01 December 2016
EMA/PRAC/127425/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 24-27 October 2016

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scope listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the PRAC meeting highlights once the procedures are finalised.

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 24-27 October 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 Chairperson welcomed Nikica Mirošević Skvrce as the new member for Croatia replacing Marina Dimov Di Giusti, and Laurence de Fays as the new alternate for Belgium replacing Veerle Verlinden. In addition, the Chairperson welcomed Caroline Laborde as the new alternate for France replacing Claire Ferard who becomes the member for France.

1.2. Adoption of agenda of the meeting of 24-27 October 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 of 26-29 September 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 26-29 September 2016 were published on the EMA website on 21 February 2017 (EMA/PRAC/123588/2017).

2. EU referral procedures for safety reasons: urgent EU procedures

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

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

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

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

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

Background

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

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusions reached by the Scientific Advisory Group on human immunodeficiency virus (HIV)/viral diseases (SAG HIV/Viral Diseases) held on 10 October 2016. In addition, the PRAC discussed the preliminary conclusions reached by the Rapporteurs and adopted a second list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for conducting the review (EMA/PRAC/196120/2016 Rev.3). Finally, the PRAC agreed a list of questions (LoQ) on HCC to the ANRS[1] collaborative group (French cohorts).

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

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

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Brigitte Keller-Stanislawski

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of factor VIII-containing medicines (antihemophilic factor (recombinant), human coagulation factor VIII (antihemophilic factor A), human coagulation factor VIII (inhibitor bypassing fraction), human coagulation factor VIII/human von Willebrand factor (Vocento), moroctocog alfa (Refacto AF), octocog alfa (Advate, Helixate Nexgen, Iblias, Kogenate, Kovaltry)) indicated for the treatment of haemophilia A to assess the impact of the results of the SIPPET study by *Peyvandi et al*.[2] recently published in the New England Journal of Medicine, with further consideration of any potential for risk minimisation measures or other changes to the marketing authorisations of these medicinal products. For further background, see PRAC minutes July 2016.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusions reached by the Rapporteurs and adopted a list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for conducting the review (EMA/PRAC/471536/2016 Rev.1). In addition, the PRAC concurred on the need to consult an ad-hoc expert group. Therefore, the PRAC adopted a list of questions (LoQ) for the ad-hoc expert group meeting scheduled on 22 February 2017.

[1] Agence nationale de recherche sur le sida et les hépatites virales (French national agency for research on acquired immunodeficiency syndrome (AIDS) and viral hepatitis

[2] F. Peyvandi et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N. Eng.l J. Med. 2016 May 26;374(21):2054-64) (SIPPET study)

3.2.3. Paracetamol[3] (NAP) - EMEA/H/A-31/1445

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

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of modified- and prolonged-release paracetamol-containing medicines, following the recent publication by *Salmonson H et al.*[4] of a retrospective pharmacokinetic (PK) and clinical analysis, in order to assess ways to minimise possible harm in case of overdosing and to consider whether the recommendations to manage such cases can be further improved. In addition, the procedure includes a review of measures to minimise the risk associated with poisoning with modified- and prolonged-release formulations taking into account the benefit-risk balance for all indications of such modified- and prolonged-release formulations. For further background, see PRAC minutes July 2016.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusion reached by the Rapporteurs and adopted a list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for conducting the review (EMA/PRAC/460935/2016). In addition, the PRAC agreed on the need to consult an ad-hoc expert group. Therefore, the PRAC adopted a list of questions (LoQ) for the ad-hoc expert group meeting scheduled end of February 2017.

3.2.4. Sodium-glucose co-transporter 2 (SGLT2) inhibitors[5]: Canaglifozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP); dapaglifozin – EDISTRIDE (CAP), FORXIGA (CAP); dapaglifozin, metformin – XIGDUO (CAP), EBYMECT (CAP); empaglifozin – JARDIANCE (CAP); empaglifozin, metformin – SYNJARDY (CAP) - EMEA/H/A-20/1442

Applicant: Janssen-Cilag International N.V. (Invokana; Vokanamet); AstraZeneca AB (Edistride, Forxiga; Xigduo, Ebymect); Boehringer Ingelheim International GmbH (Jardiance; Synjardy)

PRAC Rapporteur: Valerie Strassmann; PRAC Co-rapporteur: Menno van der Elst

Scope: Review of the benefit-risk balance of SGLT2 inhibitors following notification by European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for sodium-glucose co-transporter-2 (SGLT2)-containing medicines (canaglifozin (Invokana),

[3] Modified release formulations
[4] Salmonson H, et al. The standard treatment protocol is inadequate following overdose of extended release paracetamol: a pharmacokinetic and clinical analysis of 53 cases. Clin Toxicol 2016;54:424 (Abstract 124)
[5] Previously canagliflozin only

canagliflozin/metformin (Vokanamet), dapaglifozin (Edistride, Forxiga); dapaglifozin/metformin (Xigduo, Ebymect), empaglifozin (Jardiance), empaglifozin/metformin (Synjardy) to review the potential increased risk of lower limb amputation, following observation of such an increased risk (primarily of the toe) in ongoing clinical trials[6] with canagliflozin, to assess ways to minimise this risk and to evaluate its impact on the benefit-risk balance of SGLT2-containing medicines. In the initial notification letter dated 15/04/2016 initiating the procedure for canagliflozin-containing medicines, the European Commission (EC) also requested the EMA to consider whether the review should be extended to other SGLT2-inhibitors if necessary, given that they all share the same mechanism of action. In July 2016, following investigation of a possible evidence of an increased risk of lower limb amputation with other SGLT2 inhibitors (dapagliflozin- and empagliflozin-containing medicines), the scope of the procedure was broadened to the whole class of SGLT2-inhibitors as a class effect could not be excluded. For further background, see PRAC minutes April 2016, PRAC minutes June 2016 and PRAC minutes July 2016.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusion reached by the Rapporteurs and adopted a second list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for conducting the review (EMA/PRAC/271123/2016 Rev.2).

3.3. Procedures for finalisation

None

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

None

3.5. Others

None

4. Signals assessment and prioritisation[7]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

[6] CANVAS: randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus; CANVAS-R: Randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with type 2 diabetes mellitus

[7] 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

4.1.1. Nivolumab - OPDIVO (CAP); pembrolizumab – KEYTRUDA (CAP)

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of transplant rejection

EPITT 18781 – New signal

Background

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) indicated, as monotherapy or in combination with ipilimumab, for the treatment of advanced (unresectable or metastatic) melanoma in adults, for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults; as well as in monotherapy for the treatment of advanced renal cell carcinoma after prior therapy in adults.

Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) indicated, as monotherapy, for the treatment of advanced (unresectable or metastatic) melanoma in adults as well as for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) and who have received at least one prior chemotherapy regimen.

Opdivo, a centrally authorised medicine containing nivolumab, is estimated to have been used by 38,556 patients cumulatively in clinical trials and postmarketing exposure up to January 2016.

Keytruda, a centrally authorised medicine containing pembrolizumab, is estimated to have been used by an estimated 22,494 patients in worldwide clinical practice cumulatively up to March 2016.

During routine signal detection activities, a signal of transplant rejection was identified by EMA, based on five cases with Opdivo (nivolumab) and four cases with Keytruda (pembrolizumab) including two well documented suggestive literature reports. The respective Rapporteurs for Opdivo and Keytruda confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Based on the available evidence from case reports in EudraVigilance and in the literature, and on biological plausibility, the PRAC considered that a causal association with transplant rejection could not be excluded. Therefore, the PRAC agreed that the MAHs of Opdivo (nivolumab) and Keytruda (pembrolizumab) should respectively submit a detailed review of cases suggestive of transplant rejection, taking into account all sources of information from studies, literature, and spontaneous reports. Cases reporting abnormal laboratory values, such as creatinine elevations in kidney transplant recipients that could be indicative of gradually developing kidney graft rejection, should also be included in the review. In addition, the MAHs should provide an estimate of the size of the population of solid organ and tissue transplant recipients receiving nivolumab and pembrolizumab. Moreover, a detailed discussion should be provided on the potential pathophysiological mechanisms and presence of potential confounders. Finally, the MAHs should propose to amend the product information and/or the RMP as applicable.

The PRAC appointed Brigitte Keller-Stanislawski as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Opdivo (nivolumab) and Keytruda (pembrolizumab) should submit to the EMA, within 60 days, a detailed review of cases of transplant rejection together with a proposal to amend 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.

4.2. New signals detected from other sources

4.2.1. Flucloxacillin (NAP)

Applicant: various

PRAC Rapporteur: Margarida Guimarães

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

EPITT 18773 – New signal

Lead Member State: PT

Background

Flucloxacillin is a narrow-spectrum beta-lactam antibiotic of the penicillin class indicated for the treatment of various infections as well as to prevent infections during major surgical procedures, particularly in heart or orthopaedic surgery.

During routine pharmacovigilance activities, a signal of acute generalised exanthematous pustulosis (AGEP) was identified by the Netherlands, based on three spontaneous case reports as well as on three identified literature reports. In two case reports, the diagnosis was confirmed by histopathology or EuroSCAR[8] validation score, plausible latency, response to withdrawal, and positive patch test to flucloxacillin. Portugal confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, and the known association between flucloxacillin and immune skin reactions, the PRAC agreed that a variation of the product information for flucloxacillin-containing products is warranted to include a warning on AGEP advising to discontinue treatment with flucloxacillin and contraindicate any subsequent administration of flucloxacillin. AGEP should be also added as an undesirable effect with an unknown frequency.

The PRAC appointed Margarida Guimarães as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH(s) of flucloxacillin-containing products should submit a variation to the relevant National Competent Authorities, within 90 days, to amend the product

[8] European study of severe cutaneous adverse reactions (EuroSCAR): a multinational case-control study

information[9] to include a warning on AGEP and reflect it as an undesirable effect.

For the full PRAC recommendation, see EMA/PRAC/700146/2016 Corr published on 21/11/2016 on the EMA website.

4.3. Signals follow-up and prioritisation

4.3.1. 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 September 2016

Background

At the September 2016 meeting, the PRAC adopted a recommendation for amending the product information of cobicistat-containing products and corticosteroid-containing products (excluding cutaneous formulations) following a signal of adrenal suppression/insufficiency and Cushing's syndrome occurring in relation to co-administration of corticosteroids with cobicistat. For background information, see PRAC minutes September 2016.

