4

Applicants: Eli Lilly Nederland B.V. (Ariclaim, Cymbalta, Duloxetine Lilly, Xeristar, Yentreve), various

PRAC Rapporteur: Claire Ferard

Scope: Signal of risk of autistic spectrum disorders (ASD) after in utero exposure to selective serotonin reuptake inhibitors (SSRI)

EPITT 14082 – Follow-up to May 2016

Background

In May 2016, the PRAC considered the available evidence provided by the MAHs on neurodevelopmental disorders including autism spectrum disorders (ASD), reported after use of selective serotonin reuptake inhibitors (SSRI)/serotonin–noradrenaline reuptake inhibitors (SNRI) during pregnancy. The PRAC noted that the results from available studies illustrate the issue of confounding by indication and the importance of considering hereditary factors and environmental influences. The apparent link between SSRI and ASD is judged, on the basis of the current evidence, to be likely because of factors other than SSRIs themselves. For further background, see [PRAC minutes May 2016](#).

Discussion

The PRAC considered the critical review of evidence on the risk of ASD following maternal exposure to SSRI antidepressants during pregnancy and agreed that the current evidence does not support a causal association. The PRAC agreed that the available studies on the risk of ASD after in utero exposure to SSRIs are conflicting, in part due to different study designs and study populations chosen for analysis. Those studies which did show an increased risk are studies where there were a number of limitations such as hereditary factors and environmental influences as well as important confounders (severity of depression, paternal history of psychiatric disorders). On the other hand, better quality sibling designed studies which controlled for all time-fixed confounding such as genetics were not supportive of an increased risk. Methodologically the PRAC agreed that the sibling study design appears to be the most appropriate to examine such risks in relation to exposure during pregnancy.

Summary of recommendation(s)

- The MAH for all SSRI- and SNRI-containing medicines should continue to monitor neurodevelopmental disorders, including autism spectrum disorders, following in utero exposure, as part of routine safety surveillance.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I. 15.1.

5.1.1. Aceneuramic acid - EMEA/H/C/004176, Orphan

Applicant: Ultragenyx UK Limited

Scope: Treatment of hereditary inclusion body myopathy (HIBM)

5.1.2. Adalimumab - EMEA/H/C/004212; EMEA/H/C/004373

Scope: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease and ulcerative colitis

5.1.3. Alectinib - EMEA/H/C/004164

Scope: Treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive

5.1.4. Brodalumab – EMEA/H/C/003959

Scope: Treatment of moderate to severe plaque psoriasis

5.1.5. Chlormethine - EMEA/H/C/002826, Orphan

Applicant: Actelion Registration Ltd

Scope: Treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL)

5.1.6. Eryaspase - EMEA/H/C/004055, Orphan

Applicant: Erytech Pharma S.A.

Scope: Treatment of leukaemia

5.1.7. Insulin aspart - EMEA/H/C/004046

Scope: Treatment of diabetes mellitus in adults

5.1.8. Insulin glargine -- EMEA/H/C/004101

Scope: Treatment of diabetes mellitus

5.1.9. Lonoctocog alfa - EMEA/H/C/004075

Scope: Treatment of haemophilia A

5.1.10. Lutetium (¹⁷⁷Lu) dotatate - EMEA/H/C/004123, Orphan

Applicant: Advanced Accelerator Applications

Scope (accelerated assessment): Treatment of gastro-entero-pancreatic neuroendocrine tumours

5.1.11. Nonacog beta pegol – EMEA/H/C/004178, Orphan

Applicant: Novo Nordisk A/S

Scope: Treatment of haemophilia B

5.1.12. Tenofovir alafenamide - - EMEA/H/C/004169

Scope: Treatment of chronic hepatitis B in adults

5.1.13. Teriparatide - EMEA/H/C/004368; EMEA/H/C/003916

Scope: Treatment of osteoporosis

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

See Annex I. 15.2.

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

See also Annex I. 15.3.

5.3.1. Conestat alfa - RUCONEST (CAP) - EMEA/H/C/001223/X/0034

Applicant: Pharming Group N.V

PRAC Rapporteur: Rafe Suvarna

Scope: Addition of a new pharmaceutical form 'powder and solvent for solution for injection' with self-administration kit

Background

Conestat alfa is a haematological agent indicated for the treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.

The CHMP is evaluating a line extension for Ruconest, a centrally authorised product containing conestat alfa, to add a new pharmaceutical form 'powder and solvent for solution for injection' with self-administration kit. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this line extension procedure.

Summary of advice

- The RMP version 14.0 for Ruconest (conestat alfa) in the context of the variation

under evaluation by the CHMP could be acceptable provided that satisfactory responses to a request for supplementary information are received.

- The PRAC considered that the existing registry protocol¹² should be updated to allow adequate focus on the study in terms of potential adverse events related to self-administration, related adverse drug reactions (ADRs) and self-administration related medication errors. In addition, the MAH should include a clearly defined secondary objective on self-administration related ADRs and self-administration related medication errors in order to allow data comparisons, as well as on adverse events of special interest (AESIs) to cover self-administration related ADRs and self-administration related medication errors. Furthermore, the MAH should include a plan to stratify the registry data by home/self-treatment and clinical setting groups, and perform a separate analysis of the registry data on all ADR self-administration related ADRs and self-administration related medication errors; and finally update the treatment questionnaire to further contribute to the evaluation of the effectiveness of conestat alfa in the real world setting taking into account adverse events related to self-administration.

5.3.2. Florbetapir (¹⁸F) - AMYVID (CAP) - EMEA/H/C/002422/II/0022

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to introduce quantitative read as an adjunct to visual read of florbetapir (¹⁸F) positron emission tomography (PET) scans. The RMP (version 2.0) is updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10.0)

Background

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

The CHMP is evaluating a type II variation for Amyvid, a centrally authorised product containing florbetapir (¹⁸F), to include quantitative read as an adjunct to visual read of florbetapir (¹⁸F) positron emission tomography (PET) scans. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 2.0 for Amyvid (florbetapir (¹⁸F)) in the context of the variation under evaluation by the CHMP could be acceptable provided that satisfactory responses to a request for supplementary information are received.
- The PRAC considered that the MAH should continue to offer both in-person and online training as per agreement of the educational material with the responsible national

¹² C1 inhibitor treatment registry to assess the safety and immunological profile of Ruconest in the treatment of hereditary angioedema (HAE) attacks

competent authorities and provide further clarification and discussion on the planned updates of educational material, the status of training of physicians in EU Member States and the impact of the new reading method on the ongoing study evaluating the effectiveness of Amyvid reader training.

5.3.3. Tadalafil - ADCIRCA (CAP) - EMEA/H/C/001021/WS0993/0025, CIALIS (CAP) - EMEA/H/C/000436/WS0993/0085

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 4.4 of the SmPC in order to add a new warning on the risk of non-arteritic anterior ischemic optic neuropathy (NAION) based on the final results of study H6D-MC- LVHQ (category 3 study). In addition, the RMP (version 8.0) is updated accordingly

Background

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) indicated for the treatment of erectile dysfunction in adult males (Cialis) and in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (Adcirca).

The CHMP is evaluating a type II worksharing variation procedure for Adcirca and Cialis, centrally authorised products containing tadalafil, to add a new warning on the risk of non-arteritic anterior ischemic optic neuropathy (NAION) based on the final results of study H6D-MC- LVHQ¹³ (category 3 study). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 8.0 for Adcirca and Cialis (tadalafil) in the context of the type II worksharing variation procedure under evaluation by the CHMP could be acceptable provided that satisfactory responses to a request for supplementary information are received.
- The PRAC agreed that the potential risk of NAION should be maintained in the RMP for all indications. The PRAC suggested some amendments on the wording in the warnings section for the consideration of the CHMP Rapporteur to clarify that NAION could occur with exposure to tadalafil, regardless of the therapeutic indication.

6. Periodic safety update reports (PSURs)

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

See also Annex I. 16.1.

¹³ Prospective case crossover study including subjects taking tadalafil, sildenafil and vardenafil for erectile dysfunction (ED)

6.1.1. Acridinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/00009005/201601

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Acridinium bromide is an anticholinergic indicated 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 risk-benefit balance of Bretaris Genuair and Eklira Genuair, centrally authorised medicines containing acridinium bromide, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bretaris Genuair and Eklira Genuair (acridinium bromide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'anaphylactic reaction' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied¹⁴.
- The MAH should submit to the EMA, within 60 days, a detailed review of the scientific evidence to support its proposal to amend the existing contraindications of the product information on 'hypersensitivity to acridinium bromide, atropine and its derivatives including ipratropium, oxitropium or tiotropium' and 'hypersensitivity to acridinium bromide or to excipients'.
- In the next PSUR, the MAH should submit cumulative reviews of pneumonia and related events, falls, fractures and related events and also provide a discussion of the frequency of drug dose omission events including any pattern of concern.

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. Agomelatine - THYMANAX (CAP); VALDOXAN (CAP) - PSUSA/00000071/201602

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

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

Background

Agomelatine is a melatonergic agonist (MT₁ and MT₂ receptors) and 5-HT_{2C} antagonist

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

indicated for the treatment of adults with major depressive episodes.

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of Thymanax and Valdoxan, centrally authorised medicines containing agomelatine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Thymanax and Valdoxan (agomelatine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning to reflect that treatment with agomelatine should only be prescribed after careful consideration in patients with alcohol use disorder. In addition, 'akathisia' should be added as undesirable effect with a rare frequency. Finally, the product information should be amended to update the frequencies of adverse reactions based on updated pooled clinical trial data. Therefore the current terms of the marketing authorisation(s) should be varied¹⁵.
- In the next PSUR, the MAH should provide a detailed review of cases of 'gynacomastia' including case summaries.

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. Brimonidine¹⁶ - MIRVASO (CAP) - PSUSA/00010093/201602 (with RMP)

Applicant: Galderma International

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Background

Brimonidine, a selective alpha2-adrenergic receptor agonist, is indicated for the symptomatic treatment of facial erythema of rosacea in adult patients.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Mirvaso (brimonidine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'pallor at the application site' as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied¹⁷.

¹⁵ 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

¹⁶ centrally authorised product only

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

- In the next PSUR, the MAH should continue to discuss cases in which Mirvaso was prescribed and/or applied more than once a day and to highlight any cases in which there is evidence of rebound or the therapeutic effect wearing off prematurely, and any cases involving systemic effects. In addition, the MAH should provide a thorough assessment of the effectiveness of the updated risk minimisation measures relating to symptom exacerbation after implementation of further updates required in another ongoing procedure (see LEG 006 under 6.4.1.).

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. Daclatasvir - DAKLINZA (CAP) - PSUSA/00010295/201601

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

Background

Daclatasvir is a direct-acting antiviral indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Daklinza (daclatasvir) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained¹⁸.
- In the next PSUR, the MAH should provide a detailed review of all cases reporting cardiac failure/cardiac toxicity with daclatasvir-containing regimens. In addition, the MAH should provide a cumulative review of possible interactions with vitamin K antagonists and changes in international normalised ratio (INR) with daclatasvir as agreed by the PRAC for all direct acting antivirals (DAAs) (see 4.3.3.). The MAH should discuss whether further changes to the product information are warranted. Moreover, the MAH should provide further details on individual safety data/narratives for all fatal cases.

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

6.1.5. Etanercept - ENBREL (CAP) - PSUSA/00001295/201602

Applicant: Pfizer Limited

¹⁸ Without prejudice to the outcome of the ongoing procedure on direct-acting antiretrovirals (DAAV) indicated for the treatment of hepatitis C (interferon free) under Article 20 of Regulation (EC) No 726/2004

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Background

Etanercept is a tumour necrosis factor alpha (TNF- α) inhibitor indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis (AS) and plaque psoriasis under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Enbrel (etanercept) 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 continue to monitor raised liver enzymes with comments on any information regarding the risks in different groups, continue to monitor the issue of cervical cancer raised in the literature and provide any further data emerging from registry studies or other relevant sources with an appropriate timing.
- The MAH should submit to the EMA, within 90 days, a detailed analysis on the apparent increase in reports of adverse events linked to elevated liver function tests (LFT) including a discussion on the consequent need for additional risk minimisation measures and should re-submit the proposed amendments to the product information as part of an appropriate variation. In addition, the MAH should comment on whether the underlying reason for the change in frequency of the LFT abnormalities at the time of granting the marketing authorisation may also apply to any other adverse drug reactions currently listed in the product information. Finally, the MAH should provide information on the timing of availability of statistical analysis results for BSRBR¹⁹, RABBIT²⁰ and BADBIR²¹ registries.

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. Florbetaben (¹⁸F) - NEURACEQ (CAP) - PSUSA/00010094/201602

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Florbetaben (¹⁸F) is a diagnostic radiopharmaceutical indicated for positron emission

¹⁹ British Society for Rheumatology Biologics Register

²⁰ Rheumatoid Arthritis: Beobachtung der Biologika-Therapie

²¹ British Association of Dermatologists Biologic Interventions Register

tomography (PET) imaging of β -amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Neuraceq (florbetaben (^{18}F)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on increased uptake identified in bone. Therefore, the current terms of the marketing authorisation(s) should be varied²².

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

6.1.7. Gimeracil, oteracil monopotassium, tegafur - TEYSUNO (CAP) - PSUSA/00002875/201601

Applicant: Nordic Group B.V.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor, oteracil potassium, an orotate phosphoribosyltransferase (OPRT) inhibitor and tegafur, a 5-fluorouracil (5-FU) prodrug are indicated in combination in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Teysuno (gimeracil/oteracil monopotassium/tegafur) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'limbal stem cell deficiency' as an undesirable effect part of corneal disorders with a very common frequency. Therefore the current terms of the marketing authorisation(s) should be

²² Update of SmPC section 4.4 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

varied²³.

- In the next PSUR, the MAH should provide a full comparison of the product information authorised in Japan and in the EU including a discussion and justification of any differences in particular when considering hepatitis B reactivation and nephrotic syndrome.

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

6.1.8. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201601

Applicant: Leo Pharma A/S

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Picato (ingenol mebutate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'application site scarring' as an undesirable effect with a rare frequency. Therefore, the current terms of the marketing authorisation(s) should be varied²⁴.

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

6.1.9. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/201601 (with RMP)

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

²³ 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

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

Lomitapide is a selective inhibitor of microsomal transfer protein (MTP) indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Lojuxta (lomitapide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the potential risk of dehydration in relation to gastrointestinal side effects and to advise patients to take precautions to avoid fluid depletion. In addition, alopecia and myalgia should be added as undesirable effects with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied²⁵.

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

6.1.10. Nalmefene - SELINCRO (CAP) - PSUSA/00010120/201602

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Selincro (nalmefene) in the approved indication(s) remains unchanged.
- Nevertheless, the package leaflet should be updated to include references to methadone and buprenorphine as examples of opioid substances that are contraindicated. Therefore, the current terms of the marketing authorisation(s)

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

should be varied²⁶.

- In the next PSUR, the MAH should provide a detailed review of cases of withdrawal syndrome including cases with concurrent use of methadone and buprenorphine and cases with concurrent use of other opioids over time to allow assessment of the appropriateness of the routine risk minimisation measures. In addition, the MAH should provide a detailed discussion on the need for further additional risk minimisation activities. Moreover, the MAH should provide a detailed discussion on cases of myalgia and associated terms and propose to update the product information as applicable. Finally, the MAH should provide a detailed analysis of cases of diarrhoea.

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.

6.1.11. Paclitaxel albumin - ABRAXANE (CAP) - PSUSA/00010123/201601

Applicant: Celgene Europe Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Paclitaxel albumin is an antineoplastic agent indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated. It is also indicated in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, and with carboplatin for the first-line treatment of non-small cell lung cancer (NSCLC) in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Abraxane (paclitaxel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include that caution should be exercised when paclitaxel is concomitantly administered with medicines known to inhibit either cytochrome P450 2C8 (CYP2C8) or cytochrome P450 3A4 (CYP3A4) such as clopidogrel because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. In addition, administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 is not recommended because efficacy may be compromised due to lower paclitaxel exposure. Therefore, the

²⁶ Update of package leaflet section 2. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

current terms of the marketing authorisation(s) should be varied²⁷.

- In the next PSUR, the MAH should provide a discussion on 'syndrome of inappropriate antidiuretic hormone secretion', 'posterior reversible encephalopathy syndrome (PRES)', 'optic nerve disorder and capillary leak syndrome' should new relevant safety information arise.

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

6.1.12. Pregabalin - LYRICA (CAP); PREGABALIN PFIZER (CAP) - PSUSA/00002511/201601

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Lyrica (pregabalin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on seizures in the context of overdose. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.
- In the next PSUR, the MAH should provide a detailed discussion of cases of use in pregnancy with the outcomes, and with an analysis of data from existing antiepileptic registries. The MAH should also provide a detailed assessment on misuse, abuse and drug dependence presenting the total numbers and reporting rates stratified by EU countries, and should present an analysis of the study by *Tjaderborn M. et al.*²⁹. In addition, the MAH should provide a detailed analysis of cases of agranulocytosis and pancytopenia. Further to the addiction vigilance survey conducted in France and to the change of prescription status in Norway, the MAH should provide information about any additional action or change in France or Norway and discuss the impact of

²⁷ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁸ Update of SmPC section 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁹ Tjaderborn M, Bardage C, Hagg S, et al. Patterns of prescription refill and pregabalin: A 5-year prospective cohort study on high consumption. *Pharmacoepidemiology and Drug Safety* 2015; 24:126. Abstract 223

such measures on reporting rates.

