10 May 2016
EMA/PRAC/319149/2016
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the PRAC meeting on 11-14 April 2016

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 11-14 April 2016 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Raymond Anderson, as the new PRAC member nominated by the European Commission to represent healthcare professionals' organisations. In addition, the Chair also welcomed Thierry Trenque as an independent scientific expert member nominated by the European Commission, replacing Jane Ahlqvist-Rastad who stepped down from her role after the March 2016 PRAC plenary meeting.

1.2. Agenda of the meeting of 11-14 April 2016

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

1.3. Minutes of the previous meeting on 14-17 March 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 14-17 March 2016 were published on the EMA website on 3 May 2016 (EMA/PRAC/259752/2016).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

3.1.1. Canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP) - EMEA/H/A-20/1442

Applicant: Janssen-Cilag International N.V.

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

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

Background

The European Commission (EC) sent a letter of notification dated 15/04/2016[1] of a referral under Article 20 of Regulation (EC) No 726/2004 for the review of medicines containing canagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, indicated as a monocomponent (Invokana) or in combination with metformin, a biguanide (Vokanamet), for the treatment of type 2 diabetes mellitus (T2DM) in adults aged 18 years old and older under certain conditions.

The review was initiated following PRAC discussion at the current meeting of a new signal of potential increased risk of lower limb amputation (primarily of the toe) with an approximately two-fold increase in canagliflozin-treated subjects compared to placebo in an ongoing randomized clinical trial CANVAS[2], a MAH-sponsored long-term cardiovascular outcomes study. In addition, an analysis of CANVAS-R[3], an ongoing clinical trial with a similar population as CANVAS also showed a numerical imbalance with regard to amputation events. For further background, see New Signal - 4.2.1.

The EC requested the EMA to assess the potential increased risk of lower limb amputation associated with the use of canagliflozin-containing products and ways to minimise this risk, to evaluate its impact on the benefit-risk balance of canagliflozin-containing medicines and to give an opinion by 31 March 2017. In addition, the EC requested the EMA to give its opinion as to whether provisional measures are necessary to ensure the safe and effective use of canagliflozin-containing medicines. Moreover, the EC requested the EMA to consider

[1] Day following the closure of the April 2016 PRAC plenary meeting. A follow-up PRAC teleconference took place on 19 April 2016 to agree the next steps for the referral procedure under Article 20 of Regulation (EC) No 726/2004
[2] Randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus
[3] Randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with type 2 diabetes mellitus

extending this review to other SGLT2 inhibitors if necessary, given that they all share the same mechanism of action.

Discussion

At a follow-up PRAC teleconference organised on 19 April 2016, the PRAC noted the notification letter from the European Commission. The PRAC appointed Valerie Strassmann as Rapporteur and Menno van der Elst as Co-Rapporteur for the procedure, and discussed a list of questions to be addressed by the MAH for canagliflozin-containing products as well as a timetable for conducting the review.

In addition, the PRAC agreed by consensus that based on the available information, the most effective risk minimisation at this stage was targeted communication to healthcare professionals via a Direct Healthcare Professional Communication (DHPC) as agreed within the signal procedure. Therefore, it was considered that provisional measures were not necessary.

In addition, the PRAC agreed a list of questions to the MAHs of other SGLT2 inhibitors (dapagliflozin- and empagliflozin-containing products) to further investigate any possible evidence of an increased risk of lower limb amputations associated with the other medicinal products of the same class. See New Signal - 4.2.1.

Summary of recommendation(s)/conclusions

The Committee adopted a list of questions (EMA/PRAC/271175/2016) and a timetable for the procedure (EMA/PRAC/271123/2016).

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: Extension of the scope for the 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

The European Commission sent an addendum to the notification dated 14/04/2016 for the ongoing referral under Article 20 of Regulation (EC) No 726/2004 for the review of direct-acting antivirals (DAAV) (daclatasvir (Daklinkza), dasabuvir (Exviera), ombitasvir/paritaprevir/ritonavir (Viekirax), simeprevir (Olysio), sofosbuvir (Sovaldi), sofosbuvir/ledipasvir (Harvoni)) indicated for the interferon-free treatment of chronic hepatitis C in adults under certain conditions, following discussion at PRAC of the available evidence for a new signal of unexpected early hepatocellular carcinoma recurrence associated with the use of DAAV based on published literature, particularly the article by

Reig M. et al.[4]. Considering the seriousness of the events, a thorough evaluation was considered warranted and it was deemed appropriate to extend the scope of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV to consider the risk of hepatocellular carcinoma (HCC). See New Signal - 4.2.2. The PRAC had also appointed Margarida Guimarães as Rapporteur and Dolores Montero Corominas as Co-Rapporteur for the procedure. For further background, see PRAC minutes March 2016.

Discussion

The PRAC noted the addendum to the notification letter from the European Commission and discussed an addendum on HCC to the previous list of questions to be addressed by the MAHs as well as a revised timetable for conducting the review.

Summary of recommendation(s)/conclusions

The Committee adopted an addendum to the list of questions (EMA/PRAC/196081/2016) and a revised timetable for the procedure (EMA/PRAC/196120/2016 Rev.1).

3.3. Procedures for finalisation

None

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

None

3.5. Others

None

4. Signals assessment and prioritisation[5]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Adalimumab – HUMIRA (CAP)

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of acute febrile neutrophilic dermatosis (Sweet's syndrome)

EPITT 18630 – New signal
Lead Member State: SE

Background

[4] Reig, M., Mariño, Z., Perelló, C., Iñarrairaegui, M., Ribeiro, A., Lens, S., Díaz, A., Vilana, R., Darnell, A., Varela, M., Sangro, B., Calleja, J.L., Forns, X., Bruix, J., Unexpected early tumor recurrence in patients with hepatitis C virus -related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution, Journal of Hepatology (2016), doi: http://dx.doi.org/10.1016/j.jhep.2016.04.008

[5] 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

Adalimumab is a tumour necrosis factor alpha (TNF-α) inhibitor indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease in adults and children, and ulcerative colitis under certain conditions.

The exposure for Humira, a centrally authorised medicine containing adalimumab, is estimated to have been more than 2.9 million patients-years worldwide, in the period from first authorisation in 2003 until December 2013.

Following the publication of the article by *Banse C. et al.*[6], a signal of acute febrile neutrophilic dermatosis (Sweet's syndrome) was identified by the EMA, based on 6 supportive cases retrieved from EudraVigilance and from the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from case reports in EudraVigilance and the scientific literature. Taking into account that 5 cases reported a positive de-challenge and one a positive re-challenge, the PRAC considered that the MAH for Humira should provide a cumulative review of cases of neutrophilic dermatosis in association with adalimumab.

Summary of recommendation(s)

- The MAH for Humira (adalimumab) should submit to the EMA, within 60 days, a cumulative review of cases of neutrophilic dermatosis (Sweet's syndrome) in association with adalimumab. The MedDRA[7] preferred terms 'neutrophilic dermatosis' and 'acute febrile neutrophilic dermatosis' should be used as search terms and the review should include post marketing reports, published literature and data from clinical trials. Information on dechallenge/rechallenge and histological investigations should be presented when available. In addition, the MAH should discuss the possible causal relationship as well as comment on possible mechanisms. The MAH should also discuss the need for any potential amendment to the product information and/or the RMP and make a proposal for changes to the relevant sections as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: following a request from the PRAC Rapporteur, the PRAC agreed that that the MAH should submit their responses within 90 days instead of 60 days as originally agreed by the PRAC.

4.1.2. Agomelatine – THYMANAX (CAP), VALDOXAN (CAP)

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Signal of urinary retention

EPITT 18637 – New signal
Lead Member State: NO

[6] Banse C, et al. Occurrence of Sweet syndrome under anti-TNF. Clin Rheumatol. 2015 Nov;34(11):1993
[7] Medical Dictionary for Regulatory Activities

Background

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist indicated for the treatment of adults with major depressive episodes.

The post-marketing exposure to Valdoxan and Thymanax, centrally authorised medicines containing agomelatine, is estimated to have been 23,000,000 patient-months worldwide, in the period from first authorisation in 2009 until February 2016.

During routine signal detection activities, a signal of urinary retention was identified by the EMA on 24 February 2016, based on 6 supportive cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from case reports in EudraVigilance. Taking into account amongst others that all cases reported a positive dechallenge and 2 cases a positive rechallenge, the PRAC considered that the MAH for Valdoxan and Thymanax should provide a cumulative review of all cases of urinary retention with agomelatine.

Summary of recommendation(s)

- The MAH for Valdoxan and Thymanax (agomelatine) should submit to the EMA, within 60 days, a cumulative review of all cases of urinary retention with agomelatine. This review should include information from clinical and pre-clinical studies, spontaneous reports and the scientific literature, as well as information on the possible mechanism (e.g. as 5-HT_{2C} receptors are a therapeutic target for the treatment of urinary incontinence). The MAH should also discuss the need for any potential amendment to the product information and/or the RMP and make proposals for changes to the relevant sections as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Agomelatine – THYMANAX (CAP), VALDOXAN (CAP)

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Signal of leukopenia

EPITT 18638 – New signal
Lead Member State: NO

Background

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist indicated for the treatment of adults with major depressive episodes.

The post-marketing exposure to Valdoxan and Thymanax, centrally authorised medicines containing agomelatine, is estimated to have been 23,000,000, patient-months worldwide, in the period from first authorisation in 2009 until February 2016. During routine signal detection activities, a signal of leukopenia was identified by the EMA on 24 February 2016, based on 9 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from case reports in EudraVigilance. Taking into account amongst others that 7 cases reported a positive dechallenge and that time to onset is plausible for an association, the PRAC considered that the MAH for Valdoxan and Thymanax should provide a cumulative review of all cases of leukopenia and neutropenia associated with agomelatine and also of all incidents of leukocyte values in peripheral blood below 4000/mm³ and neutrophil values below 1500/mm³ in the available study reports.

Summary of recommendation(s)

- The MAH for Valdoxan and Thymanax (agomelatine) should submit to the EMA, within 60 days, a cumulative review of all cases of leukopenia and neutropenia associated with agomelatine and identified by the narrow searches of the standardised MedDRA queries (SMQs) 'haematopoietic leukopenia' and 'agranulocytosis'. The review should include post marketing reports and a scientific literature review. In addition, a cumulative review should be performed of all incidents of leukocyte values in peripheral blood below 4,000/mm³ and neutrophil values below 1,500/mm³ in the available study reports. In addition, the MAH should submit a meta-analysis of randomized, placebo-controlled clinical trials to assess the absolute as well as the relative risk, with confidence intervals, of leukopenia associated with agomelatine by patient-years. This should also be performed using the narrow searches of the SMQs 'hematopoietic leukopenia' and 'agranulocytosis', as well as subjects experiencing the above-mentioned lab values. The MAH should discuss the possible mechanism of action. Based on these measures, the MAH should discuss the need to update the product information and/or the RMP and make a proposal for changes to the relevant sections as appropriate. The MAH should also provide a discussion on whether the closed signal of thrombocytopenia should be reopened.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

Applicant: 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 – New signal
Lead Member States: FR, IT, UK

Background

Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily indicated as a pharmacokinetic enhancer of atazanavir (an azapeptide human immunodeficiency virus (HIV)-1 protease inhibitor), darunavir (an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease), elvitegravir (an HIV-1

integrase strand transfer inhibitor), emtricitabine (a nucleoside analogue of cytidine) or tenofovir (a nucleotide reverse transcriptase inhibitor), as part of antiretroviral combination therapy in HIV-1 infected adults.