Discussion

At the current meeting, the PRAC discussed the amendments recommended to the product information of corticosteroid-containing products (excluding cutaneous formulations) and agreed to further refine some wording specific to beclomethasone and the wording for all corticosteroids other than beclomethasone. PRAC noted that beclomethasone is indeed less dependent upon CYP3A[10] metabolism and the risk of interaction may be lower. Nevertheless, the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded. Therefore, the PRAC agreed that the product information of beclomethasone-containing products should be amended to advise caution and appropriate monitoring when using these agents concomitantly. As for all the other corticosteroids (excluding cutaneous formulations), the PRAC agreed to remove the statement relating to case reports of Cushing's syndrome and adrenal suppression, as they were not reported in association with all corticosteroids. In addition, the advice on using alternative corticosteroids has been removed as this was considered too broad to suit all corticosteroids' product information. As a consequence, the PRAC adopted a further recommendation for corticosteroid-containing products (excluding cutaneous formulations).

Summary of recommendation(s)

- The MAHs of beclomethasone-containing products (excluding cutaneous formulations) should submit, within 90 days, to the national competent authorities of the Member

[9] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly
[10] Cytochrome P450 3A

States as applicable, a variation amending the product information to apply caution and appropriate monitoring when concomitantly using beclomethasone-containing products and strong CYP3A inhibitors, including cobicistat-containing products.

- The MAHs of other corticosteroid-containing products (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 CYP3A 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. The refinements mentioned above should be taken into account.
- The PRAC recommendation for cobicistat-containing products adopted at the September 2016 meeting remains unchanged.

For the full PRAC recommendation, see EMA/PRAC/700146/2016 Corr published on 21/11/2016 on the EMA website.

4.3.2. Fluoroquinolones: Ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), (NAP); lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

Applicant: Bayer, Sanofi, Raptor Pharmaceuticals Europe BV (Quinsair), various

PRAC Rapporteur: Martin Huber

Scope: Signal of uveitis

EPITT 18686 – Follow-up to July 2016

Background

As per the PRAC recommendation adopted at the July 2016 meeting, the PRAC discussed a further analysis of available data in EudraVigilance and a literature review[11] conducted on a possible association between systemic fluoroquinolones and uveitis, in the light of patient exposure. For background information, see PRAC minutes July 2016.

Discussion

Having considered the available evidence from the literature and spontaneous reports, the PRAC agreed, in light of the current knowledge, that no update of the product information of all systemic fluoroquinolones-containing products regarding uveitis is warranted at this stage. Nevertheless, the PRAC agreed that uveitis and iris transillumination should be further discussed in the context of the ongoing PSUSA procedure for 'moxifloxacin (systemic use)' PSUSA/00009231/201605 due for recommendation in January 2017. Furthermore, the PRAC agreed that MAHs of systemic fluoroquinolones-containing products should continue to monitor uveitis as part of their routine safety surveillance.

[11] Hinkle DM, Dacey MS, Mandelcorn E, Kalyani P, Mauro J, Bates JH, et al. Bilateral uveitis associated with fluoroquinolone therapy. Cutan Ocul Toxicol. 2012 Jun, 31:111–6 Forooghian F, Maberley D, Albiani DA, Kirker AW, Merkur AB, Etminan M. Uveitis risk following oral fluoroquinolone therapy: a nested case-control Study. Ocul Immunol Inflamm. 2013 Oct;21(5):390–3 Eadie B, Etminan M, Mikelberg FS. Risk for uveitis with oral moxifloxacin: a comparative safety study. JAMA Ophthalmol. 2015 Jan, 133(1):81–4 Sandhu HS, Brucker AJ, Ma L, VanderBeek BL. Oral fluoroquinolones and the risk of uveitis. JAMA Ophthalmol. 2015 Oct 29:1-6

In addition, the PRAC was informed about initiatives in the EU aiming at gathering data on fluoroquinolones (including a non-urgent information (NUI) and potential database studies) in light of actions recently taken by FDA regarding a restriction of indication for uncomplicated infections[12].

Summary of recommendation(s)

- Uveitis and iris transillumination should be further discussed in the context of the ongoing PSUSA procedure for 'moxifloxacin (systemic use)', PSUSA/00009231/201605.
- MAHs of systemic fluoroquinolones-containing products should continue to monitor cases of uveitis as part of their routine safety surveillance.

4.3.3. Olanzapine - ZYPADHERA (CAP) - EMEA/H/C/000890/SDA/026; ZYPREXA (CAP) - EMEA/H/C/000115/SDA/047; ZYPREXA VELOTAB (CAP) - EMEA/H/C/000287/SDA/040

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of restless leg syndrome (RLS)

EPITT 18659 – Follow-up to June 2016

Background

The MAH replied to the request for information on the signal of restless leg syndrome (RLS) and the responses were assessed by the Rapporteur. For background information, see PRAC minutes June 2016.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature as well as the evaluation of the MAH's responses to the list of questions, the PRAC considered that a plausible underlying mechanism leading to RLS could not be excluded and therefore, PRAC concluded that an update of the product information of olanzapine-containing medicinal products is warranted in order to reflect RLS as an undesirable effect.

Summary of recommendation(s)

- The MAHs for olanzapine-containing medicinal products should submit to EMA or to national competent authorities of the Member States as applicable, within 60 days, a variation for amending the product information to include restless legs syndrome as an undesirable effect[13].

For the full PRAC recommendation, see EMA/PRAC/700146/2016 Corr published on 21/11/2016 on the EMA website.

4.3.4. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/SDA/003

Applicant: Bayer Pharma AG

[12] FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects May 2016: http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm
[13] Update of SmPC section 4.8. The package leaflet is updated accordingly

PRAC Rapporteur: Julie Williams

Scope: Signal of increased mortality and serious adverse events (SAEs) in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonia (IIP) in a single clinical trial

EPITT 18681 – Follow-up to June 2016

Background

The MAH replied to the request for information on the signal of increased mortality and serious adverse events (SAEs) in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) taking riociguat in a single clinical trial and the responses were assessed by the Rapporteur. For background information, see PRAC minutes June 2016.

Discussion

The PRAC considered the further data and analyses from the RISE-IIP study and concurred that no definitive underlying mechanisms or subgroups at risk could be identified. In light of this, the PRAC agreed that no update of the product information was warranted at this stage. The PRAC agreed that further exploration of the high resolution computed tomography (HRCT) data from RISE-IIP[14] is required in order to further explore the observed trend for an increased risk in patients with pulmonary hypertension associated with idiopathic interstitial pneumonia (PH-IIP) and combined pulmonary fibrosis and emphysema (CPFE). In this respect, the PRAC noted that the MAH of Adempas (riociguat) commits to collecting further HRCT images for the RISE-IIP trial and to providing a thorough evaluation of this in the final study report for RISE-IIP which will be provided with the next PSUR submission.

Summary of recommendation(s)

- In the final study report for RISE-IIP, the MAH for Adempas (riociguat) should discuss any implications for the authorised indications of the medicinal product should any findings show that patients with PH-IIP and CPFE represent a high risk population. In particular, the MAH should consider whether emphysema may represent an independent risk factor for mortality in patients treated with Adempas, and if off-label use in patients with right heart failure, chronic obstructive pulmonary disease (COPD) and emphysema should be specifically monitored.
- The MAH for Adempas (riociguat) should keep under close monitoring the safety profile of patients with interstitial lung disease (ILD) in the authorised pulmonary arterial hypertension (PAH) indication as well as relevant data from ongoing clinical trials.

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

[14] A randomized, double-blind, placebo-controlled phase II study to investigate the efficacy and safety of riociguat (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg three times a day (TID)) in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias (IIP)

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. Anamorelin - EMEA/H/C/003847

Scope: Treatment of anorexia, cachexia or unintended weight loss in adult patients with non-small cell lung cancer (NSCLC)

5.1.2. Brodalumab – EMEA/H/C/003959

Scope: Treatment of moderate to severe plaque psoriasis

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

Scope, accelerated assessment: Treatment of breast cancer with brain metastases

5.1.4. Methotrexate - EMEA/H/C/003756

Scope: Treatment of rheumatological and dermatological diseases

5.1.5. Pentosan polysulfate sodium - EMEA/H/C/004246, Orphan

Applicant: Bene-Arzneimittel GmbH

Scope: Treatment of interstitial cystitis

5.1.6. Rolapitant - EMEA/H/C/004196

Scope: Prevention of nausea and vomiting

5.1.7. Sodium zirconium cyclosilicate - EMEA/H/C/004029

Scope: Treatment of hyperkalaemia

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. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/II/0019/G

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Rafe Suvarna

Scope: Extension of indication to include two new indications for the treatment of juvenile idiopathic arthritis and paediatric plaque psoriasis already approved for the reference medicinal product. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Annex II, the Package Leaflet, Labelling and the RMP (version 4.2) are updated accordingly. Furthermore, the product information (PI) is brought in line with the latest QRD template (version 10)

Background

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

The CHMP is evaluating an extension of the therapeutic indication for Benepali, a centrally authorised product containing etanercept, to include two new indications for the treatment of juvenile idiopathic arthritis and for the treatment of paediatric plaque psoriasis already approved for the reference medicinal product. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 4.2 for Benepali (etanercept) in the context of the procedure of extension of indications under evaluation by the CHMP is considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC considered that the safety concerns should be updated to replace 'potential for paediatric off label use' by 'potential for off label use and medication error in children'. In addition, the MAH should provide a discussion on the timelines to distribute the revised educational materials to ensure that healthcare professionals and patients are informed in a timely manner of the potential risk of medication error in children.

For future consideration, the PRAC reinforced the importance of ensuring that risk minimisation measures are consistent in the paediatric indications for all etanercept-containing products.

5.3.2. Umeclidinium bromide, vilanterol - ANORO (CAP) - EMEA/H/C/002751/WS1031/0013; LAVENTAIR (CAP) - EMEA/H/C/003754/WS1031/0014

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of section 4.8 of the SmPC in order to add the adverse reactions 'vision blurred', 'intraocular pressure increased' and 'paradoxical bronchospasm' and to change the frequency of the adverse reaction 'glaucoma' from 'not known' to 'rare'. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives in the Package Leaflet and to bring the product

information (PI) in line with the latest QRD template (version 10). The RMP is updated (version 2.0) accordingly and includes the revision requested as part of the previous PSUSA procedure outcome

Background

Umeclidinium is an inhaled long-acting muscarinic receptor antagonist (LABA) and vilanterol is a long-acting β_2-adrenergic agonist (LABA) indicated in combination as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The CHMP is evaluating a worksharing type II variation for Anoro and Laventair, centrally authorised products containing umeclidium bromide/vilanterol, to include the undesirable effects 'vision blurred', 'intraocular pressure increased' and 'paradoxical bronchospasm' in the product information and to change the frequency of 'glaucoma' from 'not known' to 'rare'. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 7.0 for Anoro and Laventair (umeclidium bromide/vilanterol) in the context of the worksharing variation under evaluation by the CHMP is considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC considered that 'glaucoma' should not be changed from an important potential risk to an important identified risk and should be deleted from the list of safety concerns as this undesirable effect is already mentioned in the product information as a warning and as an undesirable effect. As for 'urinary retention/bladder outlet obstruction/dysuria', the PRAC supported removing these from the list of safety concerns as they are also mentioned in the product information as a warning and as undesirable effects.