- The MAH should submit to the EMA, within 90 days, a detailed analysis of data collected through a follow-up questionnaire as a routine pharmacovigilance activity regarding spontaneous reports on abuse, misuse, dependence and withdrawal symptoms including a discussion on the potential added value of the collected data. In addition, the MAH should provide a detailed analysis of cases of 'hepatobiliary disorders' 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.

6.1.13. Ruxolitinib - JAKAVI (CAP) - PSUSA/00010015/201602

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Ruxolitinib is a selective inhibitor of Janus associated kinases (JAKs): JAK1 and JAK2 indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea, as well as for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Jakavi (ruxolitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the existing warning on infection, to mention that other types of opportunistic infections can occur and treatment with ruxolitinib should not start until serious active infections have resolved. In addition, patients should be evaluated for active and inactive ('latent') tuberculosis, as per local recommendations. Moreover, a new warning on lipid abnormalities should be added including recommendations relating to lipid monitoring and treatment of dyslipidaemia according to clinical guidelines. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH should provide reviews on cases of 'interstitial pneumonitis', 'haemolytic anaemia', and 'myocarditis'.

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

³⁰ 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

2001/83/EC.

6.1.14. Ulipristal acetate - ESMYA (CAP) - PSUSA/00009325/201602

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Ulipristal acetate is a selective progesterone receptor modulator with a tissue-specific partial progesterone antagonist effect indicated for pre-operative and intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Esmya (ulipristal acetate) 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 a detailed review on cases of hypersensitivity. The MAH should discuss causality for hypersensitivity reactions and propose to update the product information as applicable.
- The MAH should submit to the EMA, within 60 days, a detailed review on arterial and venous thromboembolic events (ATE/VTE). The MAH should also discuss biological plausibility based on the mechanism of action of ulipristal acetate, focusing on the role of oestrogen and progesterone. The MAH should consider updating the product information and RMP as applicable.

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

6.1.15. Vismodegib - ERIVEDGE (CAP) - PSUSA/00010140/201601

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Vismodegib is an inhibitor of the Hedgehog pathway which leads via signalling through the smoothed transmembrane protein (SMO) to the activation and nuclear localisation of glioma-associated oncogene (GLI) transcription factors and induction of Hedgehog target genes. Vismodegib is indicated for the treatment of adult patients with symptomatic metastatic basal cell carcinoma and locally advanced basal cell carcinoma

inappropriate for surgery or radiotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Erivedge (vismodegib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the current warning on the initial prescription and dispensing of Erivedge that should occur within seven days of a negative pregnancy test to specify that the day of the negative pregnancy test should count as the first day. Consequently, the healthcare professional and patient educational materials should be updated to reflect the revised warning. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.
- In the next PSUR, the MAH should provide a detailed review on cardiac failure and should propose to update the product information and the RMP as applicable. In addition, the MAH should provide a discussion on cases of 'trismus'.

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. Alitretinoin - PANRETIN (CAP); NAP - PSUSA/00000090/201601

Applicant: Eisai Ltd (Panretin), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of Panretin, a centrally authorised medicine(s) containing alitretinoin together with nationally authorised medicines containing alitretinoin, and issued a recommendation on

³¹ Update of SmPC section 4.4. Annex II.D 'conditions or restrictions with regard to the safe and effective use of the medicinal product'- additional risk minimisation measures is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of alitretinoin-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should provide a full review of cardiac risks, including a review of the literature, in association with the known ability of the product to increase lipids (including case review and a review of the literature) and propose to update the product information as applicable. In addition, the MAHs for oral formulations only should provide reviews of 'pancreatitis', 'gastrointestinal haemorrhage', 'myocardial infarction', 'malaise', 'photosensitivity reaction', 'somnolence', 'nail disorder' and 'back pain', and should propose updates to the product information as applicable.

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

6.2.2. Levetiracetam - KEPPRA (CAP), NAP - PSUSA/00001846/201511

Applicant: UCB Pharma S.A. (Keppra), various

PRAC Rapporteur: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of Keppra, a centrally authorised medicine containing levetiracetam, together with nationally authorised medicines containing levetiracetam, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of levetiracetam-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include new warnings on 'acute kidney injury' as well as 'blood dyscrasias', advising full blood cell counts in

patients experiencing significant weakness, pyrexia, recurrent infections or coagulation disorders. In addition, 'acute kidney injury', 'encephalopathy' and 'increase of blood creatine phosphokinase' should be added as undesirable effects with a rare frequency as well as 'rhabdomyolysis' with an uncommon frequency. Therefore, the current terms of the marketing authorisations should be varied³².

- In the next PSUR, the MAHs should provide a detailed review of hypokalaemia and hypomagnesaemia. In addition, the MAHs should submit a detailed review of cases of haemorrhage in association with levetiracetam, including a discussion of potential interactions (potentiation) with anticoagulant drugs and anti-platelet drugs (e.g. aspirin).
- The MAH for the originator medicinal product (Keppra) should submit to the EMA, within 120 days, a detailed analysis on the risk of teratogenicity and the risk of neurodevelopmental disorders associated with the use of levetiracetam during pregnancy, based on data from all available sources, including the complete data from the UCB antiepileptic drugs (AED) pregnancy registry if available.

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

6.2.3. Orlistat - ALLI (CAP); XENICAL (CAP); NAP - PSUSA/00002220/201602

Applicant: Glaxo Group Ltd (Alli), Roche Registration Limited (Xenical), various

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Orlistat is a long-acting inhibitor of gastrointestinal lipases precluding the hydrolysis of dietary fat (triglycerides) into absorbable free fatty acids and monoglycerides. Alli (orlistat) is indicated for weight loss in adults who are overweight (body mass index (BMI) ≥ 28 kg/m²) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet. Xenical (orlistat) is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a BMI greater or equal to 30 kg/m², or overweight patients (BMI > 28 kg/m²) with associated risk factors.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of orlistat-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.

³² Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAHs should provide detailed reviews of all cases of hepatotoxicity and nephrotoxicity with an analysis of all serious cases belonging to the MedDRA SOC³³ 'hepatobiliary disorders' and MedDRA HLGT³⁴ 'nephropathies', 'renal disorders' and 'urolithiasis' respectively. In addition, the MAHs should continue to closely monitor hepatotoxicity and nephrotoxicity as major safety concerns.
- The MAHs of Alli and Xenical should submit to the EMA, within 180 days, a detailed cumulative review of all case reports of nephrotoxicity from clinical trials, post marketing surveillance and literature. Moreover, they should discuss the causal relationship between orlistat and reports of nephrotoxicity, taking into account potential confounding factors (such as co-morbidities) and the usage of these drugs. Based on the analysis of the cumulative review, the MAHs should discuss any necessary amendments to the product information, as appropriate.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly. In addition, the PRAC agreed that no further PSURs are required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC. The EURD list is updated accordingly.

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

See also Annex I. 16.3.

6.3.1. Alizapride (NAP) - PSUSA/00000091/201601

Applicant: various

PRAC Lead: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

Background

Alizapride is a dopamine antagonist indicated in the treatment of nausea and vomiting of different origin (including cancer chemotherapy and radiation induced) and in retching.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of alizapride-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should submit a cumulative review of paediatric cases

³³ Medical dictionary for regulatory activities - System organ class

³⁴ Medical dictionary for regulatory activities - High level group terms

with a specific focus on routes of administration and administered dosages.

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. Allopurinol (NAP) - PSUSA/00000095/201512

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of allopurinol-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should provide a critical discussion on the strength of evidence supporting the use of HLA³⁵-B*58:01 genotyping as a screening tool to make treatment decisions with allopurinol, taking into consideration the CHMP 'Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products ([EMA/CHMP/281371/2013](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-on-key-aspects-for-the-use-of-pharmacogenomics-in-the-pharmacovigilance-of-medicinal-products_en.pdf)) and should comment on the publication from *Ko et al.*³⁶. Furthermore, the MAHs should comment on the possibility to use Rs9263726³⁷ instead of HLA-B*58:01 screening for patients starting allopurinol therapy. In addition, considering recent treatment guidelines and in view of the known risk of severe cutaneous adverse drug reactions (SCARs) associated with allopurinol, the MAH should discuss the need to amend the product information to support the safe use of allopurinol in patients with asymptomatic hyperuricaemia, based on the benefit-risk assessment in this patient population. The MAHs should review all available data regarding the risk of teratogenicity associated with allopurinol and propose an update of the product information as applicable. Moreover, the MAHs should provide detailed reviews of cases of renal impairment and renal failure, cases of neutropenia and pancytopenia, and cases of bone marrow depression. The MAH Biogaran should review the cases of medication error and consider the need to develop risk minimisation measures as applicable.

The frequency of PSUR submission should be revised from three-yearly to yearly and the

³⁵ human leukocyte antigen

³⁶ Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. Ko et al. *BMJ* 2015; 351:h4848

³⁷ whole-genome association study of major determinants for allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients

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

6.3.3. Antithrombin III (NAP) - PUSA/00003159/201512

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of antithrombin III-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the available evidence of harmful effects in premature infants in the unapproved indication of infant respiratory distress syndrome (IRDS), as an increased risk of intracranial bleeding and mortality is suggested in the absence of a demonstrated beneficial effect. Therefore, the current terms of the marketing authorisations should be varied³⁸
- In the next PSUR, the MAHs should provide a thorough review of off-label use in the paediatric population (including preterm infants) and provide a detailed discussion on whether available data support the need for further implementation of risk minimisation measures (RMMs).

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

6.3.4. Bendamustine hydrochloride (NAP) - PSUSA/00003162/201601

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of bendamustine hydrochloride-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the risk of reactivation of hepatitis B and to refine the existing warnings on 'tumour lysis syndrome', 'opportunistic infections' and 'skin reactions'. In addition, the following undesirable effects should be added: 'opportunistic infection' (including Herpes zoster, cytomegalovirus, hepatitis B)' and 'headache' with a very common frequency; 'dizziness' with a common frequency; '*pneumocystis jirovecii* pneumonia' (PJP), 'pancytopenia', myelodysplastic syndrome' and 'acute myeloid leukaemia' with an uncommon frequency; 'bone marrow failure' with a rare frequency as well as 'atrial fibrillation', 'Stevens-Johnson syndrome' (SJS), 'toxic epidermal necrolysis' (TEN) and 'renal failure' with an unknown frequency. Therefore, the current terms of the marketing authorisations should be varied³⁹.
- In the next PSUR, the MAH should provide a detailed analysis of cases of secondary malignancy as well as reviews of cases of encephalopathy and leukoencephalopathy, including progressive multifocal leukoencephalopathy (PML) over time. In addition, the MAHs should provide a review of cases of auto-immune haemolytic anemia (AIHA) (with bendamustine as monotherapy) including a full literature review to evaluate the potential role of bendamustine in causing AIHA, a review of cases of urticaria without concomitant use of rituximab, and perform a cumulative review on cardiac failure and myocardial infarction including causality assessment as per WHO-UMC⁴⁰. The MAHs should propose to update the product information as applicable. In addition, the MAH should provide further details on the previous review that led the MAHs to propose the inclusion of atrial fibrillation (AF) in the product information. Finally, the MAH should provide data on the outcome of opportunistic infections separately for clinical trials and post-marketing cases (in particular Herpes zoster,

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

⁴⁰ World Health Organization - Uppsala Monitoring Centre

PJP and cytomegalovirus (CMV)) and discuss the need for a direct healthcare professional communication (DHPC) as appropriate.

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

6.3.5. Botulinum neurotoxin type A (150 kD) free from complexing proteins (NAP) - PSUSA/00009084/201512

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Botulinum neurotoxin type A (150 kD) free from complexing proteins is a neurotoxic muscle relaxant protein indicated for the treatment of blepharospasm, spasmodic torticollis, post-stroke spasticity of the upper limb, glabellar frown lines, and crow's feet (also named lateral periorbital lines).

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of nationally authorised medicines containing botulinum neurotoxin type A (150 kD) free from complexing proteins, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of botulinum neurotoxin type A (150 kD) free from complexing proteins-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the educational material for healthcare professional and patients shall be discontinued as it is no longer considered necessary as sufficient experience was gained over the past years and the risks of toxin spread and dysphagia are adequately minimised by the information included in the product information. Therefore, the terms of the marketing authorisations should be varied⁴¹.
- In the next PSUR, the MAH should provide a cumulative review of cases of muscle atrophy, including a review of the literature, addressing the influence of the injection site within the muscle, the frequency and the cumulative number of injections. The MAHs should propose to amend the product information as applicable.

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

6.3.6. Botulinum toxin A (NAP) - PSUSA/00000426/201512

Applicant: various

⁴¹ Update of the conditions to the marketing authorisation(s) and RMP for nationally authorised products. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Botulinum toxin A is a neurotoxic muscle relaxant protein indicated for the treatment of blepharospasm under certain conditions, strabismus in patients 12 years of age or older, cervical dystonia (spasmodic torticollis) in adults, focal spasticity (upper and/or lower limb spasticity under certain conditions), spasmodic dysphonia, primary focal axillary hyperhidrosis interfering with daily activities, urinary incontinence due to neurogenic detrusor overactivity (NDO), overactive bladder (OAB) with certain symptoms and conditions, and for the prophylaxis of headaches in adults with chronic migraine.

Botulinum toxin A is also indicated for the treatment of upper facial rhytides including forehead, lateral canthus, and glabellar lines (GL) and for the temporary improvement in the appearance of moderate to severe lateral canthus lines (crow's feet lines (CFL)) in adults treated either alone or simultaneously with GL.

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of nationally authorised medicines containing botulinum toxin A, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of botulinum toxin A-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the educational material for healthcare professional and patients shall be discontinued as it is no longer considered necessary as sufficient experience was gained over the past years and the risks of toxin spread and dysphagia are adequately minimised by the information included in the product information. Therefore, the current terms of the marketing authorisations should be varied⁴².
- In the next PSUR, the MAH should provide a detailed analysis of cases of 'mediastinitis' and related terms with off-label oesophageal indications including data from spontaneous reporting and the published literature. In addition, the MAHs should provide a comprehensive critical evaluation of the joint subluxation signal, as well as a cumulative critical analysis of cases of eyelid ptosis and related terms reported with the lateral canthus lines (CFL) indication. The MAHs should propose to update the product information as applicable. Moreover, the MAHs should provide a detailed review of lack of efficacy, medication errors, and off label use with botulinum toxin A-containing medicinal products, together with an analysis of adverse events reported for unlicensed indications.
- The MAHs with an RMP in place should update it accordingly at the next upcoming regulatory procedure affecting the RMP or at the latest by 28 February 2017.

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.

⁴² Update of the conditions to the marketing authorisation(s) and RMP for nationally authorised products. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.7. Botulinum toxin A-haemagglutinin complex (NAP) - PSUSA/00000427/201512

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Botulinum neurotoxin type A is a neurotoxic muscle relaxant protein indicated for the treatment of spastic equinus foot deformity due to spasticity in adult patients following a stroke, symptomatic treatment for focal spasticity affecting the upper limbs in adults, local symptomatic treatment of spasticity affecting the upper and/or lower limbs in adults, dynamic equinus foot deformity due to spasticity in paediatric cerebral palsy (CP) patients, 2 years of age or older, local symptomatic treatment of spasticity affecting the lower limbs in children aged 2 years or older, spasmodic torticollis in adults, blepharospasm in adults, hemifacial spasm in adults, axillary hyperhidrosis, and moderate to severe glabellar lines.

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of nationally authorised medicines containing botulinum toxin type A-haemagglutinin complex, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of botulinum toxin type A-haemagglutinin complex-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the educational material for healthcare professionals and patients should be discontinued as it is considered no longer necessary as sufficient experience was gained over the past years and the risks of toxin spread and dysphagia are adequately minimised by the information included in the product information. Therefore, the current terms of the marketing authorisations should be varied⁴³.
- In the next PSUR, the MAHs should monitor and discuss the appearance of neutralizing antibodies with an analysis of the number of patients with neutralizing antibodies reporting loss of treatment benefit/lack of efficacy. For Dysport, the MAH should monitor and discuss the events of 'cardiac disorders', 'fatal events', 'life threatening events', 'ear and labyrinth disorders' and 'eye disorders'. For Azzalure, the MAH should monitor and discuss the events 'cardiac disorders', 'fatal outcomes' and 'ear and labyrinth disorders'.

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

6.3.8. Bupropion (NAP) - PSUSA/00000461/201512

Applicant: various

⁴³ Update of of the conditions to the marketing authorisation(s) and RMP for nationally authorised products. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines indicated for the treatment of major depressive episodes in adults, and as an aid to smoking cessation in combination with motivational support in nicotine-dependent patients in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of bupropion-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add hyponatraemia as undesirable effect with a frequency not known. Therefore, the current terms of the marketing authorisations should be varied⁴⁴.

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. In addition, the PRAC agreed that no further PSURs are required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended. The EURD list is updated accordingly.

6.3.9. Cefoperazone (NAP) - PSUSA/00000597/201601

Applicant: various

PRAC Lead: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

Background

Cefoperazone is a third-generation cephalosporin antibiotic indicated for the treatment of respiratory tract infections (upper and lower), urinary tract infections (upper and lower), peritonitis, cholecystitis, cholangitis, and other intra-abdominal infections, septicemia, meningitis, skin and soft tissue infections, infections of bones and joints, pelvic inflammatory disease, endometritis, gonorrhoea, and other infections of the genital tract when caused by susceptible organisms.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of

⁴⁴ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

cefoperazone-containing medicinal products in the approved indications remains unchanged.

- Nevertheless, the product information should be updated to include a warning on haemorrhage to ensure that patients are monitored for signs of bleeding, thrombocytopenia, and hypoprothrombinemia. Cefoperazone should be discontinued if there is persistent bleeding and no alternative explanations are identified. Therefore, the current terms of the marketing authorisations should be varied⁴⁵.
- In the next PSUR, the MAHs should define the most appropriate duration of therapy to be used for estimation of patient exposure based on clinical practice data. In addition, the MAHs should provide cumulative reviews of cases with a fatal outcome, as well as cases of drug use in pregnancy and lactation, and should monitor cases of haemorrhage and related adverse drug reactions. In addition, the MAH should present any information on antimicrobial resistance for cefoperazone.