During routine signal detection activities, a signal of drug interaction with corticosteroids leading to adrenal suppression was identified by the United Kingdom, based on 8 cases retrieved from EudraVigilance. The UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from case reports in EudraVigilance and in the scientific literature. Taking into account the available evidence, the PRAC considered that the MAH for Tybost, Stribild and Genvoya (Gilead) should provide a cumulative review and discussion of events of adrenal suppression/insufficiency and Cushing's syndrome, including events reported from clinical trials, occurring with any corticosteroid and Tybost, Stribild or Genvoya. In addition, the PRAC agreed that he MAHs for all cobicistat-containing medicinal products: Bristol-Myers Squibb (Evotaz), Janssen-Cilag Ltd (Rezolsta) as well as Gilead (Tybost, Stribild, Genvoya) should also make appropriate recommendations for risk minimisation, including changes to product information, and fully justify any differential approach for different corticosteroids based on evidence and pharmacological differences, if appropriate. Based on the results of the cumulative review from Gilead, equivalent changes to corticosteroid product information may be pursued once the position for cobicistat-containing medicinal products is agreed.

The PRAC appointed Rafe Suvarna as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Tybost, Stribild and Genvoya (Gilead) should submit to the EMA, within 60 days, a cumulative review and discussion of events of adrenal suppression/insufficiency and Cushing's syndrome, including events reported from clinical trials, occurring with any corticosteroid and Tybost, Stribild or Genvoya.
- The MAHs for all cobicistat-containing medicinal products: Bristol-Myers Squibb (Evotaz), Janssen-Cilag Ltd (Rezolsta) as well as Gilead (Tybost, Stribild, Genvoya) should submit to the EMA, within 60 days, appropriate recommendations for risk minimisation, including changes to the product information, and fully justify any differential approach for different corticosteroids based on evidence and pharmacological differences, if appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.5. Iomeprol (NAP)

Applicant: various

PRAC Rapporteur: Ingebjorg Buajordet

Scope: Signal of haemolysis

EPITT 18625 – New signal
Lead Member State: NO

Background

Iomeprol is a non-ionic iodinated contrast medium with low toxicity, indicated for peripheral arteriography, aortography, angiocardiography and left ventriculography, coronary arteriography, visceral arteriography, digital subtraction angiography, computed tomography enhancement, urography, dacryocystography, sialography, fistulography and galactography.

During routine signal detection activities, a signal of haemolysis was identified by Sweden, based on 4 supportive cases retrieved from EudraVigilance (including one published case). Norway confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from case reports in EudraVigilance. Taking into account the severity of haemolysis, and that in all 4 cases there was a close temporal association between drug exposure and the observed adverse events, the PRAC considered that the MAH for Iomeron (iomeprol) should provide a cumulative review of all cases concerning haemolysis associated with the use of iomeprol.

The PRAC appointed Ingebjorg Buajordet as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Iomeron (iomeprol) should submit to the EMA, within 60 days, a cumulative review of all cases concerning haemolysis associated with the use of iomeprol. This review should be based on data from scientific publications, clinical trials and spontaneous sources, and should include a discussion on the underlying mechanism and the possible risk factors including the underlying diseases, comorbidities and concomitant treatments. The MAH should also perform a critical assessment of any immuno-haematological methods described in the reports for the diagnosis of the event. In addition, the MAH should discuss the need for any potential amendment to the product information and/or the RMP and make a proposal for changes to the relevant sections 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. Canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of potential increased risk of lower limb amputations

EPITT 18650 – New signal
Lead Member States: DE, NL

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.

The exposure for Invokana, a centrally authorised medicine containing canagliflozin, is estimated to have been more than 890,634 patient-years worldwide, in the period from first authorisation in 2013 until September 2015. The post-marketing exposure for Vokanamet, a centrally authorised medicine containing canagliflozin and metformin, is estimated to have been more than 44,182 patient-years worldwide, in the period from first authorisation in 2014 until September 2015.

A signal of potential increased risk of lower limb amputation associated with the use of canagliflozin was identified by Germany based on a safety report on the ongoing CANVAS clinical trial submitted by the MAH to the EMA and all National Competent Authorities on 17 March 2016. CANVAS is an ongoing Phase 3, double-blind, randomized, placebo-controlled, 3-arm, parallel-group, multicentre study to evaluate the effects of canagliflozin on cardiovascular (CV) outcomes in adult subjects with type 2 diabetes mellitus (T2DM) receiving standard of care but with an inadequate glycemic control and at an elevated risk of CV events. During its ongoing review, the Independent Data Monitoring Committee (IDMC) for this study noted an increase in lower-limb amputations -primarily of the toe- in canagliflozin treated patients. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the ongoing CANVAS trial, other completed and ongoing studies, as well as other data relating to the risk of lower limb amputation risk and proposals for risk minimisation as presented by the MAH during an oral explanation. Having considered all the available evidence, the PRAC agreed that the potential increased risk of lower limb amputations with canagliflozin requires a thorough evaluation. The PRAC recommended that the MAH for canagliflozin-containing medicinal products should distribute a direct healthcare professional communication (DHPC) letter to inform about the potential increased risk of lower limb amputations, the need for appropriate routine preventive foot care as well as the advice to, as a precautionary measure, consider stopping treatment in patients that develop a significant complication such as a lower-extremity skin ulcer, osteomyelitis or gangrene according to an agreed text and communication plan. Subsequently at the request of the European Commission, an evaluation has been initiated under Article 20 of Regulation (EC) No 726/2004 (see 3.1.1. Newly triggered procedures). The PRAC also agreed to request additional data on lower limb amputation as a post-authorisation measure (LEG) from the MAHs of other medicines in the same class of SGLT-2 inhibitors to inform the decision on whether to extend the scope of the review to cover these medicines. The PRAC adopted a list of questions to the MAHs of dapagliflozin-containing medicines (Forxiga, Ebymect, Edistride, Xigduo) and the MAH of empagliflozin-containing medicines (Jardiance, Synjardy).

The PRAC appointed Valerie Strassmann as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Invokana (canagliflozin) and Vokanamet (canagliflozin, metformin) should distribute a DHPC according to the text and communication plan agreed with the PRAC and CHMP.
- The MAH for Forxiga and Edistride (dapagliflozin) and for Ebymect and Xigduo (dapagliflozin, metformin) and the MAH for Jardiance (empagliflozin) and Synjardy (empagliflozin, metformin) should submit to the EMA, within 30 days, responses to a

list of questions which will be assessed by the PRAC as post-authorisation measures (LEGs).

4.2.2. 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)

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: Not applicable

Scope: Signal of unexpected early hepatocellular carcinoma recurrence

EPITT 18653 – New signal
Lead Member States: ES, PT, UK

Background

Daclatasvir, dasabuvir, ombitasvir/paritaprevir/ritonavir, simeprevir, sofosbuvir, sofosbuvir/ledipasvir belong to the class of direct-acting antivirals (DAAV) and are indicated in combination for the interferon-free treatment of chronic hepatitis C in adults under certain conditions.

Following the publication by *Reig M. et al.*[8] of the results of follow-up of patients with hepatitis C and previous history of hepatocellular carcinoma treated with direct acting antivirals (DAAV), a signal of unexpected early hepatocellular carcinoma recurrence was identified. Spain confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the published literature (particularly the article by *Reig M. et al.*) and from EudraVigilance. Having considered the seriousness of early hepatocellular carcinoma recurrence, the PRAC agreed that a thorough evaluation should be undertaken on the risk of hepatocellular carcinoma (HCC) associated with the use of direct acting antivirals. The PRAC agreed that this evaluation should be performed within the ongoing procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV against hepatitis C (see 3.2.1. Ongoing procedures).

Summary of recommendation(s)

- The PRAC agreed that this evaluation should be performed within the ongoing procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV against hepatitis C.

[8] Reig, M., Mariño, Z., Perelló, C., Iñarrairaegui, M., Ribeiro, A., Lens, S., Díaz, A., Vilana, R., Darnell, A., Varela, M., Sangro, B., Calleja, J.L., Forns, X., Bruix, J., Unexpected early tumor recurrence in patients with hepatitis C virus -related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution, Journal of Hepatology (2016), doi: http://dx.doi.org/10.1016/j.jhep.2016.04.008

4.2.3. Fulvestrant – FASLODEX (CAP)

Applicant: AstraZeneca UK Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of interference with oestradiol assay leading to false oestradiol results

EPITT 18636 – New signal
Lead Member State: SE

Background

Fulvestrant is a competitive oestrogen receptor antagonist indicated for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen.

The post-marketing exposure for Faslodex, a centrally authorised medicine containing fulvestrant, is estimated to have been more than 415,600 patient-years worldwide, in the period from first authorisation in 2004 until April 2014.

A signal of interference with oestradiol assays leading to false oestradiol results was identified by the UK based on information provided by a manufacturer of estradiol antibody immunoassays and one published case by *Berger et al*[9]*.* The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence provided by several manufacturers of estradiol antibody immunoassays and of reported cases in the scientific literature. Taking into account the available evidence, the PRAC considered that the MAH for Faslodex (fulvestrant) should provide a cumulative review of cases indicative of a potential interference with oestradiol immunoassay in patients taking fulvestrant treatment.

Summary of recommendation(s)

- The MAH for Faslodex (fulvestrant) should submit to the EMA, within 60 days, a cumulative review of cases indicative of a potential interference with the oestradiol immunoassay in patients taking fulvestrant treatment. The MAH should also provide a comprehensive discussion on situations in clinical practice where determination of oestradiol levels in patients on fulvestrant would be indicated, including any clinical situations involving off-label use. The MAH should discuss the need for any potential amendment to the product information and make a proposal for changes to the relevant sections as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[9] Berger D., Waheed S., Fattout Y., Kazlauskaite R., Usha L. Postmenopausal patient with estrogen receptor-positive breast cancer treated; with fulvestrant; Clin Breast Cancer. 2016 Feb; 16(1):e11-3. doi: 10.1016/j.clbc.2015.07.004. Epub 2015 Jul 22.Berger DWaheed SFattout YKazlauskaite RUsha L.Clin Breast Cancer.

4.3. Signals follow-up and prioritisation

4.3.1. Olanzapine – ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

EPITT 18534 – Follow-up to December 2015

Background

For background information, see PRAC minutes December 2015. The MAH replied to the request for information on the signal of drug reaction with eosinophilia and systemic symptoms (DRESS) and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence from case reports in EudraVigilance, published case reports and the data submitted by the MAH, the PRAC agreed that the product information of olanzapine-containing medicinal products should be updated to include drug reactions with eosinophilia and systemic symptoms (DRESS) as new undesirable effect.

Summary of recommendation(s)

- The MAHs for olanzapine-containing medicinal products should submit to the EMA or to the national competent authorities of the MSs, as applicable, within 60 days, a variation to include drug reactions with DRESS as new undesirable effect.

For the full PRAC recommendations, see EMA/PRAC/135876/2016 published on 14/04/2016 on the EMA website.

4.3.2. Penicillins of the beta-lactamase resistant group: cloxacillin (NAP); dicloxacillin (NAP); flucloxacillin (NAP); nafcillin (NAP); oxacillin (NAP)

Applicant: various

PRAC Rapporteur: Margarida Guimarães

Scope: Signal of metabolic acidosis following administration of flucloxacillin in association with paracetamol

EPITT 18514 – Follow-up to December 2015

Background

For background information, see PRAC minutes December 2015. As agreed, the PRAC Rapporteur performed an additional analysis of the signal of metabolic acidosis following administration of flucloxacillin in association with paracetamol including both EudraVigilance and literature searches for flucloxacillin and other penicillins of the beta-lactamase resistant group.

Discussion

The PRAC discussed the additional analysis conducted by the PRAC Rapporteur of EudraVigilance and literature data on metabolic acidosis with beta-lactamase resistant penicillins. Considering the small number of cases as well as the confounding factors, a causal relationship between flucloxacillin or other penicillins and metabolic acidosis was not considered sufficiently robust to warrant further action at this stage. The MAHs of flucloxacillin- and other penicillin-containing products should continue to monitor metabolic acidosis as part of routine safety surveillance.

Summary of recommendation(s)

- The MAHs of flucloxacillin- and other penicillin-containing products should continue to monitor metabolic acidosis as part of routine safety surveillance.