6. Periodic safety update reports (PSURs)

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

See also Annex I.16.1.

6.1.1. Afatinib - GIOTRIF (CAP) - PSUSA/00010054/201603

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Afatinib is a protein kinase inhibitor indicated as monotherapy for the treatment of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-naive adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s),

and of locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Giotrif (afatinib) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a literature review on resistance mechanisms to afatinib as well as a discussion on the need to update the product information accordingly. In particular, the MAH should consider updating the relevant section to add 'mechanisms of resistance, including secondary resistance-related mutations, activation of alternative signalling pathways, phenotypic switch', through a LEG procedure or a variation procedure 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. 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.

6.1.2. Canagliflozin - INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/201603

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

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.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Invokana, a centrally authorised medicine containing canaglifozin, as well as Vokanamet, a centrally authorised medicine containing a canaglifozin/metformin, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Invokana (canaglifozin) and Vokanamet (canaglifozin/metformin) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAH should provide a follow-up on the cases of renal cell carcinoma (RCC). Moreover, the MAH should provide a review of cases reporting severe cutaneous adverse reactions and monitor cases of renal failure. Furthermore, the MAH

should closely monitor cases of pancreatitis and classify such cases as adverse events of special interests (AESI) with appropriate follow-up.

- The MAH should submit to EMA, within 60 days, a PASS protocol for an epidemiological study (category 3, non-imposed PASS) to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-SGLT2 inhibitor anti-hyperglycaemic agents.
- The RMP for canagliflozin-containing products should be updated to include pancreatitis as an important potential risk at the next regulatory opportunity.

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.

Based on the available evidence and in light of the data from EudraVigilance for SGLT2 inhibitors, the PRAC considered that pancreatitis should be closely monitored for all SGLT2 inhibitors within the next PSURs. The RMPs for empagliflozin-containing medicines and dapagliflozin-containing medicines should be updated to include pancreatitis as an important potential risk in the summary of safety concerns at the next regulatory opportunity.

6.1.3. Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins - CHONDROCELECT[15] - PSUSA/00000273/201604

Applicant: TiGenix NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins is an autologous cellular product indicated for the repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Chondrocelect, a centrally authorised advanced therapy medicinal product (ATMP) containing characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins, and issued a recommendation on its marketing authorisation(s).

Following the submission of the PSUR and start of the PSUSA procedure, the European Commission (EC) adopted the decision on 29 July 2016 to withdraw the marketing authorisation of Chondrocelect (characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins) due to commercial reasons to be effective from 30 November 2016. In line with the 'Guidance on handling of PSUR procedures for suspended or withdrawn / non-renewed / revoked marketing authorisations' (EMA/576230/2015) (see PRAC minutes January 2016), the PRAC discussed the need to request the submission of a further/ad-hoc PSUR.

Summary of recommendation(s) and conclusions

[15] EC decision on the MA withdrawal of ChondroCelect dated 29 July 2016

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Chondrocelect (characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

Given that additional pharmacovigilance data has become available after the cut-off date of the PSUR assessed within the current PSUSA procedure and considering it could inform on long-term safety effects of the use of Chondrocelect (characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins), the PRAC agreed that a further PSUR should be submitted to the EMA within 70 days of the data lock point 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. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/201604

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Adenuric (febuxostat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'blood creatine phosphokinase increase' as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should closely monitor cases of agranulocytosis, leukocytoclastic vasculitis and allergic vasculitis, thromboembolic events, hepatic failure, and interstitial lung disease as well as fatal cases. Moreover, the MAH should provide an analysis on a potential causal relationship between 'blood creatine phosphokinase increase' and 'rhabdomyolysis', as well as comment on its potential underlying mechanism. Finally, the MAH should provide a discussion on the potential role of ethnicity on 'blood creatine phosphokinase increase'.

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.

[16] 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

6.1.5. Fosaprepitant - IVEMEND (CAP) - PSUSA/00001471/201603

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Fosaprepitant is the prodrug of aprepitant, a selective high-affinity antagonist at human substance P neurokinin 1 (NK1) receptors, and is indicated for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy in adults as well as for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ivemend (fosaprepitant) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend an existing warning on hypersensitivity reactions to reflect that anaphylaxis/anaphylactic shock may occur during or soon after infusion of fosaprepitant. In addition, anaphylaxis/anaphylactic shock should be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[17].

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.

6.1.6. Insulin degludec, liraglutide - XULTOPHY (CAP) - PSUSA/00010272/201603

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Insulin degludec, an ultra-long-acting basal insulin analogue and liraglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist are indicated in combination for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Xultophy (insulin degludec/liraglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'increased lipase' and 'increased amylase' as undesirable effects with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[18].
- In the next PSUR, the MAH should further review cases of medication error.

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

6.1.7. Methylnaltrexone bromide - RELISTOR (CAP) - PSUSA/00002023/201603 (with RMP)

Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Background

Methylnaltrexone bromide is a selective antagonist of opioid binding at the mu-receptor indicated for the treatment of opioid-induced constipation when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Relistor (methylnaltrexone bromide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing contraindication on hypersensitivity to include patients at increased risk for recurrent obstruction or in patients with acute surgical abdomen due to the potential for gastrointestinal perforation. In addition, the warning on 'gastrointestinal perforation' should be further refined in order to ensure that patients with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract or other conditions which might result in impaired integrity of the gastrointestinal tract wall are monitored for severe, persistent, or worsening abdominal pain. Methylnaltrexone bromide should be discontinued if this symptom occurs. Moreover, a new warning on 'opioid withdrawal syndrome' should be added as patients with a disrupted blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. Finally,

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

'vomiting, abdominal pain' should be added as undesirable effects with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[19].

- In the next PSUR, the MAH should closely monitor cases of 'gastrointestinal perforations', 'opioid-withdrawal-like symptoms', 'renal failure', 'breakthrough pain'/ 'inadequate analgesia', and 'hypoglycaemia'.

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.

6.1.8. Nintedanib[20] - OFEV (CAP) - PSUSA/00010319/201604 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Nintedanib is a tyrosine kinase inhibitor (TKI) indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ofev (nintedanib) in the approved respiratory indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the current warning on hepatic function to add that that administration of nintedanib was also associated with drug-induced liver injury. In addition, 'drug-induced liver injury' should be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide a cumulative analysis of cases of 'off-label use', 'gastrointestinal and intestinal perforation', 'acute myocardial infarction and myocardial infarction' as well as of 'pulmonary embolism'. Moreover, the MAH should provide a discussion on a possible mechanism leading to suicide, suicidal ideation and depression and explore a possible class effect. Finally, the MAH should regularly perform a follow-up of each case of bleeding to better characterise the risk and to present all post-marketing cases of bleeding according to use of medications altering haemostasis. The MAH should consider the feasibility of conducting a PASS if the MAH fails to provide an appropriate analysis of well documented post-marketing bleeding cases.

[19] Update of SmPC sections 4.3, 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
[20] Indicated for the treatment of idiopathic pulmonary fibrosis (IPF)
[21] 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

- The MAH should submit an updated RMP to include 'drug-induced liver injury' as an important identified risk at the next regulatory opportunity requiring an RMP update.

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. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[22]) – EMEA/H/W/002300/PSUV/0011

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Mosquirix is a plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) indicated for active immunisation of children aged 6 weeks up to 17 months against malaria caused by Plasmodium falciparum and against hepatitis under certain conditions as per the Scientific Opinion (SO) adopted by the CHMP in the context of the cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the European Community in accordance with Article 58 of Regulation (EC) No 726/2004.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)), and issued a recommendation on its Scientific Opinion as adopted by the CHMP.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)) remains unchanged.
- The current terms of the Scientific Opinion should be maintained.
- The Scientific Opinion Holder (SOH) should submit to EMA, within 60 days, further information on studies Malaria-055[23] and Malaria-076[24], and a discussion on any potential methodological bias that may explain the observed difference in incidence rate of severe malaria before the administration of the fourth dose. Regarding the ad-hoc analysis of mortality by gender, the SOH should provide a detailed review on possible reasons for the difference of mortality observed in girls, and should consider including in study EPI-MAL-003[25] an analysis of mortality per gender on an exploratory basis, as well as a discussion, depending on the results, on how to further assess the signal. Furthermore, the SOH should clarify co-morbidities with regard to the post-hoc analysis of cerebral malaria and provide the estimated number of averted cases of clinical malaria, severe malaria, cerebral malaria, severe malaria with seizure and severe malaria with prostration and at least one other severity marker.

[22] 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)
[23] Evaluation of long-term efficacy, safety and immunogenicity of Mosquirix in infants and children in Africa
[24] Long-term follow-up of study Malaria-055
[25] Observational cohort study to estimate the incidence of protocol-defined potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with Mosquirix

- In the next PSUR, the SOH should clarify if any change in the incidence of serious adverse events (SAEs) in the target population is observed since the cut-off date for the PSUR part of the current PSUSA procedure. Moreover, as 'rebound effect', 'long-term efficacy', and 'impact/effectiveness' are listed as safety concerns, the SOH should review and discuss the literature in terms of safety as well as of efficacy/effectiveness/impact.

The next PSUR should be submitted in accordance with the requirements set out in Annex II of the CHMP Scientific Opinion.

6.1.10. Umeclidinium bromide - INCRUSE (CAP) - PSUSA/00010263/201604

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Umeclidinium bromide is a long acting muscarinic receptor antagonist 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 benefit-risk balance of Incruse, a centrally authorised medicine containing umeclidinium bromide, 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, benefit-risk balance of Incruse (umeclidinium bromide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'glaucoma', 'vision blurred', 'urinary retention', 'dysuria', as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, the MAH should provide a detailed review of overdose and medication error, including a discussion on the pattern of adverse drug reactions (ADRs) and on the possible measures to be put in place to mitigate the risk of medication error. In addition, the MAH should provide a detailed review of cases of off-label use in asthma and propose any corrective actions as applicable. Moreover, the MAH should closely monitor cases of 'urinary retention/ bladder outlet obstruction/ dysuria' to better characterize the safety risks in terms of severity and time to onset and should further investigate the type and severity of glaucoma. The MAH should include a discussion on the population at risk for glaucoma.
- The MAH should update the RMP by deleting 'urinary retention' and 'glaucoma' from the list of important potential risks at the next regulatory opportunity.