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

6.3.10. Cefoperazone, sulbactam (NAP) - PSUSA/00000598/201601

Applicant: various

PRAC Lead: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

Background

Cefoperazone sodium is a semi-synthetic third generation cephalosporin antibiotic and sulbactam sodium is a beta-lactamase inhibitor. In combination, cefoperazone/sulbactam is indicated for the treatment of respiratory tract infections (upper and lower), urinary tract infections (upper and lower), peritonitis, cholecystitis, cholangitis, and other intra-abdominal infections, septicaemia, meningitis, skin and soft tissue infections, infections of bones and joints, pelvic inflammatory disease, endometritis, gonorrhoea, and other infections of the genital tract when caused by susceptible organisms.

Cefoperazone/sulbactam can be used concomitantly with other antibiotics if such a combination is indicated.

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of nationally authorised medicines containing cefoperazone/sulbactam, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of cefoperazone/sulbactam-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on haemorrhage to ensure that patients are monitored for signs of bleeding, thrombocytopenia, and hypoprothrombinemia. Cefoperazone should be discontinued

⁴⁵ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

if there is persistent bleeding and no alternative explanations are identified. In addition, haemorrhage should be added as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisations should be varied⁴⁶.

- In the next PSUR, the MAHs should define the most appropriate duration of therapy to be used for estimation of patient exposure, based on clinical practice data, and ensure consistency in the use of daily dose estimating interval or cumulative patient exposure. In addition, the MAH should closely monitor cases of haemorrhage and related adverse drug reactions, serious cutaneous adverse reactions (SCARs) and hepatic disorders. Furthermore, the MAHs should provide further information relating to patients with fatal outcome. In addition, the MAHs should present any information on antimicrobial resistance for cefoperazone.

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

6.3.11. Doxazosin (NAP) - PSUSA/00001169/201512

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Doxazosin is an α 1-selective alpha blocker indicated for the treatment of hypertension and for the treatment of clinical symptoms in benign prostatic hyperplasia (BPH) and for reduced urinary flow associated with BPH.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of doxazosin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on emergency treatment of priapism to ensure that patients should seek immediate medical assistance in case of prolonged erections and priapism. Therefore, the current terms of the marketing authorisations should be varied⁴⁷.
- In the next PSUR, the MAHs of doxazosin-containing products without an existing safety specification should provide, in the section 'summary of safety concerns', information on the important identified and potential risks and missing information associated with use of doxazosin, based on pre- and post-authorisation experience.

⁴⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁴⁷ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- The MAHs with an RMP in place should consequently adapt their RMP in line with this within an upcoming regulatory procedure affecting the RMP.

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

6.3.12. Hydromorphone (NAP) - PSUSA/00001686/201511

Applicant: various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

Background

Hydromorphone is a semi-synthetic opioid derivative of morphine indicated for the treatment of pain under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of hydromorphone-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to reflect that prolonged use of hydromorphone during pregnancy can result in neonatal withdrawal syndrome. Therefore, the current terms of the marketing authorisations should be varied⁴⁸.
- In the next PSUR, the MAHs should provide detailed reviews of cases of neural tube defects in infants of mothers using hydromorphone during pregnancy, cases of fractures, including fractures in men aged 65 years and older on concomitant opioid therapy with an antipsychotic or with a benzodiazepine as well as cases of low libido, impotence, lack of menstruation and infertility in patients treated with hydromorphone. The MAHs should also closely monitor the occurrence of serotonin syndrome and adrenocortical insufficiency in patients treated with hydromorphone in order to update the existing evidence. MAH Mundipharma should provide a discussion on the increase in number of reports of the following adverse drug reactions (ADRs): toxicity to various agents, drug and substance dependence and drug and substance abuse from post marketing data sources. MAH Janssen-Cilag should discuss the increase in number of reports of the following ADRs: toxicity to various agents, intentional product misuse, drug abuse and completed suicide, from post marketing data sources.
- MAHs of hydromorphone-fixed dose combination products should be requested to update the product information⁴⁰ regarding the warning on neonatal withdrawal syndrome, due to the prolonged use of hydromorphone.

⁴⁸ Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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

6.3.13. Paclitaxel (NAP) - PSUSA/00002264/201512

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Paclitaxel is an antineoplastic agent indicated for the treatment of ovarian carcinoma, breast carcinoma, non-small cell lung carcinoma, gastric carcinoma and acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of paclitaxel-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning for drug interactions with inhibitors⁴⁹ or inducers⁵⁰ of CYP2C8⁵¹ and CYP3A4⁵², because the toxicity of paclitaxel may be increased due to higher paclitaxel exposure, or efficacy may be compromised because of lower paclitaxel exposures respectively. In addition, the wording for the existing undesirable effect 'alopecia' should be further strengthened and 'disseminated intravascular coagulation' should be added as an undesirable effect with a very common frequency. Therefore, the current terms of the marketing authorisations should be varied⁵³.

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

6.3.14. Testosterone (all formulations apart from topical use and testosterone undecanoate injection) (NAP) - PSUSA/00002907/201512

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

⁴⁹ E.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir

⁵⁰ E.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine

⁵¹ Cytochrome P450 2C8

⁵² Cytochrome P450 3A4

⁵³ Update of SmPC section 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Background

Testosterone is a steroid hormone that belongs to the androgens pharmaco-therapeutic group. Following the referral procedure under Article 31 of Directive 2001/83/EC for testosterone-containing medicines (see [PRAC minutes October 2014](#)), all testosterone-containing-medicinal products are indicated for testosterone replacement therapy in males with conditions associated with primary and secondary hypogonadism (either congenital or acquired) when testosterone deficiency has been confirmed by clinical features and biochemical tests.

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of nationally authorised medicine containing testosterone (apart from topical use and testosterone undecanoate injection), and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of testosterone-containing medicinal products (apart from topical use and testosterone undecanoate injection) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on thrombotic events to ensure that testosterone is used with caution in patients with thrombophilia and to present all warnings relating to clotting disorders together. Therefore, the current terms of the marketing authorisations should be varied⁵⁴.

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.

6.3.15. Testosterone (topical use only) (NAP) - PSUSA/00002908/201512

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Testosterone is a steroid hormone that belongs to the androgens pharmaco-therapeutic group. Following the referral procedure under Article 31 of Directive 2001/83/EC for testosterone-containing medicines (see [PRAC minutes October 2014](#)), all testosterone-containing-medicinal products are indicated for testosterone replacement therapy in males with conditions associated with primary and secondary hypogonadism (either congenital or acquired) when testosterone deficiency has been confirmed by clinical features and biochemical tests.

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of nationally authorised medicine containing testosterone for topical use, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

⁵⁴ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Based on the review of the data on safety and efficacy, the risk-benefit balance of testosterone-containing medicinal products for topical use in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on thrombotic events to ensure that testosterone is used with caution in patients with thrombophilia and to present all warnings relating to clotting disorders together. Therefore, the current terms of the marketing authorisations should be varied⁵⁵.

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

6.3.16. Testosterone undecanoate (injection) (NAP) - PSUSA/00010161/201512

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Testosterone is a steroid hormone that belongs to the androgens pharmacotherapeutic group. Following the referral procedure under Article 31 of Directive 2001/83/EC for testosterone-containing medicines (see [PRAC minutes October 2014](#)), all testosterone-containing medicinal products are indicated for testosterone replacement therapy in males with conditions associated with primary and secondary hypogonadism (either congenital or acquired) when testosterone deficiency has been confirmed by clinical features and biochemical tests.

Based on the assessment of the PSUR, the PRAC reviewed the risk-benefit balance of nationally authorised medicines containing testosterone undecanoate for injection, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of testosterone undecanoate-containing medicinal products (injection) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on thrombotic events to ensure that testosterone is used with caution in patients with thrombophilia and to present all warnings relating to clotting disorders together. Therefore, the current terms of the marketing authorisations should be varied⁵⁶.

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.

⁵⁵ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁵⁶ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I. 16.4.

6.4.1. Brimonidine - MIRVASO (CAP) - EMEA/H/C/002642/LEG 006

Applicant: Galderma International

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of a detailed review on an evidence-based summary of the risk-benefit balance including the proportion of patients who benefit from Mirvaso, the magnitude and persistence of the improvement (i.e. clinical relevance) taking into account data from clinical trials (including pre-authorisation randomised clinical trials and more recent data, such as from the MIRACLE study – including information on drop-outs from these studies), post-marketing usage and survey data. In addition, the MAH submitted further data on risk minimisation measures relating to test dose, possible change of excipients and other risk minimisation strategies as requested in the conclusions of PSUSA/00010093/201508 adopted by PRAC and CHMP in March 2016

Background

Brimonidine, a selective α_2 -adrenergic receptor agonist, is indicated for the symptomatic treatment of facial erythema of rosacea in adult patients.

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

Summary of advice/conclusion(s)

- Based on the review of the data presented by the MAH, the PRAC considered that the product information should be improved to better inform prescribers and patients about the dose to apply in order to minimise the risk of symptom exacerbation. In addition, PRAC supported that a user testing of the updated patient information leaflet is conducted prior to implementation in order to ensure that the risk minimisation measures are well communicated. National Competent Authorities may consider communicating the revised prescribing advice through national bulletins and learned societies.
- The MAH should be requested to submit to the EMA, within 60 days of the PRAC conclusions, a variation to update the product information to inform prescribers and patients more clearly about the dose to apply in order to minimise the risk of symptom exacerbation.

6.4.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/LEG 010

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Submission of the CIOMS⁵⁷ forms for all cases of pancreatitis and additionally the

⁵⁷ Council for International Organisations of Medical Sciences

11 reports for which multiple patients were reported as requested in the conclusions of PSUSA/00010077/201509 adopted by PRAC and CHMP in April 2016

Background

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

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

Summary of advice/conclusion(s)

- Based on the review of the submitted data regarding pancreatitis, the PRAC considered that an update of the product information to include 'acute pancreatitis' as an undesirable effect may be necessary, which should be further addressed in the context of the ongoing PSUSA procedure (PSUSA/00010077/201603) due for the adoption of a PRAC recommendation at the November meeting (24-27 October 2016). In the ongoing PSUSA procedure, the MAH should also evaluate the frequency of acute pancreatitis in association with canagliflozin treatment, and discuss the appropriateness of including a warning on pancreatitis in the product information.

6.4.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/LEG 009

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the CIOMS⁵⁸ forms for all cases of pancreatitis and additionally the 11 reports for which multiple patients were reported as requested in the conclusions of PSUSA/00010077/201509 adopted by PRAC and CHMP in April 2016

Background

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

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

Summary of advice/conclusion(s)

- Based on the review of the submitted data regarding pancreatitis, the PRAC considered that an update of the product information to include 'acute pancreatitis' as an undesirable effect may be necessary, which should be further assessed in the context of the ongoing PSUSA procedure (PSUSA/00010077/201603) due for the adoption of a PRAC recommendation at the November meeting (24-27 October 2016). In the ongoing PSUSA procedure, the MAH should also evaluate the frequency

⁵⁸ Council for International Organisations of Medical Sciences

of acute pancreatitis in association with canaglifozin treatment, and discuss the appropriateness of including a warning on pancreatitis in the product information.

6.4.4. Gefitinib - IRESSA (CAP) - EMEA/H/C/001016/LEG 021

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a detailed literature review on a resistance mechanism to gefitinib by transformation of non-small cell lung cancer (NSCLC) and lung adenocarcinoma to small cell carcinoma as requested in the conclusions of PSUSA/00001518/201507 procedure adopted by PRAC and CHMP in January 2016

Background

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.

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

Summary of advice/conclusion(s)

- Based on the review of the detailed literature review regarding a resistance mechanism to gefitinib by transformation of non-small cell lung cancer (NSCLC) and lung adenocarcinoma to small cell carcinoma, the PRAC considered that the MAH should be requested to submit to the EMA, within 60 days, a proposal for an appropriate warning to amend the product information.

6.4.5. Gefitinib - IRESSA (CAP) - EMEA/H/C/001016/LEG 022

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a detailed analysis on a safety meta-analysis reporting a higher frequency of gefitinib-related hepatotoxicity of grade ≥ 3 in Asians compared to non-Asians (Takeda et al, Lung Cancer. 2015, Apr; 88(1): 74-9) as requested in the conclusions of PSUSA/00001518/201507 procedure adopted by PRAC and CHMP in January 2016

Background

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.

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

PRAC advice.

Summary of advice/conclusion(s)

- Based on the review of the detailed analysis on hepatotoxicity relating to increased aspartate transaminase (AST) and alanine transaminase (ALT) ALT/AST in Asian patients, the PRAC considered that the current evidence was not robust enough to amend the product information. The MAH should continue to monitor any increased aspartate transaminase (AST) and alanine transaminase (ALT) in Asian patients as part of routine safety surveillance as part of routine safety surveillance.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁵⁹

See also Annex I. 17.1.

7.1.1. Lesinurad - ZURAMPIC (CAP) - EMEA/H/C/PSP/0050

Applicant: Astra Zeneca AB

PRAC Rapporteur: Dolores Montero Corominas

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

Background

Lesinurad is a selective uric acid reabsorption inhibitor, indicated in combination with a xanthine oxidase inhibitor, for the adjunctive treatment of hyperuricaemia in adult gout patients (with or without tophi) who have not achieved target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone.

In order to investigate cardiovascular risk in association with lesinurad exposure, mainly in patients with a history of cardiovascular disorders, the MAH was requested to conduct and submit the results of an observational prospective study according to an agreed protocol.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product, as the Committee considered that that the design of the study did not fully fulfil the study objectives.
- The PRAC considered that the proposed design (propensity score (PS)-matched cohort study) may be an adequate approach, but its success in the control of confounding and the achievement of enough precision of results will depend on the variables used in the PS, and the number of patient correctly matched by their PS value. Therefore, the data sources to be used are of capital importance.

⁵⁹ In accordance with Article 107n of Directive 2001/83/EC

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

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁰

See also Annex I. 17.2.

7.2.1. Clopidogrel - CLOPIDOGREL ZENTIVA (CAP) - EMEA/H/C/000975/LEG 013

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Leonor Chambel

Scope: Submission of a protocol for study OBS014770, a non-interventional PASS: a cross-sectional drug utilisation study (DUS) using databases assessing the off-label use of clopidogrel and fixed dose combination (FDC) of clopidogrel/acetylsalicylic acid (ASA) for primary prevention of cardiovascular (CV) events in five European countries as requested in the conclusions of PSUSA/0000820/201311 adopted by PRAC and CHMP in July 2014

Background

Clopidogrel is a platelet aggregation inhibitor indicated for the prevention of atherothrombotic events in adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease under certain conditions, in adult patients suffering from acute coronary syndrome under certain conditions and for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation.

Further to the PSUSA procedure EMEA/H/C/PSUSA/00000820/201311 for 'clopidogrel and clopidogrel/acetylsalicylic acid (ASA)' concluded in July 2014 (for background, see [PRAC minutes July 2014](#)), the MAH was requested to provide a review of cases of off-label use in the primary prevention of cardiovascular events (CV) in the next PSUR. The MAH submitted a protocol for a study for the evaluation of the proportion, by country, of off-label use for primary prevention of CV events of clopidogrel, including the fixed dose combination clopidogrel/ASA, in Europe in 2015, which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for clopidogrel and clopidogrel/ASA version 1, pro-actively submitted by the MAH as an alternative to the review requested further to the PSUSA, is not considered as the most robust and accurate method to gather off-label use data on clopidogrel in primary prevention of cardiovascular events given the nature of the concern raised in the previous PSUSA procedure, the lack of knowledge regarding the safety concern across EU, the identified limitations of the study, the inconsistencies regarding data analysis and the robustness of the data to be obtained considering the research question.
- The MAH is suggested to gather all relevant information regarding the off-label use of

⁶⁰ 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

clopidogrel in primary prevention of cardiovascular events from different sources from 2013 to 2016 and to submit its review and analysis as part of the upcoming PSUSA procedure for 'clopidogrel and clopidogrel/ASA' (DLP: 17/11/2016).

7.2.2. Clopidogrel - ISCOVER (CAP) - EMEA/H/C/000175/LEG 034

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Leonor Chambel

Scope: Submission of a protocol for study OBS014770, a non-interventional PASS: a cross-sectional drug utilisation study (DUS) using databases assessing the off-label use of clopidogrel and fixed dose combination (FDC) of clopidogrel/acetylsalicylic acid (ASA) for primary prevention of cardiovascular (CV) events in five European countries as requested in the conclusions of PSUSA/0000820/201311 adopted by PRAC and CHMP in July 2014

Background

Clopidogrel is a platelet aggregation inhibitor indicated for the prevention of atherothrombotic events in adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease under certain conditions, in adult patients suffering from acute coronary syndrome under certain conditions and for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation.

Further to the PSUSA procedure EMEA/H/C/PSUSA/00000820/201311 for clopidogrel concluded in July 2014 (for background, see [PRAC minutes July 2014](#)), the MAH was requested to provide a review of cases of off-label use in the primary prevention of cardiovascular events (CV) in the next PSUR. The MAH submitted a protocol for a study for the evaluation of the proportion, by country, of off-label use for primary prevention of CV events of clopidogrel including the fixed dose combination clopidogrel/ASA, in Europe in 2015, which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

See under 7.2.1.