4.3.3. Recombinant factor VIII: antihemophilic factor (recombinant) (NAP) moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), KOGENATE (CAP)

Applicant: Baxter AG (Advate, Recombinate), Bayer Pharma AG (Kogenate, Helixate NexGen), Pfizer Limited (ReFacto AF), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of inhibitor development in previously untreated patients (PUPs)

EPITT 18134 – Follow-up to March 2016

Background

For background information, see PRAC minutes November 2014, PRAC minutes December 2014, PRAC minutes January 2015, PRAC minutes March 2015, PRAC minutes May 2015, PRAC minutes of January 2016 and PRAC minutes March 2016.

Discussion

The PRAC discussed the updated Co-Rapporteur's assessment report. The PRAC noted the results from the meta-analysis, which showed a trend towards an increased risk for inhibitor development, not reaching consistently statistical significance, in previously untreated patients who were treated with Kogenate (octocog alfa) compared with those treated with Advate (octocog alfa). The PRAC considered that the meta-analysis was well conducted, but that there are remaining limitations, including the possibility of residual confounding.

The PRAC agreed that overall, the currently available data do not confirm that Kogenate or Helixate NexGen (octocog alfa) is associated with an increased risk of factor VIII inhibitors, compared with other factor VIII products in previously untreated patients. These conclusions are consistent with the previous conclusions drawn by the PRAC within the review carried out as part of the completed Article 20 referral of Regulation (EC) No 726/2004 on Kogenate/Helixate NexGen in 2013 (EMA/108793/20144).

The PRAC agreed that an update of the product information was not warranted at this point in time. The PRAC recommended that the MAHs of human coagulation factor VIII-containing products should monitor published studies on drug inhibitor development with the aim of keeping the product information up-to-date.

Summary of recommendation(s)

- MAHs of human coagulation factor VIII-containing products should monitor published studies on drug inhibitor development with the aim of keeping the product information up-to-date.

Post-meeting note: The PRAC agreed to publish a public summary report describing the analysis and assessment, considering stakeholders' interest in this topic. The report (EMA/PRAC/332348/2016) was published on 13 May 2016 together with the PRAC highlights May 2016.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 14.1.

5.1.1. Bortezomib - EMEA/H/C/004207

Scope: Treatment of multiple myeloma

5.1.2. Cediranib - EMEA/H/C/004003, Orphan

Applicant: AstraZeneca AB

Scope: Treatment of platinum sensitive relapsed (PSR) ovarian cancer

5.1.3. Enoxaparin sodium – EMEA/H/C/004264; EMEA/H/C/003795

Scope: Prophylaxis of thromboembolic disorders of venous origin

5.1.4. Methotrexate - EMEA/H/C/003983

Scope: Treatment of active rheumatoid arthritis, severe active juvenile idiopathic arthritis and severe recalcitrant disabling psoriasis

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

Applicant: NPS Pharma Holdings Limited

Scope: Treatment of hypoparathyroidism

5.1.6. Reslizumab - EMEA/H/C/003912

Scope: Treatment of asthma and elevated blood eosinophils in patients inadequately controlled on inhaled corticosteroids

5.1.7. Sirolimus - EMEA/H/C/003978, Orphan

Applicant: Santen Oy

Scope: Treatment of chronic non-infectious uveitis

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

See also Annex I 14.2.

5.2.1. Velaglucerase alfa – VPRIV (CAP) - EMEA/H/C/001249/II/0029

Applicant: Shire Pharmaceuticals Ireland Ltd.

PRAC Rapporteur: Valerie Strassmann

Scope: Submission of a revised RMP (version 9.0) in order to include an additional risk minimisation measure to mitigate the risk of serious infusion related reactions and hypersensitivity reactions in the home setting, such as educational material for healthcare professionals and patients/caregivers and a revised antibody testing request form

Background

Velaglucerase alfa is a glycoprotein that supplements or replaces beta-glucocerebrosidase and is indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.

The PRAC is evaluating a type II variation procedure for Vpriv, a centrally authorised medicine containing velaglucerase alfa, to update the RMP. The proposed changes include the introduction of additional risk minimisation measures such as educational materials for healthcare professionals and patients/caregivers to mitigate the risk of serious infusion-related reactions including allergic-type hypersensitivity reactions associated with Vpriv administration in the home setting. For further background, see PRAC minutes February 2016.For further background, see PRAC minutes February 2016. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP version 9.2 for Vpriv (velaglucerase alfa) in the context of the variation under evaluation by the PRAC and CHMP is considered acceptable.
- The MAH should ensure that in each Member State where Vpriv is marketed, HCPs and patients/carers who are expected to prescribe, dispense or use Vpriv have access to/are provided with the educational material (a 'manual for patients with Gaucher disease who receive home infusion treatment'; a 'guide for healthcare professionals treating patients with Gaucher disease'; an 'infusion diary' and an 'emergency plan provided by the prescriber).
- The PRAC considered that the educational materials for use of Vpriv in home infusion, including communication media, distribution modalities and any other aspects of the programme, should be submitted within 60 days after finalisation of this variation procedure to NCAs for agreement at national level.

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

See also Annex I 14.3.

5.3.1. Carfilzomib – KYPROLIS (CAP) - EMEA/H/C/003790/II/0004/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marina Dimov Di Giusti

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add information on haemorrhagic events and update of section 4.4 and 4.6 of the SmPC in order to add information on venous thromboembolic events. The Package Leaflet and RMP are updated accordingly. In addition, the MAH took the opportunity to update the RMP with the request to better characterize infections in patients with relapsed/refractory multiple myeloma requested during the Marketing Authorisation Application (MAA) evaluation

Background

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor and is indicated in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

The CHMP is evaluating a type II variation procedure for Kyprolis, a centrally authorised product containing carfilzomib, to add safety information on haemorrhage events and on venous thromboembolic events (VTE). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 4.1 for Kyprolis (carfilzomib) in the context of the variation under evaluation by the CHMP was considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC considered that the risk of VTE in the RMP should include further information from the ENDEAVOR[10] study showing the magnitude of the VTE risk associated with carfilzomib. In addition, the proposed risk minimisation measures are not sufficient to mitigate the risk of VTE, therefore, further consideration should be given to including additional details in the proposed product information changes. With regard to the important potential risk of 'reproductive and developmental toxicity' and missing information on 'use in pregnant or breastfeeding women', the MAH should ensure that the statement relating to the 'pregnancy prevention programme for lenalidomide' is maintained in view of the currently authorised indication.
- The PRAC also considered that aspects relating to thromboprophylaxis should be discussed in the context of the extension of indication[11] currently under evaluation (variation II/01/G). The MAH should provide an updated RMP as part of II/01/G, taking into account that carfilzomib could be used without lenalidomide, and assess the impact on the measures in place for the risk of reproductive and developmental toxicity.

[10] Randomized, open-label, phase 3 study of carfilzomib plus dexamethasone vs. bortezomib plus dexamethasone in patients with relapsed multiple myeloma

[11] Extension of indication to include a new indication for Kyprolis to be used with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

5.3.2. Emtricitabine, tenofovir disoproxil – TRUVADA (CAP) - EMEA/H/C/000594/II/0126

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to add pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired human immunodeficiency virus (HIV)-1 in adults at high risk. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly

Background

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate analogue of adenosine monophosphate. Emtricitabine/tenofovir disoproxil fumarate in combination is indicated as antiretroviral combination therapy for the treatment of human immunodeficiency virus (HIV)-1 infected adults aged 18 years and over.

The CHMP is evaluating an extension of the therapeutic indication for Truvada, a centrally authorised product containing emtricitabine/tenofovir disoproxil, to include pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired human immunodeficiency virus (HIV)-1 in adults at high risk. 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 12 for Truvada (emtricitabine/tenofovir disoproxil) in the context of the variation under evaluation by the CHMP was considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC considered that the MAH should justify why some exclusion criteria intended to be reflected as contraindications are missing from the proposed safety specification. In addition, the important identified risk of 'HIV-1 acquisition in HIV-1 negative subjects' should be broadened to 'HIV-1 acquisition including infection resulting from non-adherence'. The MAH should also add 'development of resistance' to the list of safety concerns and provide a discussion on the development of theoretical resistance to hepatitis B virus (HBV) infection. Moreover, the MAH should develop a follow-up questionnaire for HIV seroconversion and should capture data in a number of areas including the reasons for non-adherence to treatment. The MAH should also conduct a drug utilisation study (DUS) and discuss the possibilities of employing this DUS to monitor adherence. In terms of risk minimisation measures (RMM), the MAH should propose as educational materials a prescriber's checklist, material for HCPs, as well as material for patients and make proposals for an HCP survey. The RMMs should contain information on baseline HIV status, adherence, safe sex advice to minimise risky behaviour and HIV status monitoring.
- The PRAC agreed that it would be beneficial to gather further experience from patients' organisations, also taking into account the existing guidelines of the European AIDS[12] Clinical Society.

[12] Acquired immune deficiency syndrome

5.3.3. Pioglitazone – ACTOS (CAP) - EMEA/H/C/000285/WS/0848; GLUSTIN (CAP) - EMEA/H/C/000286/WS/0848
pioglitazone, glimepiride – TANDEMACT (CAP) - EMEA/H/C/000680/WS/0848
pioglitazone, metformin – COMPETACT (CAP) - EMEA/H/C/000655/WS/0848; GLUBRAVA (CAP) - EMEA/H/C/000893/WS/0848

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Update of the section 4.4 of the SmPC based on the results of two long term observational cohort studies assessing bladder cancer risk with pioglitazone. The RMP is updated accordingly. Furthermore, minor editorial changes were introduced in the product information. In addition, the MAH took the opportunity to update the details of local representatives in the Package Leaflet

Background

Pioglitazone is a thiazolidinedione, indicated alone or in combination with glimepiride, a sulfonylurea antidiabetic or with metformin, a biguanide, and is indicated in the treatment of type 2 diabetes mellitus (T2DM) under certain conditions.

The CHMP is evaluating a type II worksharing variation procedure for Actos, Competact, Glustin, Glubrava and Tandemact, centrally authorised products containing pioglitazone (and combinations with glimepiride or metformin) to update the safety information based on results of long term observational cohort studies[13] assessing the risk of bladder cancer with pioglitazone. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes December 2015.

Summary of advice

- The RMPs[14] for Actos, Competact, Glustin, Glubrava and Tandemact (pioglitazone and combinations) in the context of the variation under evaluation by the CHMP could be acceptable provided that satisfactory responses to the request for supplementary information are submitted.
- Based on the epidemiological evidence and the potential uncertainties with the observational datasets beyond those reflected in confidence intervals (statistical significance), the PRAC concluded that the evidence is insufficient to substantially alter the existing product information warnings or implemented risk minimisation strategy. The PRAC supported the proposed changes by the CHMP Rapporteur as they consistently reflect the totality of the evidence and achieve clarity, namely changes in section 4.4 (warning section) to reflect that epidemiological studies have suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone-containing products, although not all studies identified a statistically significant increased risk.

[13] Results for study AD-4833/EC445: PROspective pioglitAzone clinical trial in macro Vascular Events extension study; results for study AD4833-403: cohort study of pioglitazone and cancer incidence in patients with diabetes mellitus; Results for the pan European multi database bladder cancer risk characterisation study (er12-9433)
[14] RMP versions 22.2 for Actos, Glustin, Competact and Glubrava. RMP version 20.2 for Tandemact

6. Periodic safety update reports (PSURs)

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

See also Annex I 15.1.