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.

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

The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and aligned with the data lock point (DLP) and frequency for submission for umeclidinium bromide/vilanterol. The list of Union reference dates (EURD list) will be updated accordingly.

6.1.11. Vardenafil - LEVITRA (CAP); VIVANZA (CAP) - PSUSA/00003098/201603

Applicant: Bayer Pharma AG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Vardenafil is a phosphodiesterase type 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction in adult men.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Levitra (vardenafil) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- The MAH should submit to EMA, within 60 days, a detailed review of cerebrovascular disorders. The MAH should discuss if further actions are needed, such as amendments of the product information and/or the RMP as applicable.
- In the next PSUR, the MAH should closely monitor cases of 'amaurosis fugax', 'blindness', 'blindness unilateral', 'visual acuity reduced', 'visual field defect' as well as 'epilepsy/seizure/convulsion'.

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

6.1.12. Vortioxetine - BRINTELLIX (CAP) - PSUSA/00010052/201603

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Vortioxetine is a psychoanaleptic indicated for the treatment of major depressive episodes in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Brintellix (vortioxetine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'hyponatraemia' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide detailed reviews of cases of 'dry mouth' and 'dysgeusia' and propose to update the product information accordingly as applicable. The MAH should also provide a detailed review of cases of cardiac 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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.13. Zonisamide - ZONEGRAN (CAP) - PSUSA/00003152/201603

Applicant: Eisai Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Zonisamide is an antiepileptic benzisoxazole derivative indicated as monotherapy for the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy; and as adjunctive therapy for the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Zonegran (zonisamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on 'acute myopia and secondary angle closure glaucoma' to recommend discontinuation of zonisamide and appropriate measures to reduce intraocular pressure when the syndrome is reported. Caution should be exercised when treating patients with a history of eye disorders. In addition, 'eye pain', 'myopia', 'vision blurred' and 'visual acuity reduced' should be added as undesirable effects with a very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide a detailed discussion on cases of psychiatric related reactions where a temporal association between onset of the reaction and initiation/dose change of zonisamide is identified, and a review on new cases of a

[27] 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
[28] 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

possible interaction between zonisamide and warfarin/other anticoagulants. Moreover, the MAH should provide a discussion on use of zonisamide in elderly patients. Finally, the MAH should discuss in detail any update from the North American Pregnancy Registry.

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 Annex I. 16.2.

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

See also Annex I.16.3.

6.3.1. Dorzolamide (NAP) - PSUSA/00003168/201602

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Dorzolamide is a human carbonic anhydrase II inhibitor indicated as adjunctive therapy in the treatment of elevated intra-ocular pressure (IOP) in ocular hypertension, open-angle glaucoma and pseudo-exfoliative glaucoma under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of dorzolamide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'dyspnoea' and 'foreign body sensation in eye' as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[29].
- In the next PSUR, the MAHs should provide detailed reviews of cases of severe hypersensitivity reactions, urolithiasis in patients with history of renal calculi, choroidal detachment concomitant with ocular hypotony, concomitant use with oral carbonic anhydrase inhibitors, corneal disorders, use during pregnancy and lactation, use in patients with severe renal impairment or hepatic impairment, as well as use in the

[29] 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

paediatric population. In addition, the MAHs should provide a cumulative review of thrombocytopenia taking into consideration the risk factors, average dose, outcome (including dechallenge and rechallenge), concomitant treatment and the time to onset as well as a proposal for amending 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.

6.3.2. Granisetron[30] (NAP) - PSUSA/00001568/201602

Applicant: various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

Background

Granisetron is a 5-hydroxytryptamine (5-HT_3) receptor antagonist indicated for adults and children above 2 years of age for the prevention and treatment (control) of acute and delayed nausea and vomiting associated with chemotherapy and radiotherapy, and for post-operative nausea and vomiting (PONV).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of granisetron-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on 'serotonin syndrome' when 5-HT_3 antagonists are used either alone, but mostly in combination with other serotonergic drugs. Therefore, appropriate observation of patients for serotonin syndrome-like symptoms is advised. In addition, 'serotonin syndrome' should be added as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[31].

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

6.3.3. Rabies vaccine (NAP) - PSUSA/00009277/201603

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

[30] All formulations except transdermal patch
[31] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Three types of rabies vaccines are authorised in the EU, all indicated for the pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) of rabies. The human diploid cell vaccine (HDCV) contains the PM-1503-3M strain of rabies virus prepared in MRC-5 human diploid cell culture, concentrated by ultrafiltration and inactivated with ß-propiolactone, while the purified chick embryo cell vaccine (PCECV) contains the FLURY LEP strain of rabies virus prepared in embryonated chick egg cell culture, purified and concentrated by zonal centrifugation and inactivated with ß-propiolactone. The purified Vero cell rabies vaccine (PVRV) contains the Wistar rabies PM/WI38 1503-3M strain of rabies virus prepared in Vero cell culture, purified by ultracentrifugation and inactivated with ß-propiolactone.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of the rabies vaccines containing HDCV, PCECV or PVRV in the approved indications remains unchanged.
- With regard to the PCECV rabies vaccine, the current terms of the marketing authorisation(s) should be maintained.
- With regard to the HDCV and PVRV rabies vaccines, the product information should be updated to include a warning regarding anxiety-related reactions pointing out that procedures should be in place to avoid injury from faints. Therefore the current terms of the marketing authorisations should be varied[32].
- In the next PSUR, the MAH for HDCV should monitor the potential immunosuppressive effect of HDCV and evaluate the trend of reports describing events of infectious nature or that might indicate immunosuppression.

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

6.3.4. Rocuronium (NAP) - PSUSA/00002656/201602

Applicant: various

PRAC Lead: Jana Mlada

Scope: Evaluation of a PSUSA procedure

Background

Rocuronium is an aminosteroid non-depolarizing neuromuscular blocking agent indicated in adults and paediatric patients as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction and to provide skeletal muscle relaxation during surgery. Rocuronium is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.

[32] Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of rocuronium-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 detailed reviews of cases of Kounis syndrome, cardiac arrest not related to anaphylaxis, and fatal cases associated with administration of rocuronium. In addition, the MAHs should closely monitor the potential for off-label use of rocuronium and the safety issue of malignant hyperthermia.

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. Triamcinolone[33] (NAP) - PSUSA/00010292/201603

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Triamcinolone is a glucocorticosteroid and anti-inflammatory agent indicated for use as an intraocular formulation during vitrectomy to visualize the vitreous, the inner limiting membrane, and pathologic epiretinal membranes.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of triamcinolone-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be amended to delete[34] 'retinal artery occlusion' as an undesirable effect. Therefore the current terms of the marketing authorisations should be varied[35].

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.

[33] Intraocular formulations only
[34] Available data are not supportive of a possible causal association
[35] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I.16.4.

6.4.1. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/LEG 039

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a cumulative review on cases of liver-related events (hepatotoxicity) as requested in the recommendation of PSUSA/00002653/201509 adopted by PRAC in April 2016

Background

Rivaroxaban is a highly selective direct factor Xa inhibitor indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in adult patients under certain conditions and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), for the prevention of recurrent DVT and PE in adults, and for the prevention of stroke and systemic embolism in adult patients under certain conditions.

Following the evaluation of the most recently submitted PSUR for Xarelto (rivaroxaban), the PRAC requested the MAH to submit further data. For further background, see PRAC minutes April 2016. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 60 days, a comprehensive cumulative review of cases of severe liver injury/failure including a careful assessment of causality and a clear summary of factors such as age, gender, concomitant medications, reaction reported, indication, outcome, time-to-onset, de-challenge and re-challenge, and any other potential confounding or risk factors. The MAH should ensure that the review includes a thorough analysis of cases that might imply causality and a discussion of whether risk minimisation measures are warranted.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[36]

See Annex I.17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[37]

See Annex I.17.2.

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

7.3. Results of PASS imposed in the marketing authorisation(s)[38]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[39]

See Annex I.17.4.

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

See Annex I.17.5.

7.6. Others

See Annex I.17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

None

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

8.1. Annual reassessments of the marketing authorisation

See Annex I.18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I.18.2.

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

8.3. 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

None

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

None

10.3. Other requests

10.3.1. Guanfacine – INTUNIV (CAP) – EMEA/H/C/003759/ANX/004

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: PRAC consultation on amendments to an imposed interventional PASS protocol for study SPD503-401: 'a comparative safety study of Intuniv in children and adolescents aged 6- 17 years with attention-deficit/hyperactivity disorder' which has been submitted in compliance with RMP version 1.5 dated 22 July 2015

Background

Guanfacine is a selective alpha$_{2A}$-adrenergic receptor agonist indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective.

In accordance with the conditions of the marketing authorisation(s) for Intuniv (guanfacine), the MAH submitted to EMA an amended protocol for a comparative safety study (PASS study SHP503-401) to investigate the long term safety (especially the effects on neurocognitive function) of Intuniv (guanfacine) in children and adolescents aged 6- 17 years with ADHD. In the framework of the CHMP assessment, the PRAC was requested to provide advice on the proposed amendments to the imposed interventional PASS protocol.

Summary of advice

- Based on the review of the proposed amendments to the protocol and the CHMP's assessment, the PRAC considered that the protocol was not acceptable at this stage and commented on several aspects regarding the study design. In particular, the PRAC advised on the duration of the controlled phase, proposed comparator, sample size estimation and follow-up of discontinued patients.

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Benzodiazepines: alprazolam (NAP); bromazepam (NAP); cinolazepam (NAP); clobazam (NAP); chlordiazepoxide (NAP); clotiazepam (NAP); cloxazolam (NAP); diazepam (NAP); dipotassium clorazepate (NAP); estazolam (NAP); ethyl loflazepate (NAP); etizolam (NAP); flunitrazepam (NAP); flurazepam (NAP); loprazolam (NAP); lorazepam (NAP); lormetazepam (NAP); medazepam (NAP); midazolam – BUCCOLAM (CAP), (NAP); nitrazepam (NAP); nordazepam (NAP); oxazepam (NAP); pinazepam (NAP); prazepam (NAP); quazepam (NAP); temazepam (NAP); tofisopam (NAP); triazolam (NAP); zaleplon (NAP); zopiclone (NAP); zolpidem (NAP)

Applicant: Shire Services BVBA (Buccolam), various

PRAC Lead: Julie Williams

Scope: PRAC consultation on the evaluation of a study on the impact of benzodiazepines on short-term mortality recently published in 'European Neuropsychopharmacology'

Background

Benzodiazepines are psycholeptics (anxiolytics, hypnotics and sedatives) indicated for the treatment of various conditions, in particular, panic disorder, generalized anxiety disorder, insomnia and anxiety.