7.2.3. Clopidogrel - PLAVIX (CAP) - EMEA/H/C/000174/LEG 031

Applicant: Sanofi Clir SNC

PRAC Rapporteur: Leonor Chambel

Scope: Submission of a protocol for study OBS014770, a non-interventional PASS: a cross-sectional drug utilisation study (DUS) using databases assessing the off-label use of clopidogrel and fixed dose combination (FDC) of clopidogrel/acetylsalicylic acid (ASA) for primary prevention of cardiovascular (CV) events in five European countries as requested in the conclusions of PSUSA/0000820/201311 adopted by PRAC and CHMP in July 2014

Background

Clopidogrel is a platelet aggregation inhibitor indicated for the prevention of atherothrombotic events in adult patients suffering from myocardial infarction, ischaemic

stroke or established peripheral arterial disease under certain conditions, in adult patients suffering from acute coronary syndrome under certain conditions and for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation.

Further to the PSUSA procedure EMEA/H/C/PSUSA/00000820/201311 for clopidogrel and clopidogrel/acetylsalicylic acid concluded in July 2014 (for background, see [PRAC minutes July 2014](#)), the MAH was requested to provide a review of cases of off-label use in the primary prevention of cardiovascular events (CV) in the next PSUR. The MAH submitted a protocol for a study for the evaluation of the proportion, by country, of off-label use for primary prevention of CV events of clopidogrel including the fixed dose combination clopidogrel/ASA, in Europe in 2015, which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

See under 7.2.1.

7.2.4. Clopidogrel, acetylsalicylic acid - CLOPIDOGREL/ACETYLSALICYLIC ACID ZENTIVA (CAP) - EMEA/H/C/001144/LEG 008

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Leonor Chambel

Scope: Submission of a protocol for study OBS014770, a non-interventional PASS: a cross-sectional drug utilisation study (DUS) using databases assessing the off-label use of clopidogrel and fixed dose combination (FDC) of clopidogrel/acetylsalicylic acid (ASA) for primary prevention of cardiovascular (CV) events in five European countries as requested in the conclusions of PSUSA/0000820/201311 adopted by PRAC and CHMP in July 2014

Background

Clopidogrel and acetylsalicylic acid (ASA) are platelet aggregation inhibitors. In combination, clopidogrel acetylsalicylic acid is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and ASA, as well as for continuation of therapy in non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous coronary intervention, and ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

Further to the PSUSA procedure EMEA/H/C/PSUSA/00000820/201311 for clopidogrel concluded in July 2014 (for background, see [PRAC minutes July 2014](#)), the MAH was requested to provide a review of cases of off-label use in the primary prevention of cardiovascular events (CV) in the next PSUR. The MAH submitted a protocol for a study for the evaluation of the proportion, by country, of off-label use for primary prevention of CV events of clopidogrel including the fixed dose combination clopidogrel/ASA, in Europe in 2015, which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

See under 7.2.1.

7.2.5. Clopidogrel, acetylsalicylic acid - DUOPLAVIN (CAP) - EMEA/H/C/001143/LEG 011

Applicant: Sanofi Clir SNC

PRAC Rapporteur: Leonor Chambel

Scope: Submission of a protocol for study OBS014770, a non-interventional PASS: a cross-sectional drug utilisation study (DUS) using databases assessing the off-label use of clopidogrel and fixed dose combination (FDC) of clopidogrel/acetylsalicylic acid (ASA) for primary prevention of cardio-vascular (CV) events in five European countries as requested in the conclusions of PSUSA/0000820/201311 adopted by PRAC and CHMP in July 2014

Background

Clopidogrel and acetylsalicylic acid (ASA) are platelet aggregation inhibitors. In combination, clopidogrel acetylsalicylic acid is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and ASA, as well as for continuation of therapy in non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous coronary intervention, and ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

Further to the PSUSA procedure EMEA/H/C/PSUSA/00000820/201311 for clopidogrel concluded in July 2014 (for background, see [PRAC minutes July 2014](#)), the MAH was requested to provide a review of cases of off-label use in the primary prevention of cardiovascular events (CV) in the next PSUR. The MAH submitted a protocol for a study for the evaluation of the proportion, by country, of off-label use for primary prevention of CV events of clopidogrel including the fixed dose combination clopidogrel/ASA, in Europe in 2015, which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

See under 7.2.1.

7.3. Results of PASS imposed in the marketing authorisation(s)⁶¹

7.3.1. Cyproterone, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0003

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: Netherlands, United Kingdom and Italy

Background

In line with the conclusions of a referral under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for cyproterone/ethinylestradiol-containing medicines

⁶¹ In accordance with Article 107p-q of Directive 2001/83/EC

([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 draft protocol for this study was assessed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. For background information, see [PRAC minutes April 2014](#), [PRAC minutes September 2014](#), [PRAC minutes October 2014](#), [PRAC minutes December 2014](#), [PRAC minutes April 2015](#), [PRAC minutes April 2016](#) and [PRAC minutes June 2016](#).

Summary of advice

- Based on the review of the final report of the non-interventional PASS, the PRAC considered that supplementary information should be requested before a recommendation can be made.

7.3.2. Cyproterone, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0005

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

Background

In line with the conclusions of a referral 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 draft protocol for this study was assessed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. For background information, see [PRAC minutes April 2014](#), [PRAC minutes September 2014](#), [PRAC minutes October 2014](#), [PRAC minutes December 2014](#), [PRAC minutes April 2015](#), [PRAC minutes April 2016](#) and [PRAC minutes June 2016](#).

Summary of advice

- Based on the review of the final report of the non-interventional PASS, the PRAC agreed that supplementary information should be requested to the MAHs before a recommendation can be made.

7.3.3. Cyproterone, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0006

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, the Czech Republic, France, the Netherlands, and Spain

Background

In line with the conclusions of a referral under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for cyproterone/ethinylestradiol-containing medicines ([EMA/H/107i/1357](#)), the MAHs were required to conduct a PASS to evaluate the effectiveness of the additional risk minimisation measures (educational materials for healthcare professionals and patients highlighting the risks and warning of venous thromboembolism (VTE). The draft protocol for this study was assessed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. For background information, see [PRAC minutes April 2014](#), [PRAC minutes September 2014](#), [PRAC minutes October 2014](#), [PRAC minutes December 2014](#), [PRAC minutes April 2015](#), [PRAC minutes April 2016](#) and [PRAC minutes June 2016](#).

Summary of advice

- Based on the review of the final report of the non-interventional PASS, the PRAC agreed that supplementary information should be requested to the MAHs before a recommendation can be made.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁶²

See also Annex I. 17.4.

7.4.1. Imatinib - GLIVEC (CAP) - EMA/H/C/000406/II/0100

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final clinical study report (CSR) for study CSTI571A2403: 'a global Gleevec/Glivec and Tasigna pregnancy exposure registry' (category 3 study)

Background

Glivec is a centrally authorised medicine containing imatinib. It is indicated for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment, with Ph+ CML in the chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis, with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy, with relapsed or refractory Ph+ ALL as monotherapy, with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements, with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFR α rearrangement. Glivec (imatinib) is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), as adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST and for the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

⁶² 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

Further to the limited data on the use of Glivec (imatinib) in pregnant woman, a non-imposed PASS (prospective observational registry (CSTI571A2403)) was listed in the RMP and designed to monitor pregnancies exposed to Glivec in order to estimate the prevalence of birth defects. The Rapporteur assessed the MAH's responses to the request for supplementary information on the final results of study CSTI571A2403 entitled 'a global Gleevec/Glivec and Tasigna Pregnancy exposure Registry'.

Summary of advice

- Based on the MAH's responses to the request for supplementary information, the PRAC agreed that an update of the product information⁶³ regarding women of childbearing potential and pregnancy was warranted. The PRAC suggested some minor amendments to the proposed wording.

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

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

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

None

⁶³ Advice to update SmPC section 4.6

8.2. Conditional renewals of the marketing authorisation

None

8.3. Renewals of the marketing authorisation

See Annex I.18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the 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. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0086/G

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: PRAC consultation on 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

See also under 15.3.14.

Background

Eculizumab is a recombinant humanised monoclonal IgG_{2/4k} antibody indicated in adults and children for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uremic syndrome (aHUS).

A grouped type II variation proposing to update the product information of Soliris (eculizumab) to include a warning and precautions with guidance on vaccination in patients with complement-mediated disease treated with eculizumab, particularly with vaccines against serogroup B meningococcal infection, 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 agreed on the proposal to amend the warning and precautions on timing of meningococcal vaccination. The PRAC suggested some refinements to the wording.

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

None

10.3. Other requests

10.3.1. Edoxaban – LIXIANA (CAP); lixisenatide – LYXUMIA (CAP)

Applicant: Daiichi Sankyo Europe GmbH (Lixiana), Sanofi-Aventis Groupe (Lyxumia)

PRAC Rapporteur: Julie Williams (Lixiana); Qun-Ying Yue (Lyxumia)

Scope: PRAC consultation on a case of potential for name-related confusion with Lixiana (edoxaban), Lyxumia (lixisenatide) and Lysanxia (prazepam) identified in the post-authorisation phase

Background

Lixiana contains edoxaban, a direct and reversible inhibitor of factor Xa, indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) under certain conditions as well as for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Lyxumia contains lixisenatide, a selective glucagon-like peptide-1 (GLP-1) receptor agonist, and is indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin under certain conditions.

Prazepam is a benzodiazepine derivative indicated for the short-term treatment of anxiety. Lysanxia is a nationally authorised medicine containing prazepam.

The CHMP requested advice from the PRAC, based on the potential for name related confusion between the two centrally authorised medicinal products (Lixiana and Lyxumia)

and a nationally authorised product (Lysanxia).

Summary of advice

- Based on the available data, the PRAC supported further differentiation for Lysanxia (prazepam) and Lixiana (edoxaban) packaging as a risk minimisation measure as this may reduce the likelihood of dispensing errors and errors at the patient level. As for Lixiana (edoxaban) and Lyxumia (lixisenatide), the PRAC considered that further differentiation in terms of packaging was unlikely to increase the chances of preventing medication errors since the existing clear differences in pharmaceutical form, storage and other risk minimisation measures together with patient education material are considered to contribute to correct selection and administration of the products and to mitigate this risk. As the respective RMP already includes the monitoring of medication errors, the PRAC concluded that the inclusion of this as an important potential risk was not warranted.

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Glibenclamide (NAP) - NAT/H/1134/01/II/126

Applicant: Sanofi (Daonil), various

PRAC Rapporteur: Veerle Verlinden

Scope: PRAC consultation on a variation procedure for Daonil (glibenclamide) NAT/H/1134/01/II/126 relating to the risk of cardiovascular mortality

Background

Glibenclamide is a sulfonylurea anti-diabetic agent indicated for the treatment of type II diabetes mellitus under certain conditions.

Based on a systematic review and network meta-analysis by *Simpson SH et al.*⁶⁴ suggesting that sulfonylureas would increase the risk of major adverse cardiovascular events, cardiovascular mortality and/or all-cause mortality, with an apparent lower risk of all-cause and cardiovascular-related mortality with gliclazide and glimepride compared to glibenclamide, the MAH for the originator product containing glibenclamide (Daonil) submitted a type II variation (NAT-H-1134-01-II-126) at national level to amend the product information to add a warning on the risk of cardiovascular mortality. In the context of the evaluation of this variation procedure, Belgium requested PRAC advice on

⁶⁴ Simpson SH et al. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol* 2015; 3:43-51

its assessment.

Summary of advice

- Based on the review of the available information, the PRAC acknowledged the clear limitations in the Simpson *et al.* systematic review and network meta-analysis in terms of the confounding factors and data analysis bias, but also took into account mixed evidence in the literature with regard to an increased risk of cardiovascular mortality associated with glibenclamide, as well as the declining use of glibenclamide, particularly in the elderly in whom there is a higher absolute risk for cardiovascular events than in younger patients. As a consequence, the PRAC considered by majority that there is insufficient evidence to take further regulatory action for glibenclamide in the light of the current knowledge.

11.2. Other requests

11.2.1. Chlormadinone, ethinyl estradiol (NAP)

Applicant: Gedeon Richter, various

PRAC Rapporteur: Valerie Strassmann

Scope: PRAC consultation on the statistical analysis plan (SAP) for an imposed PASS comparing the risk of venous thromboembolism (VTE) with chlormadinone/ethinylestradiol (CMA/EE) versus levonorgestrel/ethinylestradiol (LVG/EE) following the PRAC endorsement in January 2016 of its protocol (EMA/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 (EMA/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 CHC finalised in 2013. For further background, see [PRAC minutes January 2016](#).

As the statistical analysis plan (SAP) for the PASS could not be fully assessed within procedure EMA/H/N/PSP/j/0012.3, the Lead Member State (Germany) conducted a review at national level and requested PRAC advice at the current meeting on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC considered that the primary analysis strategy should be described in more detail in the SAP to avoid data-driven analysis and suggested further sensitivity analyses for the proposed regression analysis.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

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

As a follow-up to the previous PRAC discussion (see [PRAC minutes May 2016](#)), the EMA secretariat updated the PRAC on the development of the draft GVP chapter for special populations with a special focus on the paediatric population, in particular the section on post-authorisation safety studies (PASS) and on objectives to align the [paediatric investigation plans](#) (PIP) and RMP. Further discussion is scheduled at PRAC in November 2016.

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

12.3.1. Scientific Advice Working Party (SAWP) – Pilot phase on involving the PRAC in non-imposed PASS protocols

At the organisational matters teleconference held on 15 September 2016, the PRAC was updated on the experience gained following a 12-month pilot designed to encourage scientific advice on safety studies focusing on protocols for non-imposed post-authorisation safety studies (PASS). Further discussion is scheduled at the October 2016 PRAC meeting (scheduled on 26-29 September 2016).

12.4. Cooperation within the EU regulatory network

12.4.1. Seasonal influenza vaccines enhanced safety surveillance systems - EMA review

At the organisational matters teleconference held on 15 September 2016, and as a follow-up to previous PRAC discussion (see [PRAC minutes January 2016](#)), a progress update on the review of enhanced safety surveillance systems (ESS) for seasonal influenza vaccines was given to PRAC. The review shows that ESS is an innovative regulatory requirement for real-time detection of potential safety signals following vaccination with seasonal influenza vaccines, that ESS raised awareness of HCPs and vaccinees of the importance of reporting adverse events (AEs) following vaccination, and that there were challenges for the timeliness of submitting the safety data for regulatory review. In addition, the review showed that efforts to implement a strengthened system of surveillance should continue (ESS guidance requirements in place, supplemented by

the EMA's continuous interaction with vaccine manufacturers). Finally, PRAC will continue to evaluate ESS for CAPs while providing the Vaccines Working Party (VWP) with continuous oversight on guidance development. The PRAC welcomed the review.

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. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, 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 September 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 in September 2016, the updated EURD list was adopted by the CHMP and CMDh at their September 2016 meetings and published on the EMA website on 22/09/2016, 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. Guideline on 'Electronic reaction monitoring reports (eRMR) user manual'

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 15 September 2016, the EMA secretariat presented to the PRAC, on behalf of the Signal Management Review Technical (SMART) work stream (WS) WS2-3, the draft 'electronic reaction monitoring reports (eRMR) user manual' (see [PRAC minutes June 2016](#)). The aim of the manual is to describe the structure of the eRMR and capture practicalities and recommendations on how to use the eRMR tool further to the changes implemented to increase effectiveness following testing performed during a prospective pilot phase. PRAC delegates were invited to provide comments by 6 October 2016. As next steps, two webinars to train the EU regulatory network on eRMR will be organised in October 2016, the new eRMR files will be distributed to the network as of 9 November 2016, and the eRMR user manual is planned for publication on the EMA website in November 2016.

12.11.2. Guideline on 'Screening for adverse drug reactions in EudraVigilance'

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 15 September 2016, the EMA secretariat presented to the PRAC, on behalf of the Signal Management Review Technical (SMART) work stream (WS) WS2-3, the draft Guideline on 'screening for adverse drug reactions in EudraVigilance' (see [PRAC minutes June 2016](#)). The draft guideline aims at describing the methods of routine signal detection as used in EudraVigilance (EV) and

clarifying changes implemented to increase effectiveness with a focus on insight into the thinking behind the eRMR and EudraVigilance Data Analysis System (EVDAS), as well as on what is proved to be effective. PRAC delegates were invited to provide comments by 6 October 2016.

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

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the September 2016 SMART Working Group (SMART WG) work stream WS1. The WS1 discussed aspects relating to the handling of emerging safety issues (ESI) as well as aspects relating to the handling of signals for drug-drug interactions between substances included in nationally approved products (NAPs).

12.11.4. Signal management – List of substances subject to worksharing

The EMA Secretariat reminded the PRAC that a call for volunteers was ongoing to appoint new Lead Members States (MSs) for signal management. The worksharing for signal management allows for better monitoring of EudraVigilance data for substances contained in nationally authorised medicinal product(s) (i.e. through national, mutual recognition or decentralised procedures) authorised in more than one EU MS and less duplication of effort between MSs (see [list of substances subject to worksharing for signal management](#)). Lead MSs are responsible, on behalf of the EU network, for monitoring EudraVigilance, validating and confirming signals for specific substance(s) contained in nationally authorised medicinal product(s). The support provided by the EMA was further described, e.g. provision of electronic reaction monitoring reports (eRMRs) to Lead MSs.

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 28/09/2016 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. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – 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 - Dry-run outcome

As a follow-up to the public hearing dry run exercise held in July 2016 within the framework of the PRAC meeting to test the process and procedures for public hearings by using a fictional scenario of a safety review ([PRAC minutes July 2016](#)), the EMA

secretariat presented to the PRAC some lessons learnt. Overall, all aspects were implemented and while some fine tuning is needed, no major aspects were overlooked in preparing for future public hearings and the exercise confirmed that the aims of the dry run were achieved. As a next step, in line with the the [PRAC work plan 2016](#) and based on the work of the PRAC topic group, procedural and best practice guidance for PRAC members on public hearings' will be discussed at PRAC in November 2016.