6.1.1. Alemtuzumab – LEMTRADA (CAP) - PSUSA/10055/201509

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

Alemtuzumab is a recombinant IgG1 kappa monoclonal antibody indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Lemtrada (alemtuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on the risk of bradycardia as an infusion associated reaction, and on the risk of developing listeriosis/listeria meningitis. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- The MAH should submit to the EMA, within 60 days (or in the following available date according to the EMA procedural timetable), a type II variation including an update of the RMP to include progressive multifocal leukoencephalopathy (PML) as an important potential risk. The update should include a description of the pharmacovigilance activities targeting the potential risk of PML. The MAH should also specify which case definition is used.
- In the next PSUR, the MAH should specify whether patients with herpes viral infection were treated prophylactically with an anti-herpes agent as recommended, and the type of prophylaxis implemented if this recommendation is followed by physicians. The MAH should also discuss whether patients at increased risk of opportunistic infection should be treated with alemtuzumab. As inconsistencies in the number of severe cases of bradycardia caused by alemtuzumab have been observed, the MAH should clarify if the additional three cases of severe bradycardia have been included in the MAH's analysis. If not, a complete analysis including all severe cases should also be presented. The MAH should elaborate on whether additional information on the severity of bradycardia

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

is necessary and should consider updating the product information as appropriate. In addition, the MAH should explain the potential mode of action of bradycardia caused by alemtuzumab.

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

6.1.2. Apremilast – OTEZLA (CAP) - PSUSA/10338/201509

Applicant: Celgene Europe Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Apremilast is an inhibitor of phosphodiesterase 4 (PDE4) indicated alone or in combination with disease modifying antirheumatic drugs (DMARDs) for the treatment of active psoriatic arthritis (PsA) and for the treatment of moderate to severe chronic plaque psoriasis in adult patients under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Otezla (apremilast) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include gastrointestinal haemorrhage as a new undesirable effect with an uncommon 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 muscle spasms and cases of hypoglycaemia. The MAH should also provide a cumulative review of suicidal ideation using the suicide/self-injury standardised MedDRA query (SMQ). In addition, the MAH should review the incidence of malignancies, particularly, eye-related neoplasms in psoriasis patients.

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

6.1.3. Canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP) - PSUSA/10077/201509

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

[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

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 (DLP: 28/09/2015), the PRAC reviewed the benefit-risk balance of Invokana and Vokanamet, centrally authorised medicines containing canagliflozin and canagliflozin/metformin respectively, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Invokana (canagliflozin) and Vokanamet (canagliflozin/metformin) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a cumulative review and discussion of cases of renal cell cancer and of cases on lithium interactions. Cases of Stevens-Johnson syndrome (SJS) should be closely monitored.
- The MAH should be requested to submit to the EMA, within 30 days, further information on pancreatitis cases.

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

6.1.4. Dapagliflozin – FORXIGA (CAP) - PSUSA/10029/201510

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Dapagliflozin is a sodium-dependent glucose co-transporter (SGLT)-2 inhibitor indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Forxiga (dapagliflozin) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

- In the next PSUR, the MAH should provide a cumulative review of the serious cases with 'clinical consequences of increased haematocrit' in order to judge whether the safety concern of increased haematocrit remains unchanged. In addition, any new cases of hepatic disorders should be closely monitored. Finally the MAH should provide a cumulative review of cases reporting urosepsis/pyelonephritis including narratives, and justification on whether there is a need to update the product information.
- The MAH should submit to the EMA, within 60 days, a cumulative review of hypersensitivity reactions. The MAH is requested to separate the group of 'all controls' between placebo and comparators in clinical trials, and present new numbers of hypersensitivity reactions in the different arms and related terms. The MAH should perform and submit a clear causality assessment case by case taking into account confounding factors, time-to-onset and information regarding de-challenge and re-challenge. The MAH should provide causality assessment of the post-marketing reports of Steven-Johnsons syndrome (SJS) as well as CIOMS reports. The MAH should also perform and provide a clear causality assessment of the 16 serious adverse events with the preferred term 'rash' taking into account confounding factors, time-to-onset and information regarding de- and re-challenge. In addition, CIOMS forms should also be submitted. The MAH should provide the CIOMS forms for the 5 events of hypersensitivity reactions identified with positive de-challenge. The MAH should clarify discrepancies noted in the total of 'rash' events from the time from first dose to onset of the event. Finally, the MAH should propose to update the product information as necessary.
- The MAH should be requested to upgrade 'renal impairment' from an important potential to an identified risk in the next update of the RMP.

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

6.1.5. Daptomycin – CUBICIN (CAP) - PSUSA/00931/201509

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Daptomycin is a cyclic lipopeptide that is active against Gram positive bacteria indicated only for the treatment of complicated skin and soft-tissue infections (cSSTI), right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* and *Staphylococcus aureus* bacteraemia (SAB) when associated with cSSTI or RIE.

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

Summary of recommendation(s) and conclusions

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

- Nevertheless, the product information should be updated to include 'acute generalized exanthematous pustulosis' as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should review the risk of 'organising pneumonia' associated with the use of daptomycin and discuss the need to update the current product information.
- The MAH should be requested to update the RMP at the next regulatory opportunity to include 'acute generalised exanthematous pustulosis (AGEP)' as an important identified risk.

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

6.1.6. Denosumab – PROLIA (CAP) - PSUSA/00954/201509

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Prolia (denosumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to the EMA, by Q3 2016, a type II variation, containing the final clinical study report for study 20110153. Based on these data, the MAH should discuss the safety of denosumab in long term use, use following other anti-resorptive therapies and whether or not any additional recommendations relating to use in these situations are needed in the product information.

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

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

6.1.7. Eculizumab – SOLIRIS (CAP) - PSUSA/01198/201510

Applicant: Alexion Europe SAS

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Soliris (eculizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should address the following issues: sudden death in a HUS kidney transplant, serious cutaneous adverse reactions, cardiac disorders, including ventricular fibrillation, fatal cases, angioedema, pyelonephritis. Summaries narratives of the relevant cases should be provided.
- The MAH should submit to the EMA, within 60 days, a variation to amend the 'special warnings and precautions for use' section of the product information around vaccination. In addition, the MAH proposed as part of this variation to add some guidance in the educational materials to help physicians in the management of potential adverse events triggered by vaccination in patients with complement-mediated disease.

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

6.1.8. Ranibizumab – LUCENTIS (CAP) - PSUSA/02609/201510

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A) indicated for the treatment in adults of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) and visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Lucentis (ranibizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should further evaluate 'poor short term healing of non-ocular wounds in DME', 'macular hole' and 'seizures'.
- The MAH should be requested to update the RMP by removing the important identified risk of 'hypersensitivity', as this risk is adequately addressed in the product information.
- The MAH should submit to the EMA, within 60 days, a type II variation, or alternatively a post-authorisation measure (LEG) including a justification of why there is no need to update the product information. The MAH should include a detailed discussion on the data regarding vascular death, all-cause mortality, and main vascular events observed in the RIDE and RISE studies[18]. These discussions should be supported by relevant pharmacokinetic (PK)-data on systemic exposure following the most intensive treatment as in RIDE and RISE, and address risk groups for these types of events. The MAH should propose updates of the product information as necessary.

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. Rivaroxaban – XARELTO (CAP) - PSUSA/02653/201509

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

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.

[18] RIDE (CRFB002D4168g): Phase III randomized study of ranibizumab injection in subjects with clinically significant macular edema (ME) with center involvement secondary to diabetes mellitus; RISE (CRFB002D4170g): Phase III randomized study of ranibizumab injection in subjects with clinically significant ME with center involvement secondary to diabetes mellitus

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Xarelto (rivaroxaban) in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should present a review of all available data, including pharmacokinetic data, related to the concomitant use of amiodarone and Xarelto. The focus should be on patients with reported haemorrhage after concomitant use of Xarelto and amiodarone, and special attention should be paid to patients who had been stable on rivaroxaban and in whom a haemorrhage was reported after starting amiodarone. In addition, the MAH should provide a cumulative, detailed review of renal failure cases. Finally the MAH should provide a review of cases of alopecia, dyspnoea, paraesthesia and hypoesthesia, as a large number of reports have been noted.
- Considering the reporting of liver failure including fatal cases in recent publications the MAH should submit to the EMA, within 90 days, a thorough cumulative review of hepatotoxicity concentrating on liver failure. The review should cover spontaneous adverse drugs reaction reports including a careful assessment of causality including factors such as time to onset, de-challenge and re-challenge information and also discuss data from any other available sources.

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

6.1.10. Trastuzumab – HERCEPTIN (CAP) - PSUSA/03010/201509

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Trastuzumab is a recombinant humanised immunoglobulin (Ig)G1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2) indicated for the treatment of adult patients with HER2 positive metastatic breast cancer under certain conditions, for the treatment of adult patients with HER2 positive early breast cancer under certain conditions, and in combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Herceptin (trastuzumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to the EMA, within 60 days, a proposal for a Direct Healthcare Professional Communication (DHPC) to the treating oncologists and/or oncologists to ensure that prescribers are aware of the need to follow the current guidance on cardiac monitoring during and after completion of treatment with Herceptin and to highlight the need for cardiac monitoring particularly during handover of patient management to other physicians.
- In the next PSUR, in order to measure the effectiveness of the DHPC, the MAH should present an update of the RMP reflecting the data of the two surveys on cardiac monitoring, together with a proposal for an additional survey to measure the effectiveness of the DHPC. Depending on the results of the additional survey to measure effectiveness of the DHPC communication, the PRAC may consult with healthcare professionals in evaluating the MAH's results of the additional survey.

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

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

See also Annex I 15.2.

6.2.1. Anagrelide – XAGRID (CAP), NAP - PSUSA/00208/201509

Applicant: Shire Pharmaceutical Contracts Ltd., various

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

Background

Anagrelide is an inhibitor of the cyclic adenosine monophosphate (AMP) phosphodiesterase III indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of anagrelide-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 address several issues, including the submission of a cumulative review of cases of pulmonary hypertension and the close monitoring for several adverse events (e.g. thrombo-haemorrhagic events in the context of the review of the potential risk of lack of efficacy).
- In addition, the MAH for Thromboreductin should also discuss the impact of newly reported thrombo-haemorrhagic events on the risk-benefit balance of anagrelide as first-line therapy.
- The MAH for Xagrid should submit to the EMA the final clinical study report for study SPD422-403 through the appropriate variation with a deadline of January 2017. Based on data discussed in the interim safety report and in this PSUR, the MAH should also further discuss as part of this variation the increased risk of major thrombotic events observed in the anagrelide arm. The MAH should also pursue the discussion of cases of transformation to myelofibrosis, including a focus on the risk observed in female patients. Finally, the MAH should discuss the reason for the difference in duration of treatment between both treatment arms.

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

6.2.2. Irbesartan – APROVEL (CAP); IRBESARTAN ZENTIVA (CAP), NAP - PSUSA/01782/201508

Applicant: Sanofi Clir SNC (Aprovel), Sanofi-Aventis Groupe (Irbesartan Zentiva, Karvea), various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Irbesartan is a selective angiotensin-II receptor antagonist and is indicated for the treatment of essential hypertension in adults and for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of irbesartan-containing medicinal products in the approved indications remains unchanged.

- Nevertheless, the product information should be updated to include thrombocytopenia as a new undesirable effect with a not known frequency. Therefore the current terms of the marketing authorisations should be varied[19].
- In the next PSUR, the MAH Sanofi should provide a cumulative review of alopecia cases with more detailed information, as was requested as part of the irbesartan/hydrochlorothiazide PSUSA/001653/201309. The MAH should also provide the cumulative evidence of the following ongoing signals: metabolic acidosis/lactic acidosis/blood lactic acid increase, tendonitis, lichen planus/lichenoid dermatitis. The MAH should closely monitor depression and photosensitivity reactions, presenting and analysing all new evidence observed during the period including the case narratives and providing details of cases observed in clinical trials.

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 data lock point for the next PSUR has been aligned with that of the combination irbesartan/hydrochlorothiazide to allow the next PSURs to be evaluated in parallel following the same procedural timetable.