In 2012, a study by *Kripke et al.*[40] suggested an association between the use of hypnotics and increased risk of mortality as well an association with cancer. The study and other relevant published literature were considered by the EMA's Pharmacovigilance Working Party (PhVWP) in April 2012. Given the studies limitations and inconclusive results, the PhVWP concluded that a causal association between the use of all hypnotics or a specific hypnotic medication and an increased risk of death or cancer could not be established from the available evidence. Further to those discussions, EMA commissioned a study to further characterise the potential association between hypnotics/anxiolytics and an increased risk of mortality. The study focused on exploring the impact of benzodiazepines on short-term (1 year) mortality. The authors, *Palmaro et al.*[41], concluded that there was a moderate increase in all-cause mortality associated with benzodiazepines and that this issue requires monitoring. According to the authors, mortality was significantly increased early after exposure in new users which may indicate a short-term effect rather than a cumulative effect.

The United Kingdom having evaluated the study by *Palmaro et al.* identified several limitations, in particular, pooling of data for a wide range of products, residual confounding by indication, inclusion of patients with serious illness at baseline, lack of censoring in the benzodiazepine cohort, and lack of an exploration of a dose-response relationship or an association with duration of use. Due to these limitations, the United Kingdom considered that the study did not provide enough robust evidence that use of benzodiazepines, including short-term use, is associated with an increased risk of mortality. The United Kingdom requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the assessment of the United Kingdom concluding that the study by *Palmaro et al.* does not provide sufficient evidence that use of benzodiazepines, including short-term use, is associated with an increased risk of mortality and as such no regulatory action is proposed. Furthermore, the PRAC agreed that, given the limitations, additional analysis of the data presented in the study is unlikely to help to further elucidate the findings.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC working group - best practice guide – update on the implementation goals

PRAC lead: Martin Huber, Rafe Suvarna, Ulla Wändel Liminga

Following the adoption at PRAC of the best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016) and of the implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016), the PRAC was updated at the organisational matters teleconference on 10 November 2016 on quantitative measures collected for the first three-month period during the July, September

[40] Kripke DF et al. Hypnotics' associated with mortality or cancer: a matched cohort study. BMJ Open 2012; 2:1-8
[41] Palmaro A et al. 2015. Benzodiazepines and risk of death: results from two large cohort studies in France and UK. European Neuropsychopharmacology (2015) 25, 1566-1577

and October 2016 PRAC meetings. The PRAC discussed some improvements observed since the adoption of the BPG in communication of assessment reports and explanation describing the issues. The PRAC requested the 'PRAC working group on using PRAC plenary time efficiently and effectively' to work on some further improvements.

12.2. Coordination with EMA Scientific Committees or CMDh-v

12.2.1. Joint Paediatric Committee (PDCO)-PRAC Working Group – organisation of an extraordinary meeting – paediatric development and pharmacovigilance: maximising synergies

PRAC lead: Jolanta Gulbinovic

At the organisational matters teleconference held on 10 November 2016, the PRAC was updated on the Joint Paediatric Committee (PDCO)-PRAC Working Group meeting held on 30 September 2016. The PRAC also noted the organisation of a Joint Paediatric Committee (PDCO)-PRAC Working Group extraordinary meeting on 2 December 2016 aiming at maximising synergies between paediatric development and pharmacovigilance.

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

12.3.1. Post-authorisation efficacy study (PAES) - scientific guidance

PRAC lead: Stephen Evans, Almath Spooner

Action: For adoption

Following the public consultation on the draft scientific guidance on post-authorisation efficacy studies (PAES) developed in accordance with article 108a of Directive 2001/83/EC (see PRAC minutes October 2015), the PRAC was updated on the addressed comments. The PRAC adopted the guidance.

Post-meeting note: the final Scientific guidance on PAES (EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015) was published on the EMA website on 22 December 2016 for an entry into force on 1 June 2017.

12.4. Cooperation within the EU regulatory network

12.4.1. EMA reflection paper on extrapolation across age groups - report on the multi-stakeholders extrapolation workshop

As a follow-up to previous discussions on the EMA 'reflection paper on extrapolation of efficacy and safety in paediatric medicine development' (EMA/199678/2016) (see PRAC minutes March 2016) and its public consultation, the EMA Secretariat reported to PRAC at the organisational matters teleconference held on 10 November 2016, on the comments received and the outcome of the 'Workshop on extrapolation of efficacy and safety in medicine development across age group' held on 17-18 May 2016.

12.4.2. PRAC strategic review and learning meeting, 11-12 April 2017

PRAC lead: Amy Tanti, John Joseph Borg

The PRAC was presented with the draft agenda for the PRAC strategic review and learning meeting (SRLM) to be held on 11-12 April 2017 under the Maltese presidency of the Council of the EU.

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

At the organisational matters teleconference held on 10 November 2016, the PRAC was further updated on the SCOPE Joint Action project initiated by the European Commission (EC) following the implementation of the revised EU pharmacovigilance legislation in 2012 to help medicines regulators to collaboratively operate pharmacovigilance systems to the EU legislative requirements (see also PRAC minutes July 2016). A status update on the progress made by the eight Work Packages (WP)[42] was presented with their deliverables and timelines together with an overall sustainability plan. The sustainability plan foresees maximizing the impact of SCOPE by ensuring continuous access to the SCOPE deliverables by liaising with the European Network Training Centre (EU NTC) learning platform and by contributing to the Pharmacovigilance training curriculum. An overview of the trainings held in September and October 2016 was presented. The PRAC welcomed receiving regular updates on the progress of SCOPE.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. 2017 PRAC work plan – preparation

At the organisational matters teleconference on 10 November 2016, the EMA Secretariat presented to the PRAC an update on the development of the draft PRAC work plan for 2017. PRAC members welcomed the progress made and offered ongoing support in this important exercise. A refined version of the draft 2017 PRAC work plan will be presented in January/February 2017.

[42] WP1: Governance; WP2: Dissemination; WP3: Evaluation; WP4: ADR collection; WP5: Signal management; WP6: Risk communications; WP7: Quality management systems; WP8: Lifecycle pharmacovigilance

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - PRAC work tracking including quarterly workload measures and performance indicators for the last three months - predictions

As part of the new governance of the move to full operation of EU pharmacovigilance that requires oversight of performance of the EU system and measuring its impact, the EMA secretariat presented, at the organisational matters teleconference held on 10 November 2016, quarterly figures on EU pharmacovigilance system-related workload, and key performance indicators as well as some predictions in terms of workload by procedure type, when available, and per NCA for the upcoming months.

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. 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.

12.10.2. PSURs repository

None

12.10.3. Roadmap for PSUR issues: Explanatory note to 'Guideline on good pharmacovigilance practices (GVP) module VII on Periodic safety update report' - Questions & Answers (Q&A) to assessors

PRAC lead: Margarida Guimarães; Menno van der Elst

Following the previous PRAC discussions (see PRAC minutes February 2016, PRAC minutes

March 2016, PRAC minutes April 2016 and PRAC minutes May 2016), the EMA Secretariat presented to PRAC an overview of the comments received from Member States on the draft explanatory note to GVP module VII on 'Periodic safety update reports (PSURs)' and on the draft 'Questions & Answers (Q&A) on PSUSA for NAPs: Guidance document for assessors', developed as follow-up actions from the joint PRAC/CMDh recommendation paper on common understanding on EU PSUR single assessment. The PRAC adopted the 'Q&A'[43] and endorsed the 'explanatory note' to GVP module VII on PSURs[44].

12.10.4. Roadmap for PSUR issues: revision of the assessment report template for the evaluation of PSUSA for NAPs only

PRAC lead: Margarida Guimarães; Menno van der Elst; Jolanta Gulbinovic

At the organisation matters teleconference held on 10 November 2016, the EMA Secretariat presented to PRAC, as part of the roadmap exercise for PSUR issues (see PRAC minutes February 2016, PRAC minutes March 2016, PRAC minutes April 2016 and PRAC minutes May 2016), the revised Assessment Report template for PSUR single assessment (PSUSA) procedures covering nationally authorised products (NAPs) only. Following a description of the changes, the PRAC adopted the template and agreed with starting a pilot phase to implement the use of the template for procedures starting as of 8 December 2016 and to collect comments until March 2017.

12.10.5. Union reference date (EURD) 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 data lock point (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 November 2016 (held on 24-27 October 2016), the updated EURD list was adopted by the CHMP and CMDh at their November 2016 meetings and published on the EMA website on 18/11/2016, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the November 2016 SMART Working Group (SMART WG) work stream WS1. The WG WS1 held a discussion on non-confirmed signals

[43] Also adopted at CMDh and due for inclusion in the PSUR assessment report template
[44] Also endorsed at CMDh and due for discussion at the tenth industry platform on the operation of EU pharmacovigilance legislation scheduled on 3 February 2017

since PRAC was established in 2012. It was considered helpful to discuss in more detail the approach to follow for non-confirmed signals in light of the Implementing Regulation (EU) No 520/2012. In addition, the WG WS1 further discussed aspects relating to PRAC adoption of signal recommendations outside plenary meetings as part of the pilot exercise. Follow-up discussion will be held in December 2016. Finally, the WG WS1 discussed the signal management work undertaken in SCOPE, noting that deliverables, presentations and training materials are available on the website, which is updated regularly (see under 12.4.3.).

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 24/10/2016 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 - EudraVigilance auditable requirement project update - Article 57[45] reports

As a follow-up to previous meetings (see PRAC minutes September 2016), the PRAC was updated on the anticipated release of additional dashboards for Article 57 reports as part of the EudraVigilance auditable requirement project. Since 2015, the reliance on Article 57 reports for industry notification of changes to the qualified person for pharmacovigilance (QPPV) and the pharmacovigilance system master file (PSMF) location has been supported by EMA. Further to the first set of reports already made available in 2016, an expanded set of reports will be delivered in early 2017 to retrieve information on authorised medicinal products (with addition of data elements such as indications, ATC[46] codes, excipients), MAHs (with addition of SME[47] details), pharmacovigilance system master file locations (PSMFLs) (with addition of a comment field to support cross-references for PSMFs shared across

[45] Article 57 of Regulation (EC) No 726/2004
[46] Anatomical therapeutic chemical
[47] Small and medium-sized enterprises

companies) and aggregated data reports providing an overview and statistics (e.g. list of authorisation procedure type and country) to national competent authorities (NCA).