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

None

12.20.1. EMA Scientific Committees support – organisational adjustments

The PRAC was informed of the EMA's organisational and strategic amendments of its corporate management structure that come into effect on 1 September 2016.

The first change consists of creation of a new function dedicated to strengthening the collaboration between the EMA and National Competent Authorities (NCAs) by overseeing the implementation of the joint network strategy to 2020, promoting innovation in regulatory science across the European regulatory system for medicines, and addressing the increasing complexity of the committees' activities coordination. The second adjustment aims at simplifying the EMA internal organisation dealing with human medicines resulting in one division responsible for support to medicines' developers, one for the evaluation of medicines, bringing scientific and procedure management under one umbrella, and one for the oversight of medicines, including pharmacovigilance and inspections. Finally, regarding Scientific Committees, their support is moved to the Department of Committees and Inspections to further strengthen the matrix work across the EMA human divisions.

12.20.2. Good Pharmacovigilance Practices (GVP) – adoption of revised GVP modules in 2016-2017

At the organisational matters teleconference held on 15 September 2016, the EMA secretariat presented to the PRAC a further overview of the GVP status following the implementation of the revised EU network governance for pharmacovigilance (see [PRAC minutes June 2016](#)). The PRAC was provided with an update on the ongoing or planned work on new or revised GVP modules together with their scope, proposed timelines for PRAC discussion and adoption.

12.20.3. Initial marketing authorisation application (MAA) procedures: early background summaries – review of experience

The topic was deferred to the October 2016 PRAC meeting.

12.20.4. Strategy on measuring the impact of pharmacovigilance - reflection paper on PRAC criteria to prioritise collaborative impact research

PRAC lead: Marieke De Bruin

Following the last discussion on the 'PRAC strategy on measuring the impact of pharmacovigilance activities' ([EMA/790863/2015](#)) (see [PRAC minutes July 2016](#)) and in line with the [PRAC work plan 2016](#), the PRAC adopted a reflection paper on 'PRAC criteria to prioritise collaborative impact research'.

12.20.5. Strategy on measuring the impact of pharmacovigilance - PRAC Interest Group impact proposal for prioritised topics

PRAC lead: Marieke De Bruin

In line with the [PRAC work plan 2016](#) as part of the 'PRAC strategy on measuring the impact of pharmacovigilance activities', based on the reflection paper on 'PRAC criteria for prioritisation of collaborative impact research', the EMA Secretariat presented to the PRAC, based on the EMA reviewers' independently applied criteria, safety topics discussed at PRAC since 2012 for which risk minimisation measures were decided. Based on the criteria, the PRAC considered some topics proposed by the PRAC Interest Group (IG) for potential impact research through either a collaborative network study or as an EMA funded study. Based on the comments, further discussion will be scheduled at PRAC in November 2016.

12.20.6. Effects tables in selected important benefit/risk reviews - Pilot phase

PRAC lead: Rafe Suvarna

In line with the [PRAC work plan 2016](#) and based on the CHMP experience, the PRAC was presented with the second effects table of the pilot that was recently initiated to explore the utility of such tables in post-authorisation procedures. The PRAC welcomed the initiative and encouraged further work on using effects tables in selected important benefit-risk reviews as part of the pilot exercise at the level of the PRAC.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁶⁵

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 timetables⁶⁶.

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Azacitidine – VIDAZA (CAP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of pericarditis and pericardial effusion

EPITT 18733 – New signal

Lead Member State: NL

14.1.2. Lenalidomide – REVLIMID (CAP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Signal of hemophagocytic lymphohistiocytosis (HLH)

EPITT 18689 – New signal

Lead Member State: FR

14.1.3. Ritonavir – NORVIR (CAP)

Applicant: AbbVie Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Signal of retinal pigment epitheliopathy

EPITT 18703 – New signal

Lead Member State: NL

⁶⁵ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

⁶⁶ Either MAH'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

14.2. New signals detected from other sources

14.2.1. Darbepoetin alfa – ARANESP (CAP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of incorrect use of device associated with adverse reactions including underdose, drug dose omission, accidental exposure to product and injection site reactions

EPITT 18718 – New signal

Lead Member State: DE

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. Emtricitabine, tenofovir disoproxil - EMEA/H/C/004215

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

15.1.2. Ivabradine - EMEA/H/C/004217

Scope: Treatment of angina pectoris

15.1.3. Parathyroid hormone - EMEA/H/C/003861, Orphan

Applicant: NPS Pharma Holdings Limited

Scope: Treatment of hypoparathyroidism

15.1.4. Sildenafil - EMEA/H/C/004289

Scope: Treatment of patients with pulmonary arterial hypertension

15.1.5. Tadalafil - EMEA/H/C/004297

Scope: Treatment of pulmonary arterial hypertension (PAH)

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. Abiraterone - ZYTIGA (CAP) - EMEA/H/C/002321/II/0045

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of the RMP to modify the planned dates for assessment in the risk minimisation measures for all important identified and potential risks as well as missing information

15.2.2. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/II/0014

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Update of the RMP (version 2.0) to include progressive multifocal leukoencephalopathy (PML) as an important potential risk, to describe the pharmacovigilance activities associated to PML and to include a standardize case definition for the diagnosis of PML

15.2.3. Aliskiren - RASILEZ (CAP) - EMEA/H/C/000780/WS0771/0104; aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/WS0771/0075

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of the RMP with regard to identified risks, missing information, concomitant use of other medicines, drug-drug interactions, removal of safety issues attributed to the withdrawn aliskiren/amlodipine (Rasilamlo) and aliskiren/amlodipine/HCTZ (Rasitrio). The variation is supported by study report SPA100A: antihypertensive effects and long-term safety of aliskiren in elderly patients

15.2.4. 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)

15.2.5. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0045

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP in order to reflect details of the category 3 study HGS1006-C1112/BEL115471: a phase 3/4, multicentre, double-blind, randomized, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab in adult subjects of black race with systemic lupus erythematosus (SLE). The final due date of the study is amended accordingly

15.2.6. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0020

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

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 updates on renal impairment/renal failure; hypersensitivity and DKA. In addition, the MAH proposed to revise the dates for completion of clinical studies and included additional studies as requested in the Article 20 procedure

15.2.7. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0016

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

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 updates on renal impairment/renal failure; hypersensitivity and DKA. In addition, the MAH proposed to revise the dates for completion of clinical studies and included additional studies as requested in the Article 20 procedure

15.2.8. Catridecacog - NOVOTHIRTEEN (CAP) - EMEA/H/C/002284/II/0015

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Claire Ferard

Scope: Update of the RMP (version 13) in order to add final data from completed study F13CD-3720 (a multicentre, open-label, single-arm, and multiple dosing trial on safety of monthly replacement therapy with recombinant factor XIII (rFXIII) in patients with congenital factor XIII deficiency). The MAH took the opportunity to update the RMP to include other information based on the new data lock point of 31 March 2016

15.2.9. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS0968/0012; XIGDUO (CAP) - EMEA/H/C/002672/WS0968/0023 Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS0968/0009; FORXIGA (CAP) - EMEA/H/C/002322/WS0968/0028

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMP in order to implement 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, upgrade of a drug utilisation study (DUS) from category 4 to 3 as well as the addition of a description of an ongoing mechanistic study. Finally, the RMP is updated to add a description of a DKA epidemiological study assessing the incidence of DKA

15.2.10. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0051

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Update of the RMP (version 13.0) in order to remove any reference to a new tradename to be implemented for the new film-coated tablets formulation (approved as part of X/43) as a new routine risk minimisation measure. The MAH took the opportunity to update the educational materials to reflect changes from recently approved procedures (II/45, R/47 and PSUSA/00000939/201510)

15.2.11. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0026

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Update of the RMP (version 7) in order to include the outcome of the evaluation from WS/689 (PML added as an important identified risk). The draft PASS protocol for category 3 study 109MS419 (a retrospective, multicentre, observational study to assess the effect of Tecfidera delayed-release capsules on lymphocyte subsets in subjects with relapsing forms of multiple sclerosis) was also submitted. In addition, a discussion on the overall totality of the non-clinical and clinical work being undertaken to further understand lymphopenia associated with Tecfidera treatment is included

15.2.12. Dronedarone - MULTAQ (CAP) - EMEA/H/C/001043/II/0035

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP to propose revised additional risk minimisation measures to facilitate healthcare professionals' (HCP) compliance and to modify the timelines for study EFFECT-AF: a historic-prospective cohort with dynamic exposure and stratified competitive recruitment with balanced comparison groups of dronedarone versus alternative antiarrhythmic drugs of interest (EFFECT-AF/OBS13687. Annex II.D ('conditions or restrictions with regard to the safe and effective use of the medicinal product') of the Marketing Authorisation is updated accordingly

15.2.13. 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

15.2.14. [Human fibrinogen, human thrombin - EVICEL \(CAP\) - EMEA/H/C/000898/II/0039](#)

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Submission of a revised RMP (version 14) including updates on data exposure, medication error cases and effectiveness of risk minimisations measures related to the potential risk of air/gas embolism associated with spray application

15.2.15. [Human protein C - CEPROTIN \(CAP\) - EMEA/H/C/000334/II/0093](#)

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Update of the RMP (version 1.0) following the completion of procedure PSUSA/00002563/201507 to add the following risks to the summary of safety concerns: bleeding episodes as an identified risk; hypersensitivity reactions as identified risk; injection site reactions as a potential risk; inhibitor development as a potential risk as well as heparin induced thrombocytopenia as a potential risk

15.2.16. [Ibandronic acid - BONDRONAT \(CAP\) - EMEA/H/C/000101/WS0942/0074;](#) [BONVIVA \(CAP\) - EMEA/H/C/000501/WS0942/0056](#)

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Implementation of the PRAC recommendation to add patient reminder cards as an additional risk minimisation measure to the ibandronic acid risk management plan, following the PRAC recommendation adopted in February 2016 as part of the PSUSA/00001702/201506 procedure

15.2.17. [Influenza vaccine \(split virion, inactivated\) - IDFLU \(CAP\) - EMEA/H/C/000966/WS1012/0047;](#) [INTANZA \(CAP\) - EMEA/H/C/000957/WS1012/0050](#)

Applicant: Sanofi Pasteur

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the RMP (version 11.0) to include information on the enhanced safety surveillance for the Northern hemisphere (NH) 2016-2017 influenza season

15.2.18. [Insulin degludec - TRESIBA \(CAP\) - EMEA/H/C/002498/II/0022](#)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMP (version 6) in order to upgrade the risk of mix-up between basal and bolus insulin from a potential to an important identified risk; to include paediatric patients in the additional risk minimisation activities to mitigate the important potential risk of medication errors due to mix-up between different strengths of Tresiba as well as to remove the category 4 studies: EX1250-4080 (DEVOTE: trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events), NN1250 4129 (a multicentre, prospective, open-label, single-arm, non-interventional, post marketing surveillance (PMS) study of insulin degludec to evaluate long term safety and efficacy in patients with diabetes mellitus in routine clinical practice in India), NN1250-4061 (a multicentre, open label, observational, non-interventional, PMS to evaluate safety and effectiveness during long-term treatment with insulin degludec in patients with diabetes mellitus requiring insulin therapy under normal clinical practice conditions), NN1250-4110 (a multicentre, prospective, open-label, single-arm, non-interventional, regulatory PMS study of insulin degludec to evaluate safety and effectiveness in patients of all age groups excluding less than 12 months old infants with diabetes mellitus in routine clinical practice in Korea) and NN1250-4189 (a multicentre, prospective, non-interventional study of insulin degludec investigating the safety and effectiveness in a real world population with type 1 and 2 diabetes mellitus)

15.2.19. [Naltrexone, bupropion - MYSIMBA \(CAP\) - EMEA/H/C/003687/II/0005/G](#)

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of amended study designs for both the renal impairment study (effect of renal impairment on the pharmacokinetics of naltrexone PR/ bupropion PR tablet (category 3 study)) and the hepatic impairment study (effect of hepatic impairment on the pharmacokinetics of naltrexone PR/bupropion PR tablet (category 3 study)) as outlined in the currently approved RMP (version 8)

15.2.20. [Vardenafil - LEVITRA \(CAP\) - EMEA/H/C/000475/WS0973/0053; VIVANZA \(CAP\) - EMEA/H/C/000488/WS0973/0049](#)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the RMP to include a safety concern (identified risk) already assessed and implemented in the Levitra/Vivanza product information (EMEA/H/C/xxxx/WS/0861) on the contraindication relating to the concomitant use of riociguat and phosphodiesterase type 5 (PDE5) inhibitors including vardenafil

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. Abiraterone - ZYTIGA (CAP) - EMEA/H/C/002321/X/0039

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Line extension to introduce a new pharmaceutical form associated with a new strength (500 mg film-coated tablets)

15.3.2. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/II/0043

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 5.3 of the SmPC in order to delete the statement that amifampridine has not been fully tested in carcinogenicity models and to provide the findings from the carcinogenicity reports required for the completion of SOB 004. The RMP (version 9) is updated accordingly. In addition, the MAH took the opportunity to request the removal in Annex II of the requirement to complete carcinogenicity testing in an appropriate model

15.3.3. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0026

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.4 and 4.5 of the SmPC to remove the interaction with inhibitors of breast cancer resistant protein (BCRP) based on the results of a drug-drug interaction study of the co-administration of ataluren and inhibitors of BCRP

15.3.4. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0027

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.8 of the SmPC to add that the safety profile of ataluren in non-ambulatory patients is similar to the safety profile in ambulatory patients following the results of a 48-week open label extension study in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD)

15.3.5. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0038

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC following the completion of the post-authorisation efficacy studies: IM103-008 (belatacept evaluation of nephroprotection and efficacy as first-line immunosuppression trial (BENEFIT) and IM103-027 (belatacept evaluation of nephro-protection and efficacy as first-line immunosuppression trial - extended criteria donors (BENEFIT-EXT)). The Package Leaflet and the RMP (version 12) are updated accordingly

15.3.6. 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, 6.5 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

15.3.7. Cabazitaxel - JEVTANA (CAP) - EMEA/H/C/002018/II/0034

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Claire Ferard

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to add information from completed study EFC11785 (randomized, open-label multicentre study comparing cabazitaxel at 20 mg/m² and at 25 mg/m² every 3 weeks in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing regimen). In addition, the MAH proposed to modify the wording in section 4.1 from 'hormone refractory' to 'castration resistant' prostate cancer to reflect the current terminology of the disease in the clinical practice. The RMP is updated accordingly and in accordance with the outcome of the latest PSUR procedure (PSUSA/000476/201506)

15.3.8. 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)

15.3.9. Carfilzomib - KYPROLIS (CAP) - EMEA/H/C/003790/II/0007/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marina Dimov Di Giusti

Scope: Update of sections 4.2 and 5.2 of the SmPC to revise the guidance on the use of carfilzomib in patients with renal and hepatic impairments further to the submission of completed studies relating to renal impairment (CFZ001: an open-label, single arm, phase 1 study of the pharmacokinetics and safety of carfilzomib in subjects with relapsed multiple myeloma and end-stage renal disease) and hepatic impairment (CFZ002: an open-label, single arm, phase 1 study of the pharmacokinetics and safety of carfilzomib in subjects with advanced malignancies and varying degrees of hepatic impairment). The RMP is updated accordingly. In addition, the MAH took the opportunity to implement some editorial changes to the Product Information

15.3.10. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0008

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 5.1 of the SmPC to reflect the final study report from study A2201 (a phase 2, multicentre, single-arm study in adult patients with anaplastic lymphoma kinase (ALK)-activated non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib) to confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib

15.3.11. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0044

Applicant: Pfizer Limited

PRAC Rapporteur: Claire Ferard

Scope: Update of section 5.2 of the SmPC in order to provide the results of the final overall survival analysis in study A8081007 (a phase 3, randomized, open-label study of the efficacy and safety of crizotinib vs standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced non-small cell lung cancer (NSCLC) harboring a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus (SOB001)). The MAH took the opportunity to request the conversion of the conditional marketing authorisation into a full marketing authorisation. The RMP (version 7.2) is updated accordingly

15.3.12. Darunavir - PREZISTA (CAP) - EMEA/H/C/000707/WS0955/0081; Darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/WS0955/0012

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report (CSR) of category 3 study GS-US-236-0130: a phase 3b, open label, single-arm trial to evaluate the safety and efficacy of cobicistat-boosted darunavir (DRV) plus two fully active nucleoside reverse transcriptase inhibitors (NRTIs) in human immunodeficiency virus (HIV)-1 infected, antiretroviral therapy (ART)-naïve and experienced adults with no DRV-resistant associated mutations (RAMs). The RMPs (version 24.0 for Prezista, version 3.0 for Rezolsta) are updated accordingly, and in accordance with changes previously requested by CHMP and PRAC

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. [Empagliflozin, metformin - SYNJARDY \(CAP\) - EMEA/H/C/003770/II/0015](#)

Applicant: Boehringer Ingelheim GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include the treatment with Synjardy as adjunct to standard care therapy in adult patients with type 2 diabetes mellitus and high cardiovascular risk when the treatment with empagliflozin and metformin is appropriate and empagliflozin is needed to reduce the risk of all-cause mortality by reducing cardiovascular death and cardiovascular death or hospitalization for heart failure. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated based on the final clinical study report of study 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). The Package Leaflet and RMP (version 5.0) is updated accordingly

15.3.18. [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)