6.2.3. Memantine – AXURA (CAP); EBIXA (CAP); MEMANTINE MERZ (CAP), NAP - PSUSA/01967/201509

Applicant: Merz Pharmaceuticals GmbH (Axura, Memantine Merz), H. Lundbeck A/S (Ebixa), various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Memantine is a voltage-dependent, moderate-affinity uncompetitive N-methyl-D-aspartate (NMDA)-receptor antagonist which modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. It is indicated for the treatment of patients with moderate to severe Alzheimer's disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Axura, Ebixa and Memantine Merz, centrally authorised medicines containing memantine, and nationally authorised medicines containing memantine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of memantine-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should provide a detailed discussion of cases related to 'overdose/medication error with the pump device'. The MAHs should clarify if the cases have been reported in or outside the EU. The MAHs should describe information on off-

[19] 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

label use and use in the paediatric population as submitted in the last two PSURs. Moreover, the MAHs should also specify the off-label indications in these cases and the number of cases by off-label indication. Finally, the MAHs should provide a detailed review of serious cases involving the risk 'hepatic disorders'.

- The MAHs Merz and Lundbeck should be requested to submit to the EMA, within 90 days, a cumulative review by standardised MedDRA query (SMQ) 'narrow hyponatremia/syndrome of inappropriate antidiuretic hormone secretion' to further review this safety topic. Data from clinical trials, post-marketing sources and literature review should be provided to support the MAHs´ conclusions. Full narratives of cases detected should also be included.

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.

6.2.4. Zoledronic acid – ZOLEDRONIC ACID MEDAC (CAP), ZOMETA (CAP), NAP - PSUSA/03149/201508

Applicant: Medac Gesellschaft fur klinische Spezialpraparate GmbH (Zoledronic Acid Medac), Novartis Europharm Ltd (Zometa), various

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Zoledronic acid is a bisphosphonate indicated for the prevention of skeletal related events in adult patients with advanced malignancies involving bone and for the treatment of adult patients with tumour-induced hypercalcaemia (TIH).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zoledronic acid Medac and Zometa, centrally authorised medicines containing zoledronic acid, and nationally authorised medicines containing zoledronic acid, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of zoledronic acid-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include acquired Fanconi syndrome as a new undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisations should be varied[20].
- In the next PSUR, the MAHs should provide a critical appraisal of all available data from clinical trials, spontaneous reports and the published literature relating to osteonecrosis of the hip and femur (and possible other locations with the exception of jaw and external auditory canal) in association with zoledronic acid. This evaluation should

[20] 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

include information regarding diagnostic criteria applied and results of diagnostic tests, a discussion regarding the potential influence of the local anatomy and a discussion regarding the underlying pathophysiological mechanism and possible risk factors. This should include similarities/differences with the pathophysiology of osteonecrosis of the jaw or external auditory canal. Based on this, the MAHs should discuss the need for updates to the product information to inform healthcare professionals and patients and the need to introduce appropriate risk minimisation measures.

- In the next PSUR, the MAH Novartis should clarify why hemiparesis was excluded from the analysis of cerebrovascular disease, and why bradycardia and syncope with tachycardia were excluded from the analysis of arrhythmia, and why anuria was excluded from the analysis of renal impairment. The MAH should provide more details on the 7 reported deaths potentially related to osteonecrosis of the jaw (ONJ) and observed in patients treated for osteoporosis in the reporting period. The MAH should clarify why patients also treated with denosumab were excluded from the analysis of atypical fractures. The MAH should look more closely at the cases of interstitial lung disease where other drugs were used simultaneously or within a reasonable time before/after Zometa exposure. Concomitant administration of other drugs has been shown to increase the risk of interstitial lung disease and has led to strong warnings. Moreover, the MAH should provide all available data supporting a similar toxicity profile in races other than Caucasians as well as a detailed analysis of similar toxicity profiles among different races before consigning this to routine monitoring, if such data are available. Finally, the MAH is requested to elaborate further on relevant endpoints when investigating skeletal-related events (SRE) and why imaging detected SRE is more important than clinical SRE in the ALLIANCE study.

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

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

See also Annex I 15.3.

6.3.1. Asparaginase (NAP) - PSUSA/00003161/201508

Applicant: various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Background

Asparaginase is an enzyme catalyzing the hydrolysis of asparagine to aspartic acid and ammonia, expressed and produced by microorganisms (e.g. *Escherichia coli, Erwinia chrysanthemi*) indicated in the treatment of acute lymphoblastic leukaemia (ALL). E-coli asparaginase is also indicated for the treatment of leukaemic meningitis, non-Hodgkin's lymphoma and acute myeloblastic leukaemia. *E. chrysanthemi* asparaginase is also indicated for lymphoblastic malignant lymphoma, other neoplastic conditions where depletion of asparagine might be expected to have a useful effect, for patients receiving

treatment with asparaginase from E.coli and who develop hypersensitivity to that enzyme and as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to E. coli-derived asparaginase.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of asparaginase-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on posterior reversible encephalopathy syndrome (PRES) and to include that in rare cases PRES has been observed during therapy with asparaginase in the 'Undesirable effects' section. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAHs should provide data on safety and efficacy in each authorised indication(s) and detailed information on the identified cases from the literature, studies and the safety database included in the PSUR. In addition, the MAHs should provide detailed responses on the toxicity effects observed in non-clinical studies OD12312 and OD13086 and the role of crisantaspase, specifically at high doses, in animal's death in these non-clinical studies. The MAH should include 'drug interaction with glucocorticoids' as an important identified risk in the list of safety concerns for E. coli L-asparaginase and crisantaspase. The MAH should keep open, monitor and provide cumulative reviews for the following signals: renal failure/renal impairment, cerebral ischaemia, osteonecrosis, secondary malignancies, and pancreatic disorders.
- The MAHs of medicinal products containing asparaginase that have an RMP in place should include 'drug interaction with glucocorticosteroids' as a new important identified risk at the time of the next 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.

6.3.2. Erythromycin, isotretinoin (NAP) - PSUSA/00001796/201508

Applicant: various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

Background

Eryhtromycin is a macrolide antibiotic with a broad and essentially bacteriostatic action against many Gram-positive and to a lesser extent Gram-negative bacteria. Isotretinoin is a

[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 CMDh for adoption of a position

retinoid compound and a vitamin A derivative that is a stereoisomer of all-trans retinoic acid (tretinoin). The combination erythromycin/isotretinoin for topical use is indicated for the treatment of mild to moderate acne vulgaris as a gel formulation.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of medicinal products containing erythromycin/isotretinoin in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a cumulative review of cases from the system organ class (SOCs) 'psychiatric disorders', 'pregnancy, puerperium and perinatal conditions', 'reproductive system and breast disorder' and 'congenital, familial and genetic disorders' due to the possibility of systemic exposure. In addition the MAHs should amend the important potential risk 'use in pregnancy/women of childbearing potential' to 'use in pregnancy/women of childbearing potential due to teratogenicity'.
- The PRAC noted that there are inconsistencies throughout the EU product information in terms of recommendations currently in place regarding use in pregnancy or in women with childbearing potential not using an effective method of contraception and therefore recommended follow up by the CMDh of this matter.

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

Post-meeting note: on 27/04/2016, the UK circulated a non-urgent information (NUI) to seek information on risk minimisation measures available for systemic and topical retinoids in different member states in relation to prevention of pregnancy and neuropsychiatric reactions.

6.3.3. Finasteride (NAP) - PSUSA/00001392/201508

Applicant: various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of type II 5 alpha-reductase, an intracellular enzyme that metabolizes the androgen testosterone to dihydrotestosterone (DHT). It is indicated for the treatment of and control of benign prostatic hyperplasia (BPH) and for the prevention of urologic events under certain conditions, and for the treatment of men with male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of finasteride-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide cumulative reviews on cataract, worsening seizures in patients with an underlying seizure disorder or history of seizures. The MAHs should also provide a cumulative review of cases of rhabdomyolysis for finasteride 1 mg and of cases of rhabdomyolysis/myopathy and myalgia/blood creatinine kinase increased for finasteride 5 mg. In addition, the MAHs should provide a cumulative review of hepatic adverse reactions and hepatobiliary disorders for finasteride 5 mg. The MAHs should closely monitor cases of suicide/self-injury and any new cases for both finasteride 5 mg and 1 mg should be reported, including any new information based on literature.
- Considering the seriousness of the events, the PRAC recommended that the MAHs should submit to the National Competent Authorities, within 60 days, an additional cumulative review of all events relating to depression or suicidality associated with the use of finasteride for male pattern hair loss, both for the approved 1 mg dose and if there are cases where higher doses have been used for the treatment of this condition and consider whether there is a need to update the product information.

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

6.3.4. Meropenem (NAP) - PSUSA/00001989/201508

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of meropenem-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to revise the current wording on breast-feeding and to include drug reaction with eosinophilia and systemic symptoms (DRESS) as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAHs should keep under close surveillance atypical lung events and present cases with a positive dechallenge. The MAHs should also make a proposal as to how the cases of atypical lung events could be further investigated. The MAHs should keep under close surveillance the following safety issues: liver disorder including vanishing bile duct syndrome and cholestasis, interaction between meropenem and colistin, leukocytoclastic vasculitis, drug rash with eosinophilia and systemic symptoms (DRESS), drug induced hypersensitivity syndrome (DIHS), depressed level of consciousness, pancytopenia, cardiac disorders, especially arrhythmias and conduction abnormalities, polyarteritis nodosa, atypical lung events and interstitial lung disease, and renal events.

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

6.3.5. Nifedipine (NAP) - PSUSA/00002156/201508

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Nifedipine is a calcium channel blocker indicated for the treatment of coronary heart disease, chronic stable angina pectoris (angina of effort), vasospastic angina pectoris (Prinzmetal's angina, variant angina), (essential) hypertension, hypertensive crisis, and primary and secondary Raynaud's syndrome.

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

Summary of recommendation(s) and conclusions

- Based on the review of data on safety and efficacy, the risk-benefit balance of nifedipine-containing containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on acute pulmonary oedema associated with tocolytic use in the 'fertility, pregnancy and lactation' section and to include pulmonary oedema as new undesirable effect with an

[22] Update of SmPC sections 4.6 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

unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied.

- In the next PSUR, the MAHs should monitor and discuss any adverse events that could be related to switching between nifedipine-containing products.
- With regard to the potential risk of pulmonary oedema with other calcium channel blockers (CCBs) used off-label use for tocolysis, the PRAC discussed whether this risk should be reflected in the product information of other products of the class, as for nicardipine- and nifedipine-containing products. Considering current treatment guidelines on tocolysis for women in preterm labour, which specifically mention nifedipine and/or nicardipine, this was not considered necessary at present. This would need to be reconsidered if a signal arises from case reports of peripheral oedema in pregnant women treated off-label with other CCBs for tocolysis.

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

6.3.6. Rilmenidine (NAP) - PSUSA/00002643/201508

Applicant: various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Background

Rilmenidine is a centrally acting antihypertensive compound that activates imidazoline-1 (I_1) receptors in the brain and in the periphery, especially in the kidneys, thus decreasing the sympathetic outflow and peripheral vascular resistance. It is indicated for the treatment of arterial hypertension in patients above 18 years of age.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of rilmenidine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on the risk of bradycardia in susceptible patients and advice on how to minimise this risk, and to include bradycardia as new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[23].

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

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 15.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[24]

See also Annex I 16.1.

7.1.1. Afamelanotide – SCENESSE (CAP) - EMEA/H/C/PSP/0033.1

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a revised protocol for a retrospective chart review study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued the use of Scenesse. The second primary objective of the study should be the assessment of the compliance with risk minimisation recommendations and the controlled access programme for patients receiving Scenesse

Background

Scenesse is a centrally authorised medicine containing afamelanotide, a melanocortin receptor agonist. It is indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

A revised protocol for a retrospective chart review study comparing long term safety data and outcome endpoints in patients receiving and not receiving Scenesse, or having discontinued the use of Scenesse, and assessing compliance with risk minimisation recommendations and the controlled access programme for patients receiving Scenesse, was submitted to the PRAC by the MAH in accordance with the conditions to the marketing authorisation(s).

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 4 in accordance with Article 107n of Directive 2001/83/EC, endorsed the protocol for the above listed medicinal product.