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

12.15.3. Antiretroviral Pregnancy Registry (APR) – participation of generic[48] medicinal products

PRAC lead: Rafe Suvarna

Antiretroviral agents are indicated for the treatment of patients affected by the human immunodeficiency virus (HIV) under certain conditions. The Antiretroviral Pregnancy Registry (APR) is a voluntary patient registry intended to provide ongoing surveillance of outcomes in pregnancies exposed to antiretroviral agents. The requirement for the APR as additional pharmacovigilance is common to innovator antiretroviral (ARV) products regardless of evidence of risk of harm in pregnancy but this requirement has been applied on an ad hoc basis to generic ARV products. For further background, see PRAC minutes September 2015 and PRAC minutes October 2015. At the current meeting, The PRAC considered whether the APR should be applied systematically to generic ARV products (and if so whether criteria could be defined to help decide when this might be appropriate), or whether an alternative approach should be adopted, taking into account experience to date and other options for gathering data. Following discussion, the PRAC agreed to follow-up on this with an updated discussion paper in February/March 2017.

[48] Article 10(1) of Directive 2001/83/EC

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public hearings - procedural and best practice guidance for PRAC members

PRAC lead: Albert van der Zeijden

In line with the PRAC work plan 2016, the PRAC Public Hearing subgroup together with the EMA Secretariat presented to PRAC the draft 'Procedural and Best Practice guidance for PRAC members on public hearings'. This document for internal use intends to provide guidance to PRAC members on the process for deciding whether or not to hold a public hearing and on the involvement of the Committee in the subsequent organisation and conduct of a public hearing, with the aim to best achieve the goals set out for public hearings. Further discussion is planned in December 2016.

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Strategy on measuring the impact of pharmacovigilance - pilot prioritising topics relevant for collaborative impact research

PRAC lead: Marieke De Bruin

Following discussions 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' (EMA/153279/2016) (see PRAC minutes September 2016). At the current meeting, the PRAC endorsed a six-month pilot for application of the criteria to certain safety

topics discussed at PRAC meetings. The pilot is anticipated to start at PRAC in December 2016.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[49]

As per agreed criteria under evaluation for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[50].

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Enzalutamide – XTANDI (CAP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Signal of hepatotoxicity

EPITT 18754 – New signal

Lead Member State: ES

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. Daptomycin - EMEA/H/C/004310

Scope: Treatment of complicated skin and soft-tissue infections

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).

[49] 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

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

15.2.1. 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. 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

15.2.3. 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

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

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

15.2.5. 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

15.2.6. 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

15.2.7. Retigabine - TROBALT (CAP) - EMEA/H/C/001245/II/0045

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 18) in order to remove a post-authorisation study (PASS) RTG116158, an open label study evaluating the effects of retigabine added to existing anti-epileptic drug(s) on urinary voiding function in subjects with partial onset seizures. In addition, routine changes have also been introduced

15.2.8. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0014

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Revised RMP in order to add off-label use in patients with idiopathic pulmonary pneumonia, with or without pulmonary hypertension as an important identified risk

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. 5-aminolevulinic acid - AMELUZ (CAP) - EMEA/H/C/002204/II/0024

Applicant: Biofrontera Bioscience GmbH

PRAC Rapporteur: Martin Huber

Scope: Extension of indication from 'treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2) and of field cancerization' to 'treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2) and of field cancerization in adults including the elderly; treatment of non-aggressive basal cell carcinoma (primary superficial or nodular basal cell carcinoma or mixed types of both, with good or intermediate prognosis) on the face, scalp, neck, trunk and extremities in adults including the elderly'. Consequently, sections 4.1, 4.2, 4.4, 4.6, 4.8 and 5.1 of the SmPC are updated. In addition, the MAH included some editorial changes to sections 2, 4.5, 4.7, 5.2, 6.5 and 9 of the SmPC. The Package Leaflet, Labelling and RMP (version 10) are updated accordingly. Furthermore, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

15.3.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0154

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include 'adolescents from 12 years of age' to the hidradenitis suppurativa indication. As a consequence, sections 4.1, 4.2, 5.1 and 5.2, of the SmPC are updated. The Package Leaflet is updated accordingly

15.3.3. 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

15.3.4. 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

15.3.5. 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/m^2 and at 25 mg/m^2 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)

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

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

15.3.7. 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

15.3.8. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/WS0996/0022; Trametinib - MEKINIST (CAP) - EMEA/H/C/002643/WS0996/0018

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the combination treatment with trametinib and dabrafenib of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Mekinist and Tafinlar SmPC are updated. The Package Leaflet and RMP are updated accordingly. In addition, the MAH took the opportunity to align the SmPCs of Mekinist and Tafinlar. Furthermore, the product information is brought in line with the latest QRD

template (version 10)

15.3.9. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0052

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Update of sections 4.4 and 5.1 of the SmPC to include final results of study ICL670F2201: 'a randomized, open-label, multicentre, two-arm phase II study to evaluate the safety of deferasirox film-coated tablet (FCT) formulation and deferasirox dispersable tablet (DT) formulation in patients with transfusion dependent thalassemia or myelodysplastic syndrome (MDS) at very low, low or intermediate risk requiring chelation therapy due to iron overload' and consequent warnings (in order to fulfil ANX 047). The MAH took the opportunity to update Annex II and the RMP (version 14) is updated accordingly

15.3.10. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS0926/0017; Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS0926/0016

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to include data from study 1275.9, a phase III, randomised, double-blind, parallel group, 24 week study to evaluate efficacy and safety of once daily empagliflozin 10 mg and 25 mg compared to placebo, all administered as oral fixed dose combinations with linagliptin 5 mg, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy. In addition, the MAH took the opportunity to remove the optional sentence on 'medicinal product subject to medical prescription' from Annex IIIA. Moreover, the RMPs (version 8.0 for Jardiance; version 6.0 for Synjardy) are updated accordingly

15.3.11. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0131

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include treatment of human immunodeficiency virus (HIV)-1 infected adolescents, with nucleoside reverse transcriptase inhibitors (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to <18 years for Truvada. 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 13) are updated accordingly

15.3.12. Esomeprazole - NEXIUM CONTROL (CAP) - EMEA/H/C/002618/X/0016

Applicant: Pfizer Consumer Healthcare Ltd

PRAC Rapporteur: Simona Kudeliene

Scope: Line extension to introduce a new pharmaceutical form (gastro-resistant capsule,

hard). The RMP (version 1.1) is updated accordingly

15.3.13. xenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0038

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final results of study 2993LAR-105: a randomized, open-label, multicentre, comparator-controlled study to examine the effects of exenatide long-acting release on glucose control (HbA1c) and safety in subjects with type 2 diabetes mellitus managed with diet modification and exercise and/or oral antidiabetic medications) to examine the effects of exenatide once weekly on glucose control and safety in subjects with type II diabetes mellitus

15.3.14. 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

15.3.15. Florbetapir (^{18}F) - 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 (^{18}F) 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 (PI) in line with the latest QRD template (version 10.0)

15.3.16. 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

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

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.8 of the SmPC in order to update the frequencies of undesirable effects to reflect the final clinical study report (CSR) from study CSLCT-BIO-08-53 in haemophilia A paediatric patients. The Package Leaflet is updated accordingly. The submission of the final clinical study report for study CSLCT-BIO-08-53 also leads to changes to the RMP (version 6.1) in order to update the Company Core Safety Information (CCSI). Submission of a revised RMP in order to remove the commitment to conduct a post-marketing study for haemophilia A patients (study CSLCT-BIO-12-78) for Voncento as a consequence of new data from study CSLCT-BIO-08-53. In addition, the MAH took the opportunity to combine different strengths in the SmPC and Package Leaflet

15.3.18. Human fibrinogen, human thrombin - EVARREST (CAP) - EMEA/H/C/002515/II/0027/G

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) submission of the final results for study BIOS-13-005 (a phase III, randomized, controlled, superiority study evaluating Evarrest fibrin sealant patch versus standard of care treatment in controlling parenchymal bleeding during hepatic surgery) updating the efficacy and safety information; 2) submission of the final results for study BIOS-13-004 (a single-blinded, randomized, controlled, comparative phase III study evaluating the safety and effectiveness of Evarrest fibrin sealant patch as an adjunct to hemostasis during cardiovascular surgery) updating the efficacy and safety information; 3) submission of the final results for study 400-12-002 (a randomized, controlled, comparative phase II study evaluating the safety and effectiveness of Evarrest fibrin sealant patch as an adjunct to haemostasis during cardiovascular surgery) updating the efficacy and safety information; 4) submission of the final results for study 400-12-005 (a non-investigational post-market trial using Evarrest fibrin sealant patch as an adjunct to haemostasis in soft tissue bleeding during intra-abdominal, retroperitoneal, pelvic and non-cardiac thoracic surgery) updating the safety information; 5) update of section 5.1 of the SmPC to include further information on main existing efficacy studies. As a consequence, sections 4.8, 5.1 of the SmPC are also updated. In addition, the product information (PI) is brought in line with the latest QRD template (version 10) and Guideline on core SmPC for plasma-derived fibrin/sealant/haemostatic products (EMA/CHMP/BPWP/598816/2010 rev.1). Furthermore, section 4.2 is updated regarding the paediatric information for children under the age of 1 month, according to the EMA waiver. The RMP (version 3) is updated accordingly, including consequential and routine changes

15.3.19. 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. The RMP (version 6.1) is updated accordingly

15.3.20. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0027/G

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Grouped variation to: 1) update of sections 4.8 in order to include Stevens-Johnson Syndrome (SJS) and onychoclasis as post-marketing adverse drug reactions (ADRs). In addition, the MAH took the opportunity to make minor editorial amendments to the SmPC, including an editorial amendment to section 4.8 to mark the existing ADR terms of tumour lysis syndrome (added in variation EMEA/H/C/003791/II/0004), erythema, angioedema, and urticaria (added in variation EMEA/H/C/003791/0008/G) to indicate they originate from spontaneous post-marketing reports; 2) update of section 4.4 to include Hypertension as one of the risk factors for atrial fibrillation/flutter. The Package Leaflet and the RMP (version 6.2) are updated accordingly