15.3.19. Ferric maltol - FERACCRU (CAP) - EMEA/H/C/002733/II/0002/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) drug-drug interaction study to investigate drug interactions with Feraccru; and (MEA 002): drug-drug interaction study to identify uridine diphosphate glucuronosyltransferase (UGT) isoenzyme(s) that are responsible for metabolism of ferric maltol. The RMP is updated accordingly

15.3.20. Glycopyrronium bromide - ENUREV BREEZHALER (CAP) - EMEA/H/C/002691/WS1001/0016; SEEBRI BREEZHALER (CAP) - EMEA/H/C/002430/WS1001/0016; TOVANOR BREEZHALER (CAP) - EMEA/H/C/002690/WS1001/0018

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Update of section 4.8 of the SmPC to include the adverse drug reaction (ADR) dysphonia. The Package Leaflet is updated accordingly

15.3.21. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0025

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Update of the SmPC section 4.4 to remove the warning and precaution regarding the effect of ibrutinib on the QT interval and section 5.1 to provide additional information regarding the pharmacodynamic effect of ibrutinib on QT/QTc intervals and cardiac electrophysiology

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

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include treatment of patients with Duchenne muscular dystrophy in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids

15.3.23. Imiquimod - ALDARA (CAP) - EMEA/H/C/000179/II/0067

Applicant: Meda AB

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to add data on the results of study X-03016-3284 (LEIDA 2, a phase IV randomised active controlled study: long-term effects of imiquimod 5% cream and diclofenac 3% gel in the treatment of actinic

keratoses on the face or scalp with respect to the risk of progression to in-situ and invasive squamous cell carcinoma) and of a meta-analysis of studies X-03016-3271 (LEIDA, a phase IV randomized active controlled study: long-term effects of imiquimod 5% cream and diclofenac 3% gel in the treatment of actinic keratoses on the face or scalp) and X-03016-3284. The RMP is updated (version 3) accordingly

15.3.24. [Indacaterol, glycopyrronium bromide - ULTIBRO BREEZHALER \(CAP\) - EMEA/H/C/002679/WS1005/0013; ULUNAR BREEZHALER \(CAP\) - EMEA/H/C/003875/WS1005/0013; XOTERNA BREEZHALER \(CAP\) - EMEA/H/C/003755/WS1005/0015](#)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Update of section 4.8 of the SmPC to add dysphonia and revise the adverse drug reactions selection and frequencies based on the MAH's review of all safety data. As a consequence, section 4.4 of the SmPC is updated. The Package Leaflet and the RMP (version 2.0) are updated accordingly. Annex II is updated in line with the latest QRD template

15.3.25. [Ivacaftor - KALYDECO \(CAP\) - EMEA/H/C/002494/II/0049](#)

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final clinical study report (CSR) for study VX11-770-109 (a phase 3, 2-arm, open-label roll-over study from study VX11-770-108 (study 108) to evaluate the long-term safety and pharmacodynamics of ivacaftor treatment in paediatric subjects with cystic fibrosis and a cystic fibrosis transmembrane conductance regulator (CFTR) gating mutation) to fulfil the RMP commitment to address the following safety concerns: hepatotoxicity, cataracts, cardiac arrhythmias, use in children between 2 to 5 years old, long-term safety. The RMP (version 5.1) is updated accordingly

15.3.26. [Lenalidomide - REVLIMID \(CAP\) - EMEA/H/C/000717/II/0089/G](#)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Extension of indication to add the treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who have undergone autologous stem cell transplantation (ASCT). The sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated accordingly. In addition, the Package Leaflet and the RMP are updated accordingly. Furthermore, the MAH introduced 7-day pack sizes for the 10 mg and 15 mg strengths with subsequent changes to the Product Information

15.3.27. [Levetiracetam - LEVETIRACETAM HOSPIRA \(CAP\) - EMEA/H/C/002783/II/0012](#)

Applicant: Hospira UK Limited

PRAC Rapporteur: Veerle Verlinden

Scope: Update of the Product Information in line with the company core safety information (CSI) (version 1.0) to include rhabdomyolysis and blood creatine phosphokinase increased as adverse drug reactions (ADR)

15.3.28. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0011/G

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Grouped variation on the final results of two in-vitro studies evaluating the potential off target activity of M6-ivacaftor to address post-authorisation measure MEA005. The RMP is updated accordingly. In addition, the MAH took the opportunity to update administrative aspects of the RMP. The RMP (version 2.5) is updated accordingly

15.3.29. Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/II/0049

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Extension of indication to cover a wider paediatric population starting from 6 weeks of age. As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP are updated accordingly.

15.3.30. Meningococcal group B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/II/0044/G

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations to: 1) update of section 4.8 of the SmPC to include fever as an adverse reaction in adolescents from 11 years of age and adults, and to include hypotonic-hyporesponsive episode (HHE) as an adverse reaction in infants and children up to 10 years of age; 2) update of sections 4.4 and 5.1 of the SmPC to reflect safety and immunogenicity data from a clinical study involving the use of Bexsero in subjects 2 through 17 years of age with increased risk of meningococcal disease. The Package Leaflet is updated accordingly

15.3.31. Methylthioninium chloride - METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP) - EMEA/H/C/002108/II/0030/G

Applicant: Provepharm SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.8 of the SmPC in order to include paresthesia, dysgeusia, syncope, presyncope, feeling of change in body temperature, chest discomfort, shoulder pain and limb discomfort based on data from two clinical studies. In addition, frequencies were added in the tabulated list of adverse reactions. The Package Leaflet and the RMP (version 2.0) are updated accordingly

15.3.32. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/II/0095

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section sections 4.2, 4.3, 4.8, 5.1 and 5.2 of the SmPC based on the results of paediatric studies 101MS028 (meta-analysis of the safety and efficacy of natalizumab in paediatric patients with multiple sclerosis) and 101MS328 (a phase 1, multicentre, open-label, single-arm, multiple dose study to evaluate the the pharmacokinetics and pharmacodynamics of natalizumab in paediatric subjects with relapsing remitting multiple sclerosis (RMS)), in accordance with the paediatric investigation plan (EMA-001095-PIP-12). The RMP (version 21) is updated accordingly

15.3.33. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/II/0097/G

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations to: 1) update of section 4.4 of the SmPC to include information about the use of plasmapheresis (PLEX) or intravenous immunoglobulin (IVIg) which can affect meaningful interpretation of serum anti- John Cunningham (JC) virus (V) antibody testing, 2) update of sections 4.4 and 4.8 of the SmPC upon request by PRAC following the assessment of procedure SDA/063 regarding a signal on necrotising retinitis. The Package Leaflet and the RMP (version 22.0) are updated accordingly

15.3.34. 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

15.3.35. Nitisinone - ORFADIN (CAP) - EMEA/H/C/000555/II/0058

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of section 5.3 of the SmPC in order to add a statement that carcinogenic potential was not shown in a 26-week carcinogenicity study

15.3.36. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0012

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the monotherapy treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL): - after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, or - after at least two prior therapies in patients who are not candidates for ASCT. 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 new indication, add a warning that patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL, and update the safety and pharmacodynamic information. The Package Leaflet and the RMP (version 5.0) are updated accordingly. Furthermore, the product information is brought in line with the latest QRD template (version 10.0)

15.3.37. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0008/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.2 and 5.2 of the SmPC with recommendations for patients with renal impairment based on the results of study D0816C00006 (MEA 006) (an open-label, non-randomised, multicentre, comparative, phase 1 study of the pharmacokinetics, safety and tolerability of olaparib following a single oral 300 mg dose to patients with advanced solid tumours and normal renal function or renal impairment) that evaluated the influence of mild and moderate renal impairment on the pharmacokinetics of olaparib. The Package Leaflet and RMP are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the product information in line with the latest QRD template version and to introduce minor corrections in the product information. Furthermore, a grouping of two type IB variations is submitted to revise the study milestones dates for the category 3 study D0816C00005 (an open-label, non-randomised, multicentre, comparative, phase 1 study to determine the pharmacokinetics, safety and tolerability of olaparib following a single oral 300 mg dose to patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment) and category 1 study D0816C00002 (phase 3 randomised, double blind, placebo controlled study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients with a complete or partial response following platinum based chemotherapy) in the RMP. Annex II is amended accordingly

15.3.38. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0009/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.2 and 5.2 of the SmPC to include information related to hepatic impairment based on the results of study D0816C00005 (MEA 005) (an open-label, non-randomised, multicentre, comparative, phase 1 study to determine the pharmacokinetics, safety and tolerability of olaparib following a single oral 300 mg dose to patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment). In addition, sections 4.4 and 4.5 are updated to include information related to moderate cytochrome P450, family 3, subfamily A (CYP3A) inducers based on

the addendum to the Simcyp modelling report. The Package Leaflet and RMP are updated accordingly

15.3.39. Oritavancin - ORBACTIV (CAP) - EMEA/H/C/003785/II/0012/G

Applicant: The Medicines Company UK Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations to: 1) update sections 4.4 and 4.5 of the SmPC in order to delete the warning related to the interaction with warfarin and include the results of the interaction study (MDCO-ORI-14-02: an open-label study to assess the drug-drug interaction potential of a single 1200 mg intravenous (IV) dose of oritavancin co-administered with warfarin in healthy subjects) respectively. The Package Leaflet and RMP (version 2.2) are updated accordingly; 2) update of the RMP (version 2.2) to delete the category 3 study MDCO-ORI-14-03 (an open-label study to evaluate the safety of a single 1200 mg IV dose of oritavancin in subjects on concomitant chronic warfarin therapy being treated for acute bacterial skin and skin structure infection (ABSSSI))

15.3.40. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0004

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.2 of the SmPC to reflect the results of study 20 performed to assess the absolute bioavailability and to evaluate the pharmacokinetic (PK) parameters of osimertinib in plasma following a single oral dose and a radio-labelled intravenous (IV) microdose of [¹⁴C] Tagrisso in healthy male subjects. In addition, the MAH took the opportunity to make a minor correction in SmPC section 6.5 and the Package Leaflet, where blister strips have been amended to blisters. The RMP (version 5.0) is updated accordingly

15.3.41. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/II/0026

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of study MO22324 (PHEREXA), a multicentre randomized phase III study to compare the combination of trastuzumab and capecitabine, with or without pertuzumab, in patients with human epidermal growth factor-2 (HER2)-positive metastatic breast cancer that have progressed after one line of trastuzumab-based therapy in the metastatic setting. Annex II is updated to reflect the fulfilment of the condition of the Marketing Authorisation. The RMP (version 7.0) is updated accordingly. In addition, the MAH took the opportunity to include in the RMP a minor amendment to the BERENICE protocol (a multicentre, multinational, phase 2 study to evaluate pertuzumab in combination with trastuzumab and standard neoadjuvant anthracycline-based chemotherapy in patients with human epidermal growth factor (HER2)-positive, locally advanced, inflammatory, or early-stage breast cancer)

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

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: 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): F. Hoffmann-La Roche Ltd, Basel, Switzerland as an alternative site responsible for quality control of the active substance; Synlab Umweltinstitut GmbH, Linz, Austria, as an alternative site responsible for quality control of the active substance

15.3.43. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - SYNFLORIX (CAP) - EMEA/H/C/000973/II/0108

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of sections 4.2 4.4, 4.8 and 5.1 of the SmPC in order to add information obtained from two clinical studies in subjects at risk for pneumococcal infections (study 10PN-PD-DIT-034 (open label, controlled study in South Africa to evaluate the immunogenicity, safety and reactogenicity of Synflorix administered as a 3-dose primary immunisation course in human immunodeficiency virus (HIV) infected infants, HIV exposed uninfected infants and HIV unexposed uninfected infants) and study 10PN-PD-DIT-064 (open, controlled study to evaluate immunogenicity, safety and reactogenicity of Synflorix administered intramuscularly to sickle cell disease subjects from 8 weeks to less than 2 years of age, as compared to age-matched healthy subjects). In addition, the MAH took the opportunity to introduce consequential changes to the RMP and to change the final due date of a post-marketing surveillance study

15.3.44. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0042/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 5.1 of the SmPC following the submission of a prospective, single-arm, non-interventional, open-label cohort study conducted to investigate the safety and effectiveness in a real-world setting, study XANTUS (SN 15914) in order to fulfil MEA 025. In addition, update of section 5.1 of the SmPC following the submission of a prospective, non-interventional, open-label cohort study that was conducted in patients with acute deep vein thrombosis (DVT) to investigate the safety and effectiveness in a real-world setting, study XALIA (SN 15915) in order to fulfil MEA 027. The RMP (version 9.0) is updated accordingly. Additionally the final clinical study reports for studies X-TRA (SN 16320, phase IIIb) and VENTURE-AF (SN 15694, phase IIIb) were also included in the RMP. Finally, the MAH took the opportunity to introduce a minor editorial change in the list of representatives in the package leaflets of all strengths

15.3.45. 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

15.3.46. Sevelamer - RENVELA (CAP) - EMEA/H/C/000993/WS0965/0035; SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/WS0965/0007

Applicant: Genzyme Europe BV

PRAC Rapporteur: Veerle Verlinden

Scope: Extension of indication to include the control of hyperphosphataemia in paediatric patients (>6 years of age and a body surface area (BSA) of >0.75 m²) with chronic kidney disease. As a consequence, section 4.2 of the SmPC is updated to detail the posology in the paediatric patients. The Package Leaflet is updated accordingly

15.3.47. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/X/0049/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Line extension to add a new pharmaceutical form (concentrate for solution for infusion), a new strength (130 mg) and a new route of administration (intravenous use) as well as an extension of indication to add as a new indication the treatment of Crohn's disease

15.3.48. Vismodegib - ERIVEDGE (CAP) - EMEA/H/C/002602/II/0025/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4, 4.6, 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information in the product information after finalisation of study MO25616 (specific obligation (SOB) 013) (a single arm, open-label, Phase 2, multicentre

study to assess the safety of vismodegib in patient with locally advanced or metastatic basal cell carcinoma (BCC)). Considering the fulfilment of the SOB, the MAH also proposed the switch of the conditional marketing authorisation (MA) to a full MA not subject to specific obligations. Data from the same study also fulfilled the analysis required in MEA 005 regarding evaluation of the time for washout of vismodegib after treatment discontinuation and in MEA 008 regarding reporting of adverse events. The Package Leaflet and the RMP are updated accordingly. Furthermore, the MAH took the opportunity to update the RMP with regard to the results from non-clinical studies subject to variation II/21 and to propose the deletion of hyponatremia as an important potential risk in the RMP and as an adverse drug reaction in the product information as per the outcome of the latest PSUR procedure (PSUSA/00010140/201407)

15.3.49. Vismodegib - ERIVEDGE (CAP) - EMEA/H/C/002602/II/0029

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC with additional information to describe the risk of epiphyses premature fusion in paediatric patients. The Package Leaflet and RMP (version 9.2) are updated accordingly. In addition, the MAH took the opportunity to include some editorial changes in the product information

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

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

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

16.1. PSUR procedures including centrally authorised products only

16.1.1. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201601

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.2. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/201601

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.3. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/201601

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.4. Axitinib - INLYTA (CAP) - PSUSA/00010022/201601

Applicant: Pfizer Limited

PRAC Rapporteur: Helga Haugom Olsen

Scope: Evaluation of a PSUSA procedure

16.1.5. Besilesomab - SCINTIMUN (CAP) - PSUSA/00000385/201601 (with RMP)

Applicant: Cis Bio International

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.6. Bevacizumab - AVASTIN (CAP) - PSUSA/00000403/201602

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.7. Brentuximab vedotin - ADCETRIS (CAP) - PSUSA/00010039/201602

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.8. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/201601

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marina Dimov Di Giusti

Scope: Evaluation of a PSUSA procedure

16.1.9. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/201602

Applicant: Roche Registration Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.10. Colistimethate sodium (dry inhalation powder) - COLOBREATHE (CAP) - PSUSA/00009112/201602

Applicant: Forest Laboratories UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.11. Copper (⁶⁴Cu) chloride - CUPRYMINA (CAP) - PSUSA/00010040/201602

Applicant: Sparkle S.r.l.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.12. Dapagliflozin, metformin - EBYMECT (CAP); XIGDUO (CAP) - PSUSA/00010294/201601

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.13. Degarelix - FIRMAGON (CAP) - PSUSA/00000944/201602 (with RMP)

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.14. Dexamethasone⁶⁷ - OZURDEX (CAP) - PSUSA/00000985/201601

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.15. Dinutuximab - UNITUXIN (CAP) - PSUSA/00010420/201602

Applicant: United Therapeutics Europe Ltd

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

⁶⁷ Indicated in uveitis and macular oedema

16.1.16. Dolutegravir - TIVICAY (CAP); dolutegravir, abacavir, lamivudine - TRIUMEO (CAP) - PSUSA/00010075/201601

Applicant: ViiV Healthcare UK Limited
PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.17. Eliglustat - CERDELGA (CAP) - PSUSA/00010351/201601

Applicant: Genzyme Europe BV
PRAC Rapporteur: Dolores Montero Corominas
Scope: Evaluation of a PSUSA procedure

16.1.18. Elosulfase alfa - VIMIZIM (CAP) - PSUSA/00010218/201602

Applicant: BioMarin Europe Ltd
PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.19. Entacapone - COMTAN (CAP); COMTESS (CAP); ENTACAPONE ORION (CAP) - PSUSA/00001223/201601

Applicant: Novartis Europharm Ltd (Comtan), Orion Corporation (Comtess, Entacapone Orion)
PRAC Rapporteur: Kirsti Villikka
Scope: Evaluation of a PSUSA procedure

16.1.20. Evolocumab - REPATHA (CAP) - PSUSA/00010405/201601

Applicant: Amgen Europe B.V.
PRAC Rapporteur: Kimmo Jaakkola
Scope: Evaluation of a PSUSA procedure