7.1.2. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSP/0020.2

Applicant: Celgene Europe Limited

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a revised PASS protocol for study CC-5013-MM-034: a product registry of previously untreated adult multiple myeloma patients who are not eligible for transplant

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

Background

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

A revised protocol for a PASS (product registry) of transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM) treated with lenalidomide, to gather safety data on the use of lenalidomide in NDMM patients, was submitted to the PRAC in accordance with the conditions to the marketing authorisation (s).

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 2 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that that the design of the study did not fulfil the study objectives. The MAH should clarify the reasons for postponing the end of the study, should specify the dates of the inclusion period, and plan an interim study report with results at 3.5 years of follow-up for assessment of cardiovascular risks. The inclusion period should also not exceed 1.5 years. The PRAC therefore recommended that:
- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[25]

See Annex I 16.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[26]

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

Applicant: Bayer Pharma AG, various

PRAC Rapporteur: To be appointed

Scope: Final study results for an imposed joint PASS: drug utilisation study (DUS) (database) for cyproterone/ethinylstradiol to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription

In line with the conclusions of a referral under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for cyproterone/ethinylestradiol-containing medicines (EMEA/H/107i/1357), MAHs were required to conduct a drug utilisation study (DUS) to

[25] 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
[26] In accordance with Article 107p-q of Directive 2001/83/EC

characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess the main reasons for prescription. The MAH on behalf of a consortium submitted the final study results of the DUS (database) for assessment by the PRAC.

Conclusion

- The PRAC appointed Menno van der Elst as PRAC Rapporteur for the assessment of the of the final study results and agreed a timetable for this procedure.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[27]

See Annex I 16.4.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[28]

See Annex I 16.5.

7.6. Others

See Annex I 16.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 17.1.

[27] 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
[28] In line with the revised variations regulation for any submission before 4 August 2013

8.2. Conditional renewals of the marketing authorisation

8.2.1. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/R/0022 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

Background

Ataluren enables ribosomal read-through of mRNA containing a premature stop codon and is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.

Translarna, a centrally authorised product containing ataluren, was authorised under a conditional marketing authorisation in 2014. Based on the fulfilment of specific obligations and safety data, the MAH submitted a request for yearly renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this conditional renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, the PRAC noted that the condition for study PTC124-GD-020-DMD[29] on efficacy primary endpoints was not fulfilled at this stage. In terms of safety outcomes, the PRAC noted that study PTC124-GD-020-DMD did not identify new or changed risks. Further considerations are to be given at the level of the CHMP.

8.3. Renewals of the marketing authorisation

See Annex I 17.3.

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.

[29] Multicentre, randomised, double-blind, placebo-controlled confirmatory study to examine efficacy and safety of ataluren 10, 10, 20 mg/kg in patients with nonsense mutation Duchenne muscular dystrophy (Study-020)

9.3. Others

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

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Ondansetron (NAP)

Applicant: Novartis, Bristol Laboratories Limited

PRAC Lead: Milena Radoha Bergoč

Scope: PRAC consultation on the assessment of additional data submitted following the finalisation of PSUSA/00002217/201502 regarding the risk of congenital cardiac septal defect in off-label use during pregnancy

Background

Ondansetron is a selective 5-hydroxytryptamine $(5\text{-HT})_3$ receptor antagonist indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (CINV/RINV) and for the management of post-operative nausea and vomiting (PONV). In the paediatric population, ondansetron is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months and for the prevention and treatment of PONV in children aged ≥1 month.

In October 2015 as part of the recommendation of the latest PSUR single assessment (PSUSA) procedure for ondansetron (PSUSA/00002217/201502), the PRAC requested the MAHs to submit to the EU NCAs within 90 days a detailed review of congenital cardiac septal defects in light of the potential risk associated with off-label use of ondansetron during pregnancy. For further background, see PRAC minutes October 2015.
In the context of the evaluation of the MAHs' submitted data, Slovenia requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC agreed with the conclusion of Slovenia and concurred that data on off-label use of ondansetron during pregnancy do not confirm or refute an increased risk of congenital cardiac septal defects. In the absence of any consistent and robust evidence, the PRAC considered the current product information of ondansetron-containing products stating that the 'use of ondansetron during pregnancy is not recommended' and concluded that no changes were warranted in light of the current knowledge. Nevertheless, the PRAC advised that MAHs should closely monitor adverse birth outcomes following off label use of ondansetron during pregnancy and should include this information in the next PSUR (next DLP: 28/02/2018) along with data on the extent of the off-label use of ondansetron.

11.2.2. Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); mirtazapine (NAP); paroxetine (NAP); sertraline (NAP)
Serotonin–noradrenaline reuptake inhibitors (SNRIs): duloxetine - ARICLAIM (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), CYMBALTA (CAP), XERISTAR (CAP), YENTREVE (CAP); sibutramine (NAP); venlafaxine (NAP)

Applicant: Eli Lilly Nederland B.V. (Ariclaim, Duloxetine Lilly, Xeristar, Yentreve), Generics UK Limited (Duloxetine Mylan), Zentiva (Duloxetine Zentiva), various

PRAC Lead: Julie Williams

Scope: PRAC consultation on the assessment of a systematic review and meta-analysis published in the BMJ on suicidality, aggression and akathisia during antidepressant treatment

Background

Selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs) are classes of drugs indicated for the treatment of major depressive disorder and anxiety disorders under certain conditions.

In a recent article published in the BMJ, *Sharma et al.*[30] conducted a systematic review and meta-analysis of serious harms associated with SSRIs and SNRIs. The main outcome was mortality and suicidality. Secondary outcomes were aggressive behaviour and akathisia.

Following a review by the CHMP Pharmacovigilance Working Party (PhVWP) in 2008 on SSRIs and SNRIs, their product information was revised to include a warning on the risk of

[30] Sharma T et al. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ (2016); 352:i65

suicidality in adults, highlighting the risk is increased in young adults. Taking into consideration this review, and the outcome of two previous procedures under Article 31 of Directive 2001/83/EC conducted by the CHMP respectively in 2004[31] and 2005[32] that led to the inclusion of information on the risk of suicidality and aggression in the paediatric population the product information of SSRIs and SNRIs in the EU, the United Kingdom requested PRAC advice on its assessment of the study results by *Sharma et al* and whether this has any implications for the current regulatory position.

Summary of advice

- Based on the review of the available data, the PRAC agreed with the UK's assessment that the findings by *Sharma et al* on the risk of suicidality and aggressive behaviour are consistent with the outcome of previous regulatory reviews and the available evidence is reflected in the current product information of SSRIs and SNRIs. Furthermore, it was considered reassuring that the findings across further reviews are very similar despite using different datasets.
- The PRAC noted the findings from a study by *Bachmann et al*[33] suggesting an overall increase in usage of antidepressants in patients between 0-19 years of age across a number of EU countries. The findings of this study do not allow the determination of whether such use was appropriate, nevertheless they may inform the need for a general reminder communication at national level on the known risks and benefits of prescribing antidepressants to children and adolescents. Key messages should be developed to aid such communications.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh

None

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

12.3.1. Guideline on safety and efficacy follow-up – Risk management plan of advanced therapy medicinal products (ATMP) - revision

PRAC lead: Julie Williams, Brigitte Keller-Stanislawski

[31] Paroxetine, completed Article 31 procedure on the risk of emotional lability, including hostility and suicidal behaviour in children and adolescents and withdrawal reactions
[32] Atomoxetine, citalopram, escitalopram, fluoxetine, fluvoxamine, mianserine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine, , completed Article 31 procedure on the risk of suicidal behaviour, including suicide attempts and suicidal ideation and/or related behaviour like self-harm, hostility and mood lability in children and adolescents
[33] Bachmann et al. Trends and patterns of antidepressants use in children and adolescents from five western countries, 2005 -2012. Eur Neuropsychopharmacol (2016) 26, 411-419

As a follow-up to the January 2016 PRAC meeting on the revision of the current 'Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMPs)' (EMEA/149995/2008) (see PRAC minutes of January 2016 and PRAC work plan 2016), the EMA secretariat presented the drafting group's proposal for a work plan including deliverables and milestones for communication and implementation. The PRAC adopted the work plan. The drafting group, composed of CAT, CHMP, PRAC and EMA members will work on the revised document and the next discussion at Committee level is provisionally scheduled for April 2017. The PRAC welcomed receiving a status update in due course.

Post-meeting note: At their April 2016 meetings, the CHMP and CAT adopted the work plan without any changes.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators - predictions

As part of the new governance of the EU pharmacovigilance move to full operation that requires oversight of performance of the EU system and measuring its impact, the EMA secretariat presented, at the organisational matters teleconference held on 28 April 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 audits

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance systems and their quality systems

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. Currently, the GPAG is discussing the EURD list inclusion/exclusion for allergens and intravenous fluids containing electrolytes and/or carbohydrates. At its April 2016 teleconference, the GPAG also adopted a work plan for 2016, including: to develop a EURD tool to support decision making on PSUR frequencies, to map EURD list entries against the Article 57 database, to continue reviewing the scientific scope of the procedures in the EURD list using the Article 57 database and to review EURD entries requiring the submission of proposals for inclusion of generic medicinal products authorised under the legal basis of Article 10(1) of Directive 2001/83/EC.

12.10.2. Periodic safety update reports

None

12.10.3. PSUR action group – roadmap for PSUR issues: Joint PRAC/CMDh recommendation paper on common understanding - finalisation

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

At the organisational matters teleconference held on 28 April 2016, following the February and March 2016 PRAC discussion (see PRAC minutes February 2016 and PRAC minutes March 2016 and PRAC minutes March 2016), the EMA Secretariat presented a revised calendar detailing the planned steps for the proposed implementation activities and a revised version of the draft joint PRAC/CMDh recommendation paper on a common understanding on the EU PSUR single assessment for nationally authorised products. Further discussion is scheduled in May 2016.

12.10.4. PSURs repository - Transition to mandatory use

The EMA secretariat provided an update to the PRAC on the transition to the mandatory use of the PSUR repository (on 13 June 2016) including some feedback on the experience gained with the PSUR Repository Advisory Group (PRAG). With the transition to mandatory use, the PSUR repository project will move into the maintenance phase and as a consequence a new governance structure will come into effect. A group of communication points in the national competent authorities acting as liaison between the EMA and the MAHs at national level is to be established. Further communication is planned in the coming weeks.

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

The PRAC endorsed the draft revised EURD list version April 2016 reflecting the PRAC comments impacting on the DLP and PSUR submission frequencies of the substances/combinations.
The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting in April 2016, the updated EURD list was adopted by the CHMP and CMDh at their April 2016 meetings and published on the EMA website on 03/05/2016, 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. Good Pharmacovigilance Practice (GVP) module IX on Signal management – revision 1 and addendum

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 28 April 2016, following consolidation by SMART Working Group (SMART WG) work stream WS1, Project Maintenance groups 1 and 2 and the EudraVigilance Expert Working Group (EV-EWG), the PRAC discussed the GVP module IX on Signal Management revision 1 as well as its Addendum I on 'Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions'. The draft GVP module and its addendum have been circulated for comments to the PRAC, CHMP, CMDh, CAT, Pharmacovigilance Inspectors Working Group (PhV IWG) and to the Pharmacovigilance Business Team for comments. PRAC delegates were invited to provide their comments by 9 May 2016.

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

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 28 April 2016, the PRAC was updated on the outcome of the April 2016 SMART Working Group (SMART WG) work stream WS1. The SMART WG WS1 continued its discussion on SCOPE[34] Work Package 5 on 'signal management', received feedback from the last WP5 meeting and the 'Strategic review and learning meeting' held in Utrecht, Netherlands in early March 2016, and noted the progress made on the elaboration of the Best Practice Guide as well as the plans for assessors' training. In addition, the handling of statistics on emerging safety issues (ESI) was discussed, and it was agreed to include both ESIs covered and not covered at the level of PRAC and those resolved outside the Committee.