15.3.21. 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

15.3.22. Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/II/0065/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations including an extension of indication to include monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in children from 4 to less than 16 years old with epilepsy. For the treatment initiation pack, it is proposed to extend only the adjunctive treatment to adolescents weighting more than 50 kg (not suitable for monotherapy and children and adolescents weighting less than 50 kg). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 12) are updated accordingly. In addition, the MAH took the opportunity to bring Annex IIIA in line with the latest QRD template (version 10) and to introduce combined SmPC for film coated tablets. Furthermore, sections 6.3 and 6.5 of the SmPC for the syrup presentation only are updated due to the extension of shelf life of the finished product after first opening from 4 weeks to

6 months and addition of a 10 mL dosing syringe for syrup, as an additional dosing device to use in the paediatric population

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

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.24. Ofatumumab - ARZERRA (CAP) - EMEA/H/C/001131/II/0045/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the combination of Arzerra with fludarabine and cyclophosphamide or in combination with bendamustine for the treatment of adult patients with relapsed chronic lymphocytic leukaemia (CLL). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 and 9 of the SmPC are updated.The Package Leaflet and the RMP (version 13) are updated accordingly

15.3.25. 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

15.3.26. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/II/0012/G

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Grouped variations to: 1) update section 4.5 of the SmPC in order to reflect data on cytochrome P450 3A4 (CYP3A4) following submission of the results of study E1508I0242 (investigation of CYP induction potential of ospemifene at clinically relevant intestinal concentrations to exclude potential CYP3A4 induction in the intestine); 2) update of section 5.2 of the SmPC to reflect the results of study E1508I0242 (evaluation of the conversion of the Z-enantiomer of ospemifene to its E-enantiomer, evaluation of the metabolism and excretion of ospemifene and its metabolites); 3) update of section 5.2 of the SmPC to include results of studies OSP-PF-046-N and OSP-PF-047-N (in vitro investigation of plasma protein binding data of M-1 in non-clinical species for interspecies comparison between non-clinical species and humans, investigation of blood-to-plasma ratio data for ospemifene in monkey and rat and the blood-to plasma ratio for M-1 in rat, monkey and human); 4) update section 5.2 of the SmPC to reflect the results of study OSP-PF-041-N (bile salt export pump (BSEP) transporter studies post-marketing). As a consequence, the RMP (version 1.2) is updated accordingly

15.3.27. Panitumumab - VECTIBIX (CAP) - EMEA/H/C/000741/II/0079

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Julie Williams

Scope: Update of section 4.6 of the SmPC in order to remove references to the pregnancy surveillance programme (PSP) and lactation surveillance programmes (LSP). The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to make further administrative updates to the RMP

15.3.28. Panitumumab - VECTIBIX (CAP) - EMEA/H/C/000741/II/0080

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Julie Williams

Scope: Update of Annex II in order to provide the results of biomarker analyses from the Vectibix clinical programme including study 20080763 (according to supplementary statistical analysis plan dated 20 September 2013), study 20070820 and study 20060447. The data submitted are in fulfilment of Annex II obligation ANX017. The RMP (version 21.0) is updated accordingly

15.3.29. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0011

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to extend the existing indication for Keytruda 50mg to include previously untreated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours express programmed death ligand 1 (PD-L1). As a

consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly

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

Applicant: Ariad Pharma Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 of the SmPC based on data from ongoing study AP24534-07-101 with a median duration of follow-up of approximately 48 months for the CP-chronic myeloid leukaemia (CML) patients and 3.6 months for the advanced phase Ph+ leukaemia patients, as well as 48-month follow-up data from the ongoing study AP24534-10-201 (PACE). The Package Leaflet and the RMP (version 14.1) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and to align the annexes with the latest QRD template (version 10)

15.3.31. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/II/0019

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Update of Annex II to remove condition relating to the ceased COAST trial (study 15983: a randomized, double-blind, placebo-controlled phase-III study of adjuvant regorafenib versus placebo for patients with stage IV colorectal cancer after curative treatment of liver metastases). In addition, section 5.1 of the SmPC has been updated in order to remove information relating to KRAS mutation status and regorafenib efficacy. The RMP (version 4.2) is updated accordingly

15.3.32. 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 (a prospective case-crossover study to evaluate the possible association between the use of phosphodiesterase type 5 (PDE5) inhibitors and the risk of acute NAION category 3 study). The RMP (version 8.0) is updated accordingly

15.3.33. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0009

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.4, 4.5 and 5.2 of the SmPC based on the completed drug-drug interaction study MK-1986-004 (a multiple-dose study to evaluate the effects of steady-state tedizolid phosphate administration on the pharmacokinetics and safety of a single dose of midazolam and rosuvastatin). The Package Leaflet is updated accordingly. In addition,

the MAH took the opportunity to implement editorial changes in the annexes and to update the annexes in line with the latest QRD template (version 10). The RMP (version 2.0) is updated by removing the missing information for potential risks for drug-drug interactions mediated by CYP3A4, as well as addressing the identified risk for drug-drug interactions mediated via inhibition of breast cancer resistance protein (BCRP), adding updates made to timelines for ongoing and planned studies for long term safety and Asian population experience

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. Alogliptin - VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone - INCRESYNC (CAP); PSUSA/00010061/201604

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.2. Aprepitant - EMEND (CAP) - PSUSA/00000229/201603

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.3. Catumaxomab - REMOVAB (CAP) - PSUSA/00000581/201604

Applicant: Neovii Biotech GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.4. Catumaxomab - REMOVAB (CAP) - PSUSA/00000581/201604

Applicant: Neovii Biotech GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.5. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/201604

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.6. Dimethyl fumarate - TECFIDERA (CAP) - PSUSA/00010143/201603

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.7. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin) (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) - HEXACIMA (CAP); HEXAXIM (Art 58[51]); HEXYON (CAP) - PSUSA/00010091/201604

Applicant: Sanofi Pasteur

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.8. Efavirenz - STOCRIN (CAP); SUSTIVA (CAP) - PSUSA/00001200/201604 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

16.1.9. Empagliflozin - JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) - PSUSA/00010388/201604

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.10. Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/201604

Applicant: Gilead Sciences International Ltd

[51] 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)

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.11. Emtricitabine, tenofovir - TRUVADA (CAP) - PSUSA/00001210/201604

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.12. Everolimus[52] - AFINITOR (CAP) - PSUSA/00010268/201603

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.13. Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/201603

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.14. Fenofibrate, pravastatin - PRAVAFENIX (CAP) - PSUSA/00001363/201604

Applicant: Laboratoires SMB S.A.

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.15. Florbetapir (^{18}F) - AMYVID (CAP) - PSUSA/00010032/201604

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.16. Histamine[53] - CEPLENE (CAP) - PSUSA/00001610/201604

Applicant: Meda AB

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

[52] Indicated for the treatment of renal cell carcinoma
[53] Indicated for treatment of acute myeloid leukaemia

16.1.17. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/201604

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.18. Insulin glulisine - APIDRA (CAP) - PSUSA/00001752/201604

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.19. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/201603

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.20. Japanese encephalitis virus (inactivated) - IXIARO (CAP) - PSUSA/00001801/201603

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.21. Macitentan - OPSUMIT (CAP) - PSUSA/00010115/201604

Applicant: Actelion Registration Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.22. Mannitol[54] - BRONCHITOL (CAP) - PSUSA/00009226/201604

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.23. Meningococcal group a, c, w135, y conjugate vaccines (conjugated to tetanus toxoid carrier protein) - NIMENRIX (CAP) - PSUSA/00010044/201604

Applicant: Pfizer Limited

[54] Indicated for the treatment of cystic fibrosis

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.24. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/201603

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.25. Netupitant, palonosetron - AKYNZEO (CAP) - PSUSA/00010393/201604

Applicant: Helsinn Birex Pharmaceuticals Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.26. Ocriplasmin - JETREA (CAP) - PSUSA/00010122/201604

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.27. Oestrogens conjugated, bazedoxifene - DUAVIVE (CAP) - PSUSA/00010321/201604

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.28. Olanzapine pamoate - ZYPADHERA (CAP) - PSUSA/00002206/201603

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.29. Para-aminosalicyic acid[55] - GRANUPAS (CAP) - PSUSA/00010171/201604

Applicant: Lucane Pharma

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[55] Centrally authorised product only

16.1.30. Raltegravir - ISENTRESS (CAP); lamivudine, raltegravir - DUTREBIS (CAP) - PSUSA/00010373/201603

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.31. Regadenoson - RAPISCAN (CAP) - PSUSA/00002616/201604 (with RMP)

Applicant: Rapidscan Pharma Solutions EU Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.32. Sofosbuvir, ledipasvir - HARVONI (CAP) - PSUSA/00010306/201604

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

16.1.33. Tacrolimus[56] - PROTOPIC (CAP) - PSUSA/00002840/201603

Applicant: Leo Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.34. Tocilizumab - ROACTEMRA (CAP) - PSUSA/00002980/201604

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.35. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/201604

Applicant: Genzyme Europe BV

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

[56] Topical formulations only

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

16.2.1. Esomeprazole - NEXIUM CONTROL (CAP); NAP - PSUSA/00001269/201603

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

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.2.2. Hepatitis B vaccine (rDNA) - HBVAXPRO (CAP); NAP - PSUSA/00001597/201602

Applicant: Sanofi Pasteur MSD SNC (HBVaxPro), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.2.3. Tenofovir - VIREAD (CAP); NAP - PSUSA/00002892/201603

Applicant: Gilead Sciences International Ltd (Viread), various

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Alprazolam (NAP) - PSUSA/00000109/201603

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.2. Amlodipine (NAP) - PSUSA/00000174/201603

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.3. Aprotinin (NAP) - PSUSA/00000230/201602

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.4. Butoconazole (NAP) - PSUSA/00000471/201602

Applicant: various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.5. Dorzolamide, timolol (NAP) - PSUSA/00001166/201602

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.6. Eletriptan (NAP) - PSUSA/00001204/201602

Applicant: various

PRAC Lead: Jana Mlada

Scope: Evaluation of a PSUSA procedure

16.3.7. Ethinylestradiol, gestodene[57] (NAP) - PSUSA/00001308/201603

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.8. Galantamine (NAP) - PSUSA/00001512/201603

Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.9. Germanium (^{68}Ge) chloride, gallium (^{68}Ga) chloride (NAP) - PSUSA/00010364/201603

Applicant: various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

16.3.10. Gliclazide (NAP) - PSUSA/00001532/201602

Applicant: various

[57] except for transdermal application

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.11. Influenza vaccine (split virion, inactivated) (NAP) - PSUSA/00010298/201603