16.1.21. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/201602

Applicant: Chiesi Farmaceutici S.p.A.
PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.22. Fampridine - FAMPYRA (CAP) - PSUSA/00001352/201601

Applicant: Biogen Idec Ltd.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.23. Fenofibrate, simvastatin - CHOLIB (CAP) - PSUSA/00010096/201602

Applicant: BGP Products Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.24. Gadoversetamide - OPTIMARK (CAP) - PSUSA/00001508/201601

Applicant: Mallinckrodt Deutschland GmbH

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.25. Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed) - FENDRIX (CAP) - PSUSA/00001598/201602

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.26. Human alpha 1-proteinase inhibitor - RESPREEZA (CAP) - PSUSA/00010410/201602

Applicant: CSL Behring GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.27. Human coagulation factor VIII, human von Willebrand factor⁶⁸ - VONCENTO (CAP) - PSUSA/00010102/201602

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.28. Idelalisib - ZYDELIG (CAP) - PSUSA/00010303/201601

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

⁶⁸ Centrally authorised product only

Scope: Evaluation of a PSUSA procedure

16.1.29. [Infliximab⁶⁹ - INFLECTRA \(CAP\); REMSIMA \(CAP\) - PSUSA/00010106/201601](#)

Applicant: Celltrion Healthcare Hungary Kft. (Remsima), Hospira UK Limited (Inflixtra)

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.30. [Insulin glargine - ABASAGLAR \(CAP\); LANTUS \(CAP\); TOUJEO \(CAP\) - PSUSA/00001751/201602](#)

Applicant: Eli Lilly Regional Operations GmbH (Abasaglar), Sanofi-aventis Deutschland GmbH (Lantus, Toujeo)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.31. [Ivacaftor - KALYDECO \(CAP\) - PSUSA/00009204/201601 \(with RMP\)](#)

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.32. [Lamivudine⁷⁰ - EPIVIR \(CAP\); lamivudine, zidovudine - COMBIVIR \(CAP\) - PSUSA/00009207/201511](#)

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.33. [Lenvatinib - LENVIMA \(CAP\) - PSUSA/00010380/201602](#)

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.34. [Lipegfilgrastim - LONQUEX \(CAP\) - PSUSA/00010111/201601](#)

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

⁶⁹ Biosimilars only

⁷⁰ Indicated in human immunodeficiency virus infections

16.1.35. Lixisenatide - LYXUMIA (CAP) - PSUSA/00010017/201601

Applicant: Sanofi-Aventis Groupe
PRAC Rapporteur: Qun-Ying Yue
Scope: Evaluation of a PSUSA procedure

16.1.36. Meningococcal group-B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - PSUSA/00010043/201601

Applicant: GSK Vaccines S.r.l
PRAC Rapporteur: Qun-Ying Yue
Scope: Evaluation of a PSUSA procedure

16.1.37. Modified vaccinia Ankara virus - IMVANEX (CAP) - PSUSA/00010119/201601

Applicant: Bavarian Nordic A/S
PRAC Rapporteur: Rafe Suvarna
Scope: Evaluation of a PSUSA procedure

16.1.38. Nilotinib - TASIGNA (CAP) - PSUSA/00002162/201601

Applicant: Novartis Europharm Ltd
PRAC Rapporteur: Doris Stenver
Scope: Evaluation of a PSUSA procedure

16.1.39. Nitisinone - ORFADIN (CAP) - PSUSA/00002169/201602

Applicant: Swedish Orphan Biovitrum International AB
PRAC Rapporteur: Carmela Macchiarulo
Scope: Evaluation of a PSUSA procedure

16.1.40. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201601

Applicant: Bristol-Myers Squibb Pharma EEIG
PRAC Rapporteur: Brigitte Keller-Stanislowski
Scope: Evaluation of a PSUSA procedure

16.1.41. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/201602

Applicant: Novartis Europharm Ltd
PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.42. Pegfilgrastim - NEULASTA (CAP); RISTEMPA (CAP) - PSUSA/00002326/201601

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.43. Peginterferon beta-1A - PLEGRIDY (CAP) - PSUSA/00010275/201601 (with RMP)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.44. Pegloticase - KRYSTEXXA⁷¹ - PSUSA/00010046/201601

Applicant: Crelta Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.45. Perampanel - FYCOMPA (CAP) - PSUSA/00009255/201601

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.46. Perflutren - LUMINITY (CAP); OPTISON (CAP) - PSUSA/00002350/201512

Applicant: GE Healthcare AS (Optison), Lantheus MI UK Ltd. (Luminity)

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.47. Phenylephrine, ketorolac - OMIDRIA (CAP) - PSUSA/00010419/201601

Applicant: Omeros London Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.48. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) - PREVENAR 13 (CAP) - PSUSA/00009263/201601

Applicant: Pfizer Limited

⁷¹ EC decision on the MA withdrawal of Krystexxa dated 30 June 2016

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.49. Pomalidomide - IMNOVID (CAP) - PSUSA/00010127/201602 (with RMP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.50. Prasugrel - EFIENT (CAP) - PSUSA/00002499/201602

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.51. Pyronaridine, artesunate - PYRAMAX (Art 58⁷²) – EMEA/H/W/002319/PSUV/0013

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.52. Rasagiline - AZILECT (CAP); RASAGILINE RATIOPHARM (CAP) - PSUSA/00002612/201601

Applicant: Teva B.V.

PRAC Rapporteur: Leonor Chambel

Scope: Evaluation of a PSUSA procedure

16.1.53. Roflumilast - DALIRESP (CAP); DAXAS (CAP); LIBERTEK (CAP) - PSUSA/00002658/201601

Applicant: Takeda GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.54. Rufinamide - INOVELON (CAP) - PSUSA/00002671/201601

Applicant: Eisai Ltd

PRAC Rapporteur: Claire Ferard

⁷² 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)

Scope: Evaluation of a PSUSA procedure

16.1.55. Sacubitril, valsartan - ENTRESTO (CAP) - PSUSA/00010438/201601

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.56. Safinamide - XADAGO (CAP) - PSUSA/00010356/201602

Applicant: Zambon SpA

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.57. Samarium (¹⁵³Sm) lexidronam - QUADRAMET (CAP) - PSUSA/00002682/201602

Applicant: Cis Bio International

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.58. Silodosin - SILODYX (CAP); UROREC (CAP) - PSUSA/00002701/201601

Applicant: Recordati Ireland Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.59. Simoctocog alfa - NUWIQ (CAP) - PSUSA/00010276/201601

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.60. Sodium phenylbutyrate - AMMONAPS (CAP); PHEBURANE (CAP) - PSUSA/00002758/201512

Applicant: Lucane Pharma (Pheburane), Swedish Orphan Biovitrum International AB (Ammonaps)

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.61. Sugammadex - BRIDION (CAP) - PSUSA/00002799/201601

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.62. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201601

Applicant: Vanda Pharmaceuticals Ltd.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.63. Trastuzumab emtansine - KADCYLA (CAP) - PSUSA/00010136/201602

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.64. Velaglucerase alfa - VPRIV (CAP) - PSUSA/00003103/201602

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.65. Vorapaxar - ZONTIVITY (CAP) - PSUSA/00010357/201601

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Alendronic acid, colecalciferol - ADROVANCE (CAP); FOSAVANCE (CAP); VANTAVO (CAP); NAP - PSUSA/00000079/201601

Applicant: Merck Sharp & Dohme Limited (Adrovanche, Fosavance, Vantavo), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.2.2. Riluzole - RILUTEK (CAP); RILUZOLE ZENTIVA (CAP); NAP - PSUSA/00002645/201512

Applicant: Aventis Pharma S.A. (Rilutek, Riluzole Zentiva), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.2.3. Rivastigmine - EXELON (CAP); PROMETAX (CAP); RIVASTIGMINE 1A PHARMA (CAP); RIVASTIGMINE HEXAL (CAP); RIVASTIGMINE SANDOZ (CAP); NAP - PSUSA/00002654/201601

Applicant: Novartis Europharm Ltd (Exelon, Prometax), 1 A Pharma GmbH (Rivastigmine 1A Pharma), Hexal AG (Rivastigmine Hexal), Sandoz GmbH (Rivastigmine Sandoz), various

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.2.4. Sufentanil - ZALVISO (CAP); NAP - PSUSA/00002798/201511

Applicant: Grunenthal GmbH (Zalviso), various

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acipimox (NAP) - PSUSA/00000050/201512

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.2. Alanine, arginine, aspartic acid, cysteine, glucose anhydrous, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, olive oil refined, ornithine, phenylalanine, proline, serine, sodium chloride, sodium glycerophosphate hydrated, soya bean oil refined, taurine, threonine, tryptophan, tyrosine, valine, potassium acetate, calcium chloride dihydrate, magnesium acetate tetrahydrate (NAP) - PSUSA/00010190/201512

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.3. Alendronate (NAP) - PSUSA/00000078/201601

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.4. Bisoprolol, hydrochlorothiazide (NAP) - PSUSA/00000420/201511

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.5. Caffeine, ergotamine (NAP) - PSUSA/00000485/201511

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.6. Carboprost (NAP) - PSUSA/00000560/201601

Applicant: various

PRAC Lead: Jana Mlada

Scope: Evaluation of a PSUSA procedure

16.3.7. Cefotaxime (NAP) - PSUSA/00000599/201512

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.8. Ciclosporin (systemic use) (NAP) - PSUSA/00000745/201512

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.9. Exemestane (NAP) - PSUSA/00001345/201512

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.10. Flumazenil (NAP) - PSUSA/00001413/201512

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.11. Flunitrazepam (NAP) - PSUSA/00001418/201601

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.12. Gaxilose (NAP) - PSUSA/00010283/201601

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.3.13. Ketamine (NAP) - PSUSA/00001804/201512

Applicant: various

PRAC Lead: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

16.3.14. Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide (NAP) - PSUSA/00010390/201601

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.15. Lubiprostone (NAP) - PSUSA/00010290/201601

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.16. Magnesium sulphate, sodium sulphate, potassium sulphate (NAP) - PSUSA/00010239/201602

Applicant: various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

16.3.17. Niflumic acid (NAP) - PSUSA/00002157/201512

Applicant: various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.18. Rupatadine (NAP) - PSUSA/00002673/20151

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.3.19. Sertindole (NAP) - PSUSA/00002695/201601

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.20. Valaciclovir (NAP) - PSUSA/00003086/201512

Applicant: various

PRAC Lead: Jana Mlada

Scope: Evaluation of a PSUSA procedure

16.3.21. Zafirlukast (NAP) - PSUSA/00003138/201512

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Basiliximab - SIMULECT (CAP) - EMEA/H/C/000207/LEG 043

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of a detailed analysis and review of cases of certain types of adverse drug reactions (ADRs) including 'new onset diabetes after transplantation (NODAT)', 'polyomavirus infections' and 'hepatotoxicity' and the exclusion criteria applied to cases with confounders, e.g. time to onset (TTO) >40 days, sepsis or unknown information on

TTO or indication as requested in the conclusions of PSUSA/00000301/201504 [PSUR#17 on three yearly frequency] adopted by PRAC and CHMP in December 2015

16.4.2. Bortezomib - VELCADE (CAP) - EMEA/H/C/000539/LEG 053.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: MAH's response to the request for supplementary information (RSI) dated April 2016 of LEG 053 on the evaluation of a cumulative review of cases reporting progressive multifocal leukoencephalopathy (PML) with the use of bortezomib submitted by the MAH as requested in the conclusions of PSUSA/00000424/201504 procedure adopted by PRAC and CHMP in November 2015

16.4.3. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/LEG 004

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a detailed review on hypersensitivity as requested in the conclusions of PSUSA/00010029/201510 procedure adopted by PRAC and CHMP in April 2016

16.4.4. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/LEG 021

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a detailed review on hypersensitivity as requested in the conclusions of PSUSA/00010029/201510 procedure adopted by PRAC and CHMP in April 2016

16.4.5. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 032

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a detailed review on hypersensitivity reactions and dermatologic reactions (including myositis and rhabdomyolysis) as requested in the conclusions of PSUSA/00009329/201508/0027 procedure adopted by PRAC and CHMP in March 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)⁷³

17.1.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSP/0041.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Mladá

Scope: MAH's response to a request for supplementary information (RSI) as per the outcome of PSP/0041 [protocol for study 20150136: an observational study measuring the safety and effectiveness of blinatumomab as well as utilisation and treatment practices] adopted by PRAC in April 2016

Action: For adoption of PRAC Assessment Report, PRAC outcome letter

17.1.2. Ethinylestradiol (NAP); ethinylestradiol, levonorgestrel (NAP) - EMEA/H/N/PSP/0037.1

Applicant: Teva Pharma B.V. (Seasonique)

PRAC Rapporteur: Claire Ferard

Scope: Submission of a revised protocol as per the outcome of PSP/0037 adopted by PRAC in March 2016 for a post-authorisation safety study to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique: a retrospective longitudinal cohort study assessing the safety of short and long-term use of Seasonique

Action: For adoption of PRAC Assessment Report, PRAC outcome letter

17.1.3. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/PSP/0040.1

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Submission of a revised protocol as per the outcome of PSP/0040 adopted by PRAC in March 2016 for a post-authorisation safety study: a multi-country, observational registry to collect clinical information on patients with Cushing syndrome patients exposed to ketoconazole (preferably using the existing European Registry on Cushing's syndrome (ERCUSYN) registry), to assess drug utilisation patterns and to document the safety and effectiveness of ketoconazole

Action: For adoption of PRAC Assessment Report, PRAC outcome letter

17.1.4. Pitolisant - WAKIX (CAP) - EMEA/H/C/PSP/0039.1

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of a revised protocol for a multicentre, observational PASS to document the drug utilisation of Wakix and to collect information on the safety of Wakix

⁷³ In accordance with Article 107n of Directive 2001/83/EC

when used in routine medical practice

17.1.5. Poly (o-2-hydroxyethyl) starch (NAP) - EMEA/H/N/PSP/j/0008

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a revised protocol for a retrospective drug utilisation study to investigate the routine use of hydroxyethyl starch (HES)-containing infusion solutions in hospitals

17.1.6. Thiocolchicoside (NAP) - EMEA/H/N/PSP/j/0030.2

Applicant: Sanofi-Aventis Recherche & Développement, other companies involved in the consortium

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of a revised protocol for a 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

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁷⁴

17.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 006.1

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of a revised protocol for a pregnancy registry study OBS13436: an international Lemtrada pregnancy exposure cohort in multiple sclerosis

17.2.2. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 003; FORXIGA (CAP) - EMEA/H/C/002322/MEA 020

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a PASS protocol to evaluate the incidence of diabetic ketoacidosis (DKA) in SGLT-2-inhibitors as an outcome of the recently completed Article 20 referral on sodium-dependent glucose cotransporters (SGLT)-2 inhibitors (EMEA/H/A-20/1419)

⁷⁴ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.3. [Dapagliflozin, metformin - EBYMECT \(CAP\) - EMEA/H/C/004162/MEA 003;](#)
[XIGDUO \(CAP\) - EMEA/H/C/002672/MEA 006](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Submission of a PASS protocol to evaluate the incidence of diabetic ketoacidosis (DKA) in SGLT-2-inhibitors as an outcome of the recently completed Article 20 referral on sodium-dependent glucose cotransporters (SGLT)-2 inhibitors (EMEA/H/A-20/1419)

17.2.4. [Eculizumab - SOLIRIS \(CAP\) - EMEA/H/C/000791/MEA 053](#)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Submission of an amended PASS protocol M07-001: a prospective registry for an observational, multicentre, multinational study of patients with paroxysmal nocturnal haemoglobinuria (PNH) , to update the list of targeted AEs for safety reporting, collect all SAEs irrespective of eculizumab treatment status, changes in language for data collection and administrative changes

17.2.5. [Edoxaban - LIXIANA \(CAP\) - EMEA/H/C/002629/MEA 005.2](#)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Submission of a revised PASS protocol for study DSE-EDO-01-14-EU: a drug utilisation study (DUS) for exploring edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study

17.2.6. [Edoxaban - LIXIANA \(CAP\) - EMEA/H/C/002629/MEA 006.2](#)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: submission of a revised PASS protocol for study DSE-EDO-04-14-EU: a non-interventional study on edoxaban treatment in routine clinical practice for patients with non valvular atrial fibrillation

17.2.7. [Edoxaban - LIXIANA \(CAP\) - EMEA/H/C/002629/MEA 007.2](#)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Submission of a revised PASS protocol for study DSE-EDO-05-14-EU: a non-interventional study on edoxaban treatment in routine clinical practice in patients with venous thromboembolism in Europe

17.2.8. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 004.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA-004.1 [PASS study 1245.97 to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 mellitus diabetes: a multi-database European study, preceded by feasibility assessment] as per request for supplementary information (RSI) adopted in May 2016

17.2.9. Fenofibrate, simvastatin - CHOLIB (CAP) - EMEA/H/C/002559/MEA 002.3

Applicant: BGP Products Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA-002.2 [revised PASS protocol for study ABT285.E.001: a drug utilisation research (DUR) study on the use of fenofibrate and simvastatin fixed combination: a European multinational study using secondary health records databases] as per the request for supplementary information (RSI) adopted in February 2016

17.2.10. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/MEA 016

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Submission of a PASS protocol for a study PCI-1103-CA: open-label, extension trial in subjects with B-cell lymphoma and chronic lymphocytic leukaemia (CLL) to determine the long-term safety of ibrutinib

17.2.11. Panobinostat - FARYDAK (CAP) - EMEA/H/C/003725/MEA 002.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA-002.1 [PASS study LBH589D2408 on panobinostat use in relapsed or relapsed/refractory multiple myeloma patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent in a real-world setting according to the current EU prescribing information and document adherence to dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of the medication error events] as per request for supplementary information (RSI) adopted in May 2016