[34] Strengthening Collaborations for Operating Pharmacovigilance in Europe

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Additional monitoring

None

12.12.2. 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 27/04/2016 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.12.3. Management and reporting of adverse reactions to medicinal products

None

12.13. EudraVigilance database

12.13.1. EudraVigilance activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Good Pharmacovigilance Practices (GVP) module VIII on PASS - revision 2 and addendum

Following the April 2015 PRAC discussion (see PRAC minutes April 2015), the EMA Secretariat presented to the PRAC a revised version of the draft GVP Module VIII on 'Post-authorisation safety studies' revision 2 as well as its Addendum on requirements for transmission of information on non-interventional post-authorisation safety studies, following the comments received during the public consultation which ended on 09/10/2015 (EMA/395730/2012 Rev 2*). The PRAC adopted the revised GVP module VIII and its Addendum.

12.15.2. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public hearings – Rules of procedure

As a follow-up to the March 2016 PRAC meeting (see PRAC minutes March 2016) and further discussion on the key characteristics of Public hearings and outcome of the impact assessment the EMA conducted, the PRAC adopted its final 'Rules of procedure on the organisation and conduct of public hearings at the Pharmacovigilance Risk Assessment Committee (PRAC)' (RoP) (EMA/363479/2015) following their adoption at the March 2016 EMA Management Board (EMA/363479/2015). In line with Article 107j of Directive 2001/83/EC, the PRAC has the possibility to hold public hearings for safety reviews conducted by the Committee under Article 20 of Regulation (EC) No 726/2004, and Articles 31 or 107i of Directive 2001/83/EC. For further background, see the press release entitled 'Listening to the public's views on the safety of medicines' (EMA/262673/2016) published on the EMA website on 15 April 2016.

12.18.2. Public hearings - Plan for a 'mock-up' public hearing

Following the adoption of the 'Rules of procedure on the organisation and conduct of public hearings at the Pharmacovigilance Risk Assessment Committee (PRAC)' (RoP) (EMA/363479/2015) and as outlined in March 2016, the EMA presented to the PRAC information and practical details on the set-up of the planned 'mock-up' (or 'dry-run') public hearings. Based on a historical pharmacovigilance referral procedure, a fictitious procedure will start in April 2016 with the 'dry-run' public hearing taking place in July 2016. The EMA secretariat together with relevant PRAC representatives as detailed in the PRAC Work Plan 2016 have started working on drafting guidance to participants and PRAC members for the conduct of public hearings. Follow-up discussion is scheduled in May 2016.

12.18.3. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Delegated Regulation[35] on safety features appearing on the packaging of medicinal products for human use

The EMA secretariat presented to the PRAC the Commission Delegated Regulation No 2016/161 setting out the characteristics of the safety features appearing on the packaging of medicinal products for human use, how medicine authenticity should be verified, and by whom, published on 9 February 2016 in the Official Journal of the European Union and which will apply as of 9 February 2019[36]. This follows the entry into force of Directive 2011/62/EU on prevention of the entry into the legal supply chain of falsified medicinal products. The Delegated Regulation provides the characteristics and technical specifications of the unique identifier; the modalities for the verification of the safety features; the provisions on the establishment, management and accessibility of the repositories system where the information on the safety features shall be contained; 'White and Black lists': medicines exempted or included; the procedures for notification to the European Commission by NCAs of non-prescription/prescription medicinal products judged/not deemed at risk of falsification as well as the procedures for a rapid evaluation of and decision on those notifications. A discussion followed on the potential uses of the repositories system, described in the Delegated Regulation, for pharmacovigilance purposes. Further discussion will be scheduled at the level of the PRAC as necessary.

12.20.2. EMA guidance on management of confidentiality and declarations of interests for observers participating in EMA scientific meetings

The PRAC was informed that the EMA has developed a new internal guidance on observers participating in EMA scientific meetings, focusing on management of confidentiality and declarations of interests. NCAs staff members are considered as European experts, therefore a declaration of interests (DoI) including a confidentiality undertaking and a *curriculum vitae* (CV) are required. Observers from European Institutions and other European Union bodies as well as observers from non-EEA authorities or organisations with a confidentiality arrangement (CA) in place with EMA do not require a personal confidentiality undertaking (no DoI/CV). Finally, observers from a non-EEA authority or organisation with no confidentiality arrangement in place with EMA require a personal confidentiality undertaking only (no DoI/CV).

[35] Delegated Regulation No 2016/161
[36] The EMA and the EC developed an 'Implementation plan for the introduction of the safety features on the packaging of centrally authorised medicinal products for human use' (EMA/785582/2014 rev.1) and the CMDh an 'Implementation plan for the introduction of the safety features on the packaging of nationally authorised medicinal products for human use' (CMDh/345/2016)

12.20.3. Industry platform on the operation of the EU pharmacovigilance legislation - Report from quarterly meeting

At the organisational matters teleconference held on 28 April 2016, the EMA secretariat reported to PRAC on the Seventh Industry Platform meeting on the operation of pharmacovigilance legislation held on 4 April 2016. The Industry Platform is held on a three-monthly basis. Discussion at the meeting included the PSUR roadmap, GVP updates, scientific advice for post-authorisation studies, signal management as well as recording and reporting off-label use.

12.20.4. EU Pharmacovigilance systems – quarterly updates to industry

At the organisational matters teleconference held on 28 April 2016, the EMA secretariat presented to PRAC the 'What's new in Pharmacovigilance - QPPV Update, Issue 1, April 2016 providing Qualified Persons for Pharmacovigilance (QPPVs) and other people working in pharmacovigilance with an update on EU pharmacovigilance topics on a three-monthly basis. This replaces the previous regular 'News bulletin for pharmacovigilance programme update' which focussed on information systems and services.

12.20.5. EMA Procedure Management department - update

At the organisational matters teleconference held on 28 April 2016, the PRAC was presented with an update on the operating model of the EMA procedure management department to become effective as of 1 June 2016. Further communication is expected in due course.

12.20.6. Good Pharmacovigilance Practices (GVP) – revised PRAC process for review and adoption of revised GVP modules in 2016-17

As part of the revised EU network governance for pharmacovigilance implemented as of April 2016 (see PRAC minutes March 2016), the EMA secretariat presented to the PRAC the new governance model for the Committee to provide oversight for Good Pharmacovigilance Practices (GVP) modules. Every new or revised GVP module should be discussed at PRAC before any further consultation of other Committees and/or Working Parties or Working Groups and will be followed by a PRAC written procedure (or discussion as necessary) for adoption before release to the European Risk Management Strategy Facilitation Group (ERMS FG) for approval before any public consultation or finalisation. Generally, PRAC discussions will take place at the monthly PRAC ORGAM teleconferences.

An overview of the ongoing or planned work on new or revised GVP modules was provided to PRAC together with their scope, proposed timelines for PRAC discussion and approval. In particular, the PRAC agreed with the proposal from the Pharmacovigilance inspectors Working Group (PhVIWG) to initiate revision of GVP module II on 'Pharmacovigilance system master file (PSMF)' and GVP module III on 'Pharmacovigilance inspections'. In addition, the PRAC agreed to review the need to revise GVP module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' in June 2016 given the overlap with GVP module V on 'Risk management systems' (currently in public consultation until 31/05/2016). Finally, a revision of GVP module VII on the 'Periodic safety update report' is planned for 2017. The PRAC noted ongoing work on other GVP chapters.

13. Any other business

None

14. Annex I – Risk management plans

14.1. 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).

14.1.1. Opicapone - EMEA/H/C/002790

Scope: Treatment of Parkinson's disease and motor fluctuations

14.1.2. Pancreas powder - EMEA/H/C/002070

Scope: Treatment in exocrine pancreatic insufficiency

14.2. 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).

14.2.1. Alogliptin – VIPIDIA (CAP) - EMEA/H/C/002182/WS0940; alogliptin, metformin - VIPDOMET (CAP) - EMEA/H/C/002654/WS0940; alogliptin, pioglitazone - INCRESYNC (CAP) - EMEA/H/C/002178/WS0940

PRAC Rapporteur: Menno van der Elst

Scope: Submission of revised RMPs for alogliptin-cntaining products to include heat failure (HF) as an important potential risk as requested by the PRAC (Vipidia: LEG 0009; Vipdomet: LEG 0008; Incresync: LEG 0008). In addition, the MAH took the opportunity to include minor outstanding updates to the RMPs

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

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

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

14.2.3. Pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) – PANDEMRIX[37] - EMEA/H/C/000832/II/0079

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Rafe Suvarna

Scope: Update of Annex II of the product information in order to delete the obligation to perform non-clinical mechanistic studies in naïve or A(H1N1) pdm09 primed 4-week old female cotton rats to evaluate the potential disruption of blood-brain-barrier integrity and the potential central nervous system (CNS) inflammation/damage following intramuscular administrations of Pandemrix, of non-adjuvanted H1N1 antigen and of AS03 adjuvant system

14.2.4. Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/WS/0903/G; tenofovir disoproxil, emtricitabine – TRUVADA (CAP) - EMEA/H/C/000594/WS/0903/G

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of a revised RMP to remove 'lactic acidosis with severe hepatomegaly with steatosis' as an important identified risk following the PRAC outcome whereby the warning statement regarding lactic acidosis has been removed from the product information for emtricitabine and tenofovir disoproxil-containing products. In addition, the RMP is revised to remove 'lipodystrophy' as an important identified risk following the PRAC outcome on lipodystrophy whereby the warning statements regarding lipodystrophy have been removed from the product information for antiretroviral products. Furthermore, the RMP is updated to amend the due date for submission of GS-US-236-0103 week 192 clinical study report from 'Q3 2015' to 'Q1 2016'

14.3. 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).

14.3.1. Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/II/0146

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of non-infectious intermediate, posterior and panuveitis in adult patients taking adalimumab. 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 is updated accordingly

14.3.2. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0016/G

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

[37] Marketing authorisation expired on 13 August 2015

Scope: Update of section 4.4 to remove precautions for use relating to the co-administration of ataluren with substrates or inducers of UGT1A9 and section 4.5 of the SmPC to remove statements relating to the potential effect of co-administration of ataluren with inducers or substrates of UGT1A9 and to add the results from studies PTC124-GD-026-HV and PTC124-GD-027-HV (MEA 011 and MEA 012). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC. Moreover, the RMP (version 4.2) is updated accordingly

14.3.3. Atazanavir – REYATAZ (CAP) - EMEA/H/C/000494/X/0094/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Isabelle Robine

Scope: Line extension for a new pharmaceutical form (oral powder), a new strength for the oral powder presentation (50 mg) and a new paediatric indication (patients from 3 months of age and weighing at least 5 kg) grouped with an update of the capsules presentation in light of new paediatric data. The RMP is also updated to include minor revisions with regard to nephrolithiasis folllowing PRAC's assesment of RMP version 7.3

14.3.4. Bevacizumab – AVASTIN (CAP) - EMEA/H/C/000582/II/0089

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of section 4.8 of the SmPC in order to update the safety information derived from phase III study GO25632. In addition, Annex II is updated to remove the investigation of suitable biomarkers to allow identification and selection of a more targeted population (ANX 068) from the list of conditions to the Marketing Authorisation (MA). Consequently, the RMP (version 24) is updated

14.3.5. Brentuximab vedotin – ADCETRIS (CAP) - EMEA/H/C/002455/II/0030/G

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.4 of the SmPC in order to add a warning on hepatotoxicity, further to the outcome of PSUSA/00010039/201502, to add a warning on gastrointestinal complications as well as to update the warning on pulmonary toxicity, providing examples of pulmonary toxicity diagnoses. Update of section 4.8 of the SmPC in order to implement data from the pivotal phase II studies. The Package Leaflet and RMP are updated accordingly

14.3.6. Everolimus – AFINITOR (CAP) - EMEA/H/C/001038/II/0048

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the treatment of unresectable or metastatic, well-differentiated non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease for Afinitor. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. Furthermore, the product information is brought in line with the latest QRD template (version 9.1)

14.3.7. Human normal immunoglobulin – PRIVIGEN (CAP) - EMEA/H/C/000831/II/0100

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to add information on signs of haemolysis and transfusion-related acute lung injury (TRALI). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to amend Annex II of the product information in line with the latest QRD template (version 9.1)