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.12. Influenza vaccine (split virion, inactivated, prepared in cell culture) (NAP) - PSUSA/00010299/201603

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.13. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/201603

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.3.14. Influenza vaccine (surface antigen, inactivated, adjuvanted) (NAP) - PSUSA/00010300/201603

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.3.15. Latanoprost[58] (NAP) - PSUSA/00001834/201604

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.16. Meningococcal group a and c polysaccharide vaccine (NAP) - PSUSA/00001970/201602

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

[58] Medicinal products with paediatric indication

Scope: Evaluation of a PSUSA procedure

16.3.17. Nicorandil (NAP) - PSUSA/00002152/201602

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.18. Pimecrolimus (NAP) - PSUSA/00002411/201603

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.19. Technetium (^{99m}Tc) pertechnetate (NAP) - PSUSA/00002866/201603

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.20. Promestriene[59] (NAP) - PSUSA/00009271/201603

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and Haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) - INFANRIX HEXA (CAP) - EMEA/H/C/000296/LEG 116.2

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of MAH's responses to LEG 116.1 (evaluation of additional information on the recently observed increase in the reported cases of regression of psychomotor development and a cumulative review of cases in relation with lack of reconstitution following the recommendation of the PSUSA/00001122/201410 procedure dated June 2015) as per request for supplementary information (RSI) adopted in April 2016

[59] Cream and vaginal capsules only

16.4.2. Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/LEG 042

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope: Submission of a review of pending cases reported before conception together with a detailed analysis as requested in the recommendation of PSUSA/00001201/201507 adopted by PRAC in February 2016

16.4.3. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/LEG 071

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a detailed review on vascular death, all-cause mortality, and main vascular events observed in RIDE (a phase III randomized study of ranibizumab injection in subjects with clinically significant macular edema (ME) with center involvement secondary to diabetes mellitus) and RISE (a phase III randomized study of ranibizumab injection in subjects with clinically significant ME with center involvement secondary to diabetes mellitus) as requested in the recommendation of PSUSA/00002609/201510 adopted by PRAC in April 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)[60]

17.1.1. Cholic acid – KOLBAM (CAP) - EMEA/H/C/PSP/0017.2

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Revised PASS protocol for a patient registry to monitor the long term safety and efficacy in patients treated with cholic acid, as requested in the conclusions of EMEA/H/C/PSP/0017.1 adopted by PRAC in July 2016

17.1.2. Domperidone (NAP) - EMEA/H/N/PSP/j/0031.2

Applicant: Janssen (Motilium), various

PRAC Rapporteur: Claire Ferard

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

Scope: Revised PASS protocol for a drug utilisation study on domperidone use in Europe using databases to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the changes in the product information and the distribution of a DHPC, as requested in the conclusions of EMEA/H/N/PSP/j/0031.1 adopted by PRAC in June 2016

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[61]

17.2.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: PASS protocol for study ALIROC07997: 'monitoring of the safety of alirocumab in human immunodeficiency virus (HIV)-infected patients, using healthcare databases'

17.2.2. Necitumumab - PORTRAZZA (CAP) - EMEA/H/C/003886/MEA 001.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Revised PASS protocol for a survey to assess physicians'/oncologists' understanding of the key conditions for the safe use of necitumumab, as per the request for supplementary information (RSI) adopted by PRAC and CHMP in June 2016

17.2.3. Necitumumab - PORTRAZZA (CAP) - EMEA/H/C/003886/MEA 002.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Revised PASS protocol for an observational prospective study to assess the incidence, severity, and sequelae of all serious life-threatening identified and potential risks for necitumumab treatment in the approved indication, as per the request for supplementary information (RSI) adopted by PRAC and CHMP in June 2016

17.2.4. Ocriplasmin - JETREA (CAP) - EMEA/H/C/002381/MEA 001.2

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: Revised protocol for a drug utilisation study TG-MV-017 on the use of intravitreal Jetrea in clinical practice, as per the request for supplementary information (RSI) adopted by PRAC and CHMP in July 2016

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

17.2.5. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/MEA 093.3

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: MAH's responses to MEA 093.2 [revised PASS registry protocol for a long-term surveillance study of rituximab (Mabthera)-treated patients with granulomatosis, with polyangiitis (GPA) or microscopic polyangiitis (MPA)] as per request for supplementary information adopted in May 2016

17.2.6. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's response to MEA-002 [PASS protocol for study No. CLCZ696B2014: a non-interventional post-authorisation European database safety study (category 3) to characterize the risk of angioedema and other specific safety events of interest in association with use of Entresto (sacubitril/valsartan) in adult patients with heart failure] as per request for supplementary information adopted in May 2016

17.2.7. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's response to MEA-004 [PASS protocol for study No. CLCZ696B2015: a non-interventional post-authorisation European database safety study (category 3) to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of sacubitril/valsartan] as per request for supplementary information adopted in May 2016

17.3. Results of PASS imposed in the marketing authorisation(s)[62]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[63]

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

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final clinical study report (CSR) for study P06-134 entitled: 'a long-term non-interventional registry to assess safety and effectiveness of Humira in

[62] In accordance with Article 107p-q of Directive 2001/83/EC
[63] 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

subjects with moderately to severely active Crohn's disease' in fulfilment of MEA 056.9. The study includes also some paediatric patients and fulfils Article 46 paediatric obligations

17.4.2. Aripiprazole - ABILIFY (CAP) - EMEA/H/C/000471/II/0122

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Leonor Chambel

Scope: Submission of the final clinical study report (CSR) for non-interventional, non-imposed PASS study 31-13-300 entitled: 'Abilify for the adolescent bipolar I mania indication tool effectiveness evaluation survey' to fulfil a post-authorisation measure (MEA 068.2). Annex II is updated to delete additional risk minimisation measures based on the study results and to delete PASS study 31-13-300 included by mistake during variation IB/112/G. Moreover, the RMP (version 10) is updated accordingly

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

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Claire Ferard

Scope: Submission of the final clinical report (CSR) for a PASS study P08518 (category 3) of boceprevir among chronic hepatitis C patients entitled: '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

17.4.4. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0050

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Submission of the final study report for study CICL670A2301 (RMP category 3) entitled 'an international sentinel surveillance of patients with transfusional hemosideroris treated with Exjade in actual practice setting'. This submission also served to comply with Article 46 of Regulation (EC) No 1901/2006

17.4.5. Nepafenac - NEVANAC (CAP) - EMEA/H/C/000818/II/0033

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final study report for the drug utilisation study entitled: 'evaluation of the use of nepafenac in selected European populations' (category 3 study) to quantify and describe off-label use of nepafenac in order to fulfil MEA 012

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[64]

17.5.1. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/MEA 005.3

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reports from ARTIS (RA0021), RABBIT (RA0020), US National Databank for Rheumatic Diseases (RA0005) and BSRBR (RA0022)

17.5.2. Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/MEA 039.4

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope: Third annual report for malignant events associated with efavirenz: diagnostic consulting network (DCN) report as a routine risk minimisations measure

17.5.3. Everolimus - VOTUBIA (CAP) - EMEA/H/C/002311/MEA 014.2

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Third interim analysis for study CRAD001MIC03 (TOSCA) a safety sub-study classified as a PASS entitled: 'international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex (TSC)'

17.5.4. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 005.5

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Sixth annual report on a German registry study RABBIT: long-term observational study of the safety of biologic treatments in rheumatoid arthritis

17.6. Other

17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.8

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Fifth interim report of the canagliflozin independent data monitoring committee

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

(IDMC) for the DIA3008 CANVAS study (a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus) as requested in the RMP additional pharmacovigilance activity

17.6.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.5

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Fourth interim report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study (a randomized, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) as requested in the RMP additional pharmacovigilance activity

17.6.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.8

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Fifth interim report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study (a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus) as requested in the RMP additional pharmacovigilance activity

17.6.4. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.5

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Fourth interim report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study (a randomized, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) as requested in the RMP additional pharmacovigilance activity

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

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0023 (without RMP)

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.2. Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/S/0022 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation

18.1.3. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0034 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0017 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Conditional renewal of the marketing authorisation

18.2.2. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/R/0022 (without RMP)

Applicant: TMC Pharma Services Ltd

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

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

Applicant: Genzyme Europe BV

PRAC Rapporteur: Claire Ferard

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Capecitabine - CAPECITABINE ACCORD (CAP) - EMEA/H/C/002386/R/0021 (without RMP)

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.2. Capecitabine - CAPECITABINE TEVA (CAP) - EMEA/H/C/002362/R/0025 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.3. Granisetron - SANCUSO (CAP) - EMEA/H/C/002296/R/0047 (without RMP)

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: 5-year renewal of the marketing authorisation

18.3.4. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/001252/R/0028 (without RMP)

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.5. Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/R/0059 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: 5-year renewal of the marketing authorisation

18.3.6. Prepandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture) - VEPACEL (CAP) - EMEA/H/C/002089/R/0015 (without RMP)

Applicant: Nanotherapeutics Bohumil Sro

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.7. Riluzole - RILUZOLE ZENTIVA (CAP) - EMEA/H/C/002622/R/0021 (without RMP)

Applicant: Aventis Pharma S.A.

PRAC Rapporteur: Julie Williams

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 24-27 October 2016 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn 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	Member	France	No interests declared	Full involvement
Caroline Laborde	Alternate	France	No interests declared	Full involvement

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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Miroslava Matíková	Alternate	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani	Expert - via	Belgium	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	
Flora Musuamba Tshinanu	Expert - via telephone*	Belgium	No interests declared	Full involvement
José Javier Sawchik Monegal	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Nathalie Morgensztejn	Expert - via telephone*	France	No interests declared	Full involvement
Simone Bergner	Expert - via telephone*	Germany	No interests declared	Full involvement
Thomas Grüger	Expert - via telephone*	Germany	No interests declared	Full involvement
Tania Meier	Expert - via telephone*	Germany	No interests declared	Full involvement
Niamh Buckley	Expert - in person*	Ireland	No interests declared	Full involvement
Anna Marie Coleman	Expert - via telephone*	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Else Carrière	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Quirine Fillekes	Expert - in person*	Netherlands	No interests declared	Full involvement
Reynold Francisca	Expert - in person*	Netherlands	No interests declared	Full involvement
Eirik Hagtvet	Expert - via telephone*	Norway	No interests declared	Full involvement
Anna-Lena Axelson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Bengt Ljungberg	Expert - via telephone*	Sweden	No interests declared	Full involvement

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

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

21. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
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/