17.2.12. Safinamide - XADAGO (CAP) - EMEA/H/C/002396/MEA 004.1

Applicant: Zambon SpA

PRAC Rapporteur: Almath Spooner

Scope: MAH's response to MEA 004 [protocol for study Z7219N02: a drug utilisation study (DUS): observational European multicentre retrospective-prospective cohort study

to observe Sofinamide safety profile and pattern of use in clinical practice during the first post-commercialisation phase] as per request for supplementary information (RSI) adopted in January 2016

17.2.13. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/MEA 021.2

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's responses to MEA 021.1 [protocol for study GS-EU-337-2030: an observational, cross-sectional post-authorisation safety study to assess healthcare providers awareness of risks related to sofosbuvir and ledipasvir/sofosbuvir (LDV/SOF)] as per request for supplementary information adopted as adopted in June 2016

17.2.14. Sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 014.2

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: MAH's responses to MEA 014.1 [protocol for study GS-EU-337-2030: an observational, cross-sectional PASS to assess healthcare providers awareness of risks related to sofosbuvir and ledipasvir/sofosbuvir (LDV/SOF)] as per request for supplementary information as adopted as adopted in June 2016

17.2.15. Telavancin - VIBATIV (CAP) - EMEA/H/C/001240/ANX 007.4

Applicant: Clinigen Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to a request for supplementary information (RSI) as per the outcome of ANX/007.3 on pregnancy exposure registry (9809-CL-1409) as adopted in June 2015

17.2.16. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA-044 [draft protocol for an adolescent registry: an observational PASS of ustekinumab in the treatment of pediatric patients aged 12 years and older with moderate to severe plaque psoriasis] as per the request for supplementary information (RSI) adopted in March 2016

17.2.17. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/MEA 026.3

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 026.2 [revised PASS protocol for vernakalant

intravenous (IV) sterile concentrate prospective safety registry study: a prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant intravenous (IV) sterile concentrate (study 6621 049-00)] as per request for supplementary information (RSI) adopted by PRAC in July 2016

17.3. Results of PASS imposed in the marketing authorisation(s)⁷⁵

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁷⁶

17.4.1. Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS0890/0107; aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/WS0890/0077

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Submission of the final results of study SPP100A2417: a multi-database cohort study to assess the incidence rates of colorectal hyperplasia among hypertensive patients

17.4.2. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/II/0037/G

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations: Submission of final study reports of two drug utilisation studies (DUS) examining the utilisation pattern of apixaban in Sweden (study B0661017) and in the Netherlands (study B0661018) to fulfil post-approval measures listed in the RMP. The RMP is updated to reflect the data from the two completed DUS, to reflect the ongoing DUS in Denmark (study B0661073), to reflect changes approved in the SmPC with regard to the administration as a crushed tablet (II/030) and to the prothrombin complex concentrates (II/029), as well as to include minor updates to various post-marketing commitment studies.

17.4.3. Betaine anhydrous - CYSTADANE (CAP) - EMEA/H/C/000678/II/0025

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

PRAC Rapporteur: Valerie Strassmann

Scope: Submission of the final report of Cystadane surveillance registry (in collaboration with the European network and registry for homocystinurias and methylation defects (E-HOD)): long-term clinical and safety information in patients with cystathionine betasynthase (CBS), 5, 10-methylenetetrahydrofolate reductase (MTHFR) or cobalamin

⁷⁵ In accordance with Article 107p-q of Directive 2001/83/EC

⁷⁶ 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

cofactor metabolism (Cbl) treated with Cystadane

17.4.4. Boceprevir - VICTRELIS (CAP) - EMEA/H/C/002332/II/0039

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Claire Ferard

Scope: Submission of the final report for the category 3 observational PASS (study P08518) of Victrelis among chronic hepatitis C patients (observational prospective follow-up study to assess the utilisation of boceprevir and the management of pre-specified health outcomes of interest (HOIs) under conditions of routine clinical care). The RMP (version 10.0) is updated accordingly

17.4.5. 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

17.4.6. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/II/0008

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of the final clinical study report (CSR) for the 100 weeks open-label extension phase of study SB4-G31-RA (a phase III study, as safety follow-up to evaluate the long-term safety, tolerability, immunogenicity and efficacy of Benepali in subjects with rheumatoid arthritis (RA) treated previously with Benepali or Enbrel (category 3 study listed in the RMP)) to fulfil MEA 001. In addition, the MAH took the opportunity to update the RMP to reflect the changes introduced to Annex II of the Product Information during the initial Marketing Authorisation (MA)

17.4.7. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0198

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of the final clinical study report (CSR) for the British Society for Paediatric and Adolescent Rheumatology (BSPAR) etanercept registry, a cohort study (category 3 study)

17.4.8. [Glycopyrronium bromide - ENUREV BREEZHALER \(CAP\) - EMEA/H/C/002691/WS1002/0017; SEEBRI BREEZHALER \(CAP\) - EMEA/H/C/002430/WS1002/0017; TOVANOR BREEZHALER \(CAP\) - EMEA/H/C/002690/WS1002/0019](#)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final study report (CSR) of study CNVA237A2401T: a multinational, multi-database drug utilisation study of inhaled NVA237 in Europe to estimate the subpopulation with cardio- and cerebrovascular co-morbidity and to identify patient groups with missing information as per the RMP. The RMP (version 6.0) is updated accordingly

17.4.9. [Influenza vaccine \(live attenuated, nasal\) - FLUENZ TETRA \(CAP\) - EMEA/H/C/002617/II/0055](#)

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final clinical study report (CSR) for PASS study MA-VA-MEDI3250-1115: a post-marketing cohort study of the safety of Fluenz Tetra in subjects from 2 to 49 years of age

17.4.10. [Influenza vaccine \(live attenuated, nasal\) - FLUENZ TETRA \(CAP\) - EMEA/H/C/002617/II/0057](#)

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final study report for PASS D2660R00002: a non-interventional study of live attenuated influenza vaccine (LAIV) utilisation to identify and characterize medication errors due to expired vaccine use in individuals 2-17 years of age in the clinical practice research datalink (CPRD)

17.4.11. [Insulin glargine - LANTUS \(CAP\) - EMEA/H/C/000284/II/0105](#)

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report for a PASS: UK SoloStar differentiation study: a study in patients with type 1 or type 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin with the current and new labels. This submission addresses MEA 037

17.4.12. [Insulin glulisine – APIDRA \(CAP\) - EMEA/H/C/000557/II/0066](#)

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Julie Williams

Scope: Submission of the final clinical study report for a PASS: UK SoloStar differentiation study, a study in patients with type 1 or type 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin with the current and new labels. This submission addresses MEA 037

17.4.13. [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/II/0038](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study report for study CA184242: a risk minimisation tool effectiveness evaluation survey. The RMP (version 12) is updated accordingly

17.4.14. [Liraglutide - SAXENDA \(CAP\) - EMEA/H/C/003780/WS0943/0009; VICTOZA \(CAP\) - EMEA/H/C/001026/WS0943/0041](#)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final results from the study and sub-study on breast cancer: 'liraglutide safety and surveillance programme using the Optum research database' (category 3 study)

17.4.15. [Romiplostim - NPLATE \(CAP\) - EMEA/H/C/000942/II/0057](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva A. Segovia

Scope: Submission of the final clinical study report (CSR) for study 20120269: a study assessing the proportion of subjects with chronic idiopathic thrombocytopenic purpura (ITP) and their caregivers who administer romiplostim correctly after receipt of the home administration training (HAT) materials

17.4.16. [Saxagliptin - ONGLYZA \(CAP\) - EMEA/H/C/001039/WS0960/0040/G; saxagliptin, metformin hydrochloride - KOMBOGLYZE \(CAP\) - EMEA/H/C/002059/WS0960/0033/G](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of the final results of five epidemiological study for: 1) study D1680R00011 (comparison of risk of major cardiovascular events between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments), 2) study D1680R00012 (comparison of risk of hospitalisation with acute liver failure between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments), 3) study D1680R00013 (comparison of risk of hospitalisation for infection between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatment), 4) study D1680R00014 (comparison of risk of hospitalisation for severe hypersensitivity (including severe

cutaneous) reactions between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatment), 5) study D1680R00015 (comparison of risk of hospitalisation for acute kidney injury between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatment). The RMP (version 11) is updated accordingly and include further routine changes. In addition, a safety review based on literature is included to investigate acute kidney injury associated with saxagliptin and saxagliptin/metformin following a previous PRAC request

17.4.17. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/II/0041

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final results of study PGL10-014 (PREMYA): a prospective multicentre non-interventional study of women treated with Esmya (ulipristal acetate) as preoperative treatment of moderate to severe symptoms of uterine fibroids. The RMP is updated accordingly

17.4.18. Voriconazole - VFEND (CAP) - EMEA/H/C/000387/II/0121

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of the results of study A1501102: a non-interventional post authorisation safety study (PASS), evaluating the effectiveness of additional risk minimisation measure that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in the European Union (EU). As a consequence, the RMP (version 5) is updated accordingly

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation⁷⁷

17.5.1. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/MEA 005.1

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Second annual report for the multicentre, multinational, observational study: Morquio A registry study (MARS)

17.5.2. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Annual interim report for study 1245.96: an observational cohort study using

⁷⁷ In line with the revised variations regulation for any submission before 4 August 2013

existing data including diabetic ketoacidosis (DKA) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors

17.5.3. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003

Applicant: Boehringer Ingelheim GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Annual interim report for study 1245.96: an observational cohort study using existing data including diabetic ketoacidosis (DKA) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors

17.5.4. Indacaterol, glycopyrronium bromide - ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/ANX 002.3; ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/ANX 003.2; XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/ANX 002.3

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Second interim report for study CQVA149A2402: a multinational database cohort study to assess RMP specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe

17.5.5. Indacaterol, glycopyrronium bromide - ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/MEA 003.4; ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/MEA 004.3; XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/MEA 003.4

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Second interim report for a drug utilisation study (DUS) CQVA 149A2401: multinational, multi-database drug utilisation study of indacaterol/glycopyrronium bromide in Europe

17.5.6. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 007.1

Applicant: Hospira UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of the MAH's response to MEA-007: annual safety and efficacy interim analysis for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra in patients with rheumatoid arthritis (EU and Korea) as per the request for supplementary information (RSI) adopted in September 2015

17.5.7. [Infliximab - INFLECTRA \(CAP\) - EMEA/H/C/002778/MEA 010.1](#)

Applicant: Hospira UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of the MAH's response to MEA-010: annual safety and efficacy interim analysis for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea) as per the request for supplementary information (RSI) adopted in September 2015

17.5.8. [Infliximab - REMSIMA \(CAP\) - EMEA/H/C/002576/MEA 007.1](#)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of the MAH's response to MEA-007: annual safety and efficacy interim analysis for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra in patients with rheumatoid arthritis (EU and Korea) as per the request for supplementary information (RSI) adopted in September 2015

17.5.9. [Infliximab - REMSIMA \(CAP\) - EMEA/H/C/002576/MEA 010.1](#)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of the MAH's response to MEA-010: annual safety and efficacy interim analysis for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea) as per the request for supplementary information (RSI) adopted in September 2015

17.5.10. [Influenza vaccine \(live attenuated, nasal\) - FLUENZ TETRA \(CAP\) - EMEA/H/C/002617/MEA 004.6](#)

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of the MAH's response to MEA-004.5 [interim results of the enhanced safety surveillance study D2560C00008: a postmarketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age] per the request for supplementary information (RSI) adopted in June 2016

17.5.11. [Insulin lispro - HUMALOG \(CAP\) - EMEA/H/C/000088/MEA 028.3](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Interim results of a category 3 PASS study: post-approval safety surveillance to

assess the changes in frequency of hypersensitivity and immunogenicity events with the new manufacturing process (sKPB) of Humalog and Liprolog

17.5.12. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/MEA 021.3

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Interim results of a category 3 PASS study: post-approval safety surveillance to assess the changes in frequency of hypersensitivity and immunogenicity events with the new manufacturing process (sKPB) of Humalog and Liprolog

17.5.13. Meningococcal group B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 017.1

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Interim progress report for study V72_36OB: an observational safety study after meningococcal B vaccine Bexsero vaccination in routine UK care settings

17.5.14. Ospemifene - SENSHIO (CAP) - EMEA/H/C/PSP/0023.3

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

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

17.5.15. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/MEA 004.4

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

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

17.5.16. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 256.8

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Claire Ferard

Scope: Interim results for study GS-EU-174-0224: a drug utilisation study (DUS) in

human immunodeficiency virus (HIV)-1 and hepatitis B virus (HBV)-infected paediatric patients to follow-up the effectiveness of the risk minimisation measures

17.5.17. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/MEA 011.2

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Third annual interim report for study H4621g (MoTHER pregnancy register): an observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with Herceptin, Perjeta in combination with Herceptin, or Kadcyla during pregnancy or within 7 months prior to conception

17.5.18. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/MEA 004

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Progress report for study NN7008-3553: a multicentre non-interventional study of safety and efficacy of turoctocog alfa (recombinant factor VIII (rFVIII)) during long-term treatment of severe and moderately severe haemophilia A (FVIII \leq 2%)

17.5.19. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 023.8

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Sixth interval safety registry report for study CNTO1275PSO4005: Nordic database initiative for exposure to ustekinumab: a review and analysis of adverse events from the Swedish national registry system

17.5.20. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.8

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Sixth annual interim report for study CNTO1275PSO4007: pregnancy research initiative (C0743T); exposure to ustekinumab during pregnancy in patients with psoriasis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers

17.6. Others

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

17.6.1. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/LEG 028

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a detailed analysis of a case of hypotension (AR-C14004-16-00020) including the CIOMS⁷⁸ form, causality assessment report

17.6.2. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/LEG 029

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a detailed analysis of a case of hypotension (ES-C14004-16-00035) including the CIOMS⁷⁹ form, causality assessment report

17.6.3. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/LEG 030

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a detailed analysis of a case of hypotension (AT-C14004-16-00066) including the CIOMS⁸⁰ form, causality assessment report

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

None

18.2. Conditional renewals of the marketing authorisation

None

⁷⁸ Council for International Organisations of Medical Sciences

⁷⁹ Council for International Organisations of Medical Sciences

⁸⁰ Council for International Organisations of Medical Sciences

18.3. Renewals of the marketing authorisation

18.3.1. 5-aminolevulinic acid - AMELUZ (CAP) - EMEA/H/C/002204/R/0023 (without RMP)

Applicant: Biofrontera Bioscience GmbH
PRAC Rapporteur: Martin Huber
Scope: 5-year renewal of the marketing authorisation

18.3.2. Azilsartan medoxomil - EDARBI (CAP) - EMEA/H/C/002293/R/0018 (without RMP)

Applicant: Takeda Pharma A/S
PRAC Rapporteur: Menno van der Elst
Scope: 5-year renewal of the marketing authorisation

18.3.3. Betaine anhydrous - CYSTADANE (CAP) - EMEA/H/C/000678/R/0024 (with RMP)

Applicant: Orphan Europe S.A.R.L.
PRAC Rapporteur: Valerie Strassmann
Scope: 5-year renewal of the marketing authorisation

18.3.4. Desloratadine - DESLORATADINE ACTAVIS (CAP) - EMEA/H/C/002435/R/0008 (without RMP)

Applicant: Actavis Group PTC ehf
PRAC Rapporteur: Jean-Michel Dogné
Scope: 5-year renewal of the marketing authorisation

18.3.5. Levetiracetam - LEVETIRACETAM SUN (CAP) - EMEA/H/C/002051/R/0013 (without RMP)

Applicant: Sun Pharmaceutical Industries Europe B.V.
PRAC Rapporteur: Veerle Verlinden
Scope: 5-year renewal of the marketing authorisation

18.3.6. Mercaptopurine - XALUPRINE (CAP) - EMEA/H/C/002022/R/0012 (without RMP)

Applicant: Nova Laboratories Limited
PRAC Rapporteur: Ulla Wändel Liminga
Scope: 5-year renewal of the marketing authorisation

18.3.7. Pasireotide - SIGNIFOR (CAP) - EMEA/H/C/002052/R/0028 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

18.3.8. Pioglitazone - GLIDIPION (CAP) - EMEA/H/C/002558/R/0009 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.9. Pioglitazone - PIOGLITAZONE ACTAVIS (CAP) - EMEA/H/C/002324/R/0009 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.10. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/R/0062 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.11. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/R/0062 (with RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: 5-year renewal of the marketing authorisation

18.3.12. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/R/0040 (with RMP)

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

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 30 August – 2 September 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
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Claire Ferard	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrimsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests	Full

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	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
Nadine Petitpain	Alternate	Luxembourg	No restrictions applicable to this meeting	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
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
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to this meeting	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Alternate - via telephone*	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Pierre Demolis	Expert - in person*	France	No interests declared	Full involvement
Caroline Laborde	Expert - in person*	France	No interests declared	Full involvement
Nils Lilienthal	Expert - via telephone*	Germany	No interests declared	Full involvement
Dirk Mentzer	Expert - via telephone*	Germany	No interests declared	Full involvement
Niamh Buckley	Expert - in person*	Ireland	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
Sophia Venzke	Expert - in person*	Netherlands	No interests declared	Full involvement
Polona Golmajer	Expert - via telephone*	Slovenia	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Patrick Batty	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Janet Nooney	Expert - in person*	United Kingdom	No interests declared	Full involvement
Victoria O'Keefe	Expert - in person*	United Kingdom	No interests declared	Full involvement
Andrew Ruddick	Expert - in person*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

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: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website:

www.ema.europa.eu/