14.3.8. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0016

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to broaden the existing indication for chronic lymphocytic leukaemia (CLL) to include all previously untreated patients including those with 17p deletion or TP53 mutation based on the results from the final clinical study report (CSR) of study PCYC-1115-CA (MEA 021). As a consequence, sections 4.1, 4.6, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP (version 5.0) is updated accordingly

14.3.9. Idelalisib – ZYDELIG (CAP) - EMEA/H/C/003843/II/0018

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis based on post-marketing experience. The Package Leaflet is updated accordingly. The RMP (version 1.5) is updated accordingly

14.3.10. Insulin aspart – NOVORAPID (CAP) - EMEA/H/C/000258/II/0111

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of sections 1, 2, 4.2, 4.4, 6.3 and 6.6 of the SmPC to add the use of the YpsoPump insulin pump for the NovoRapid PumpCart presentation.The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 9.1) and to implement minor corrections in the product information

14.3.11. Insulin degludec, insulin aspart – RYZODEG (CAP) - EMEA/H/C/002499/II/0017

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include the paediatric population from 1 to 18 years of age for Ryzodeg. 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 is updated accordingly

14.3.12. Lacosamide – VIMPAT (CAP) - EMEA/H/C/000863/II/0060/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to add monotherapy in the treatment of partial-onset seizures. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. Variation to the specification of the active substance and minor change to the test procedure for the active substance. Variation to the specification of the finished product Vimpat 10mg/ml solution for infusion (EU/1/08/470/016-17). The change applies only to the parenteral presentations. In addition, the MAH took the opportunity to update the product information in line with the latest QRD template (version 9.1)

14.3.13. Lumacaftor, ivacaftor – ORKAMBI (CAP) - EMEA/H/C/003954/II/0002

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Update of sections 4.4, 4.8 and 5.1 of SmPC to add information regarding increase of blood pressure and decrease of heart rate following the review of clinical safety data. The Package Leaflet is updated accordingly

14.3.14. Meningococcal group a, c, w135 and y conjugate vaccine – NIMENRIX (CAP) - EMEA/H/C/002226/II/0049

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

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

14.3.15. Meningococcal group a, c, w135 and y conjugate vaccine – NIMENRIX (CAP) - EMEA/H/C/002226/II/0053

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 5.1 of the SmPC to include new booster and persistence data with a follow-up of up to 5 years after vaccination with MenACWY-TT. The RMP (version 7.0) is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC

14.3.16. Obinutuzumab – GAZYVARO (CAP) - EMEA/H/C/002799/II/0007

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to add the treatment of patients with follicular lymphoma based on the results of the pivotal study GAO4753g. Consequently, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC, the Package Leaflet and RMP are updated accordingly. Furthermore, the MAH took the opportunity to make minor editorial changes to sections 4.4, 4.6, 5.3 and 6.6 of the SmPC

14.3.17. Pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/II/0007

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the second line treatment of non-small cell lung cancer (NSCLC). As a consequence, sections 4.1, 4.2 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly

14.3.18. Regorafenib – STIVARGA (CAP) - EMEA/H/C/002573/II/0015/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.1 of the SmPC based on the results from study 15967 (CONSIGN), a phase 3b trial in patients with metastatic colorectal cancer. In addition, the MAH took the opportunity to provide long-term results from study 14874 (GRID addendum clinical study report), a pivotal phase 3 trial in patients with gastrointestinal stromal tumour (GIST). The RMP (version 4.0) is updated accordingly

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

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

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

15. 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)[38] 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).

15.1. PSUR procedures including centrally authorised products only

15.1.1. Afatinib – GIOTRIF (CAP) - PSUSA/10054/201509

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

15.1.2. Albiglutide – EPERZAN (CAP) - PSUSA/10175/201509

Applicant: GlaxoSmithKline Trading Services

[38] Unless otherwise specified

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.3. Aliskiren – RASILEZ (CAP); aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); aliskiren, amlodipine – RASILAMLO (CAP) - PSUSA/00089/201509

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.1.4. Bazedoxifene, estrogens conjugated – DUAVIVE (CAP) - PSUSA/10321/201510

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

15.1.5. Bivalirudin – ANGIOX (CAP) - PSUSA/00421/201509

Applicant: The Medicines Company UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.6. Bupropion, naltrexone – MYSIMBA (CAP) - PSUSA/10366/201509

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

15.1.7. Cabozantinib – COMETRIQ (CAP) - PSUSA/10180/201509

Applicant: TMC Pharma Services Ltd

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.1.8. Cangrelor – KENGREXAL (CAP) - PSUSA/10360/201509

Applicant: The Medicines Company UK Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.1.9. Cholic acid – ORPHACOL (CAP) - PSUSA/10208/201509

Applicant: Laboratoires CTRS - Boulogne Billancourt

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.10. Ciclosporin – IKERVIS (CAP) - PSUSA/10362/201509

Applicant: Santen Oy

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.11. Dabigatran – PRADAXA (CAP) - PSUSA/00918/201509

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

15.1.12. Denosumab – XGEVA (CAP) - PSUSA/09119/201509

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

15.1.13. Dulaglutide – TRULICITY (CAP) - PSUSA/10311/201509

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.1.14. Eltrombopag – REVOLADE (CAP) - PSUSA/01205/201509

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.1.15. Etravirine – INTELENCE (CAP) - PSUSA/01335/201509

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.1.16. Florbetapir (^{18}F) – AMYVID (CAP) - PSUSA/10032/201510

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

15.1.17. Glycopyrronium bromide – ENUREV BREEZHALER (CAP); SEEBRI BREEZHALER (CAP); TOVANOR BREEZHALER (CAP) - PSUSA/10047/201509

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

15.1.18. Glycopyrronium bromide, indacaterol – ULTIBRO BREEZHALER (CAP); ULUNAR BREEZHALER (CAP); XOTERNA BREEZHALER (CAP) - PSUSA/10105/201509

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

15.1.19. Hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (adsorbed) – AMBIRIX (CAP); TWINRIX ADULT (CAP); TWINRIX PAEDIATRIC (CAP) - PSUSA/01593/201509

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

15.1.20. Insulin aspart – NOVOMIX (CAP); NOVORAPID (CAP) - PSUSA/01749/201509

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.21. Insulin degludec –TRESIBA (CAP); insulin degludec, insulin aspart - RYZODEG (CAP) - PSUSA/10036/201509

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.22. Insulin degludec, liraglutide – XULTOPHY (CAP) - PSUSA/10272/201509

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.1.23. Insulin human – INSUMAN (CAP) - PSUSA/10107/201509

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

15.1.24. Lacosamide – VIMPAT (CAP) - PSUSA/01816/201508

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.25. Naloxegol – MOVENTIG (CAP) - PSUSA/10317/201509

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

15.1.26. Oritavancin – ORBACTIV (CAP) - PSUSA/10368/201509

Applicant: The Medicines Company UK Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

15.1.27. Panitumumab – VECTIBIX (CAP) - PSUSA/02283/201509

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.28. Raltegravir - ISENTRESS (CAP); raltegravir, lamivudine – DUTREBIS (CAP) - PSUSA/10373/201509

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.29. Retigabine – TROBALT (CAP) - PSUSA/02624/201509

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

15.1.30. Riociguat – ADEMPAS (CAP) - PSUSA/10174/201509

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.31. Sulesomab – LEUKOSCAN (CAP) - PSUSA/02803/201508

Applicant: Immunomedics GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.1.32. Tedizolid phosphate – SIVEXTRO (CAP) - PSUSA/10369/201509

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

15.1.33. Telavancin – VIBATIV (CAP) - PSUSA/02879/201509

Applicant: Clinigen Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.34. Teriparatide – FORSTEO (CAP) - PSUSA/02903/201509

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.1.35. Tobramycin – VANTOBRA (CAP) - PSUSA/10370/201509

Applicant: PARI Pharma GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

15.1.36. Trabectedin – YONDELIS (CAP) - PSUSA/03001/201509

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure[39]

15.1.37. Vinflunine – JAVLOR (CAP) - PSUSA/03123/201509

Applicant: Pierre Fabre Médicament

PRAC Rapporteur: Rafe Suvarna

[39] Adoption of the recommendation via written procedure: Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Scope: Evaluation of a PSUSA procedure

15.1.38. Vortioxetine – BRINTELLIX (CAP) - PSUSA/10052/201509

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

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

15.2.1. Epoetin alfa – ABSEAMED (CAP); BINOCRIT (CAP); EPOETIN ALFA HEXAL (CAP), NAP - PSUSA/01237/201508

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG (Abseamed), Sandoz GmbH (Binocrit), Hexal AG (Epoetin Alfa Hexal), various

PRAC Rapporteur: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

15.2.2. Leflunomide – ARAVA (CAP); LEFLUNOMIDE MEDAC (CAP); LEFLUNOMIDE WINTHROP (CAP), NAP - PSUSA/01837/201509

Applicant: Sanofi-aventis Deutschland GmbH (Arava, Leflunomide Withrop), Medac Gesellschaft fur klinische Spezialpraparate GmbH (Leflunomide Medac), various

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.2.3. Measles, mumps, rubella and varicella vaccine (live) – PROQUAD (CAP), NAP - PSUSA/01936/201509

Applicant: Sanofi Pasteur MSD SNC, various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

15.3.1. Almagate (NAP) - PSUSA/00000097/201505

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

15.3.2. Ciclesonide (NAP) - PSUSA/00000742/201508

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.3. Cilostazol (NAP) - PSUSA/00010209/201508

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

15.3.4. Dalteparin sodium (NAP) - PSUSA/00000922/201508

Applicant: various

PRAC Lead: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

15.3.5. Etonogestrel (NAP) - PSUSA/00001331/201509

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

15.3.6. Fluocinolone acetonide (intravitreal implant in applicator) (NAP) - PSUSA/00010224/201508

Applicant: various

PRAC Lead: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

15.3.7. Germanium (^{68}Ge) chloride, gallium (^{68}Ga) chloride (NAP) - PSUSA/00010364/201509

Applicant: various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

15.3.8. Hexoprenaline sulfate (NAP) - PSUSA/00003170/201508

Applicant: various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

15.3.9. Influenza vaccine (split virion, inactivated) (NAP) - PSUSA/00010298/201508

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.3.10. Influenza vaccine (split virion, inactivated, prepared in cell cultures) (NAP) - PSUSA/00010299/201508

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

15.3.11. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/201508

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.3.12. Influenza vaccine (surface antigen, inactivated, adjuvanted) (NAP) - PSUSA/00010300/201508

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.3.13. Influenza vaccine (surface antigen, inactivated, virosome) (NAP) - PSUSA/00001746/201508

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

15.3.14. Olodaterol (NAP) - PSUSA/00010245/201509

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

15.4. Follow-up to PSUR procedures

15.4.1. Bortezomib – VELCADE (CAP) - EMEA/H/C/000539/LEG 053

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a cumulative review of cases reporting progressive multifocal leukoencephalopathy (PML) with the use of bortezomib submitted by the MAH following the recommendation of the PSUSA/00000424/201504 procedure adopted in November 2015

15.4.2. 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 116.1

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of MAH's responses to LEG 116 [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] as per request for supplementary information adopted in November 2015

15.4.3. Everolimus – AFINITOR (CAP) - EMEA/H/C/001038/LEG 028

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a cumulative review of cases of ejection fraction decrease submitted by the MAH following the recommendation of the PSUSA/00010268/201503 procedure adopted in November 2015

15.4.4. Piperaquine tetraphosphate, dihydroartemisinin – EURARTESIM (CAP) - EMEA/H/C/001199/LEG 015

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

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a re-analysis of the data in the effectiveness survey distributed to physicians submitted by the MAH following the recommendation of the PSUSA/00001069/201504 procedure adopted in September 2015

16. 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.

16.1. Protocols of PASS imposed in the marketing authorisation(s)[40]

16.1.1. Blinatumomab – BLINCYTO (CAP) - EMEA/H/C/PSP/0041

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Mladá

Scope: Evaluation of a protocol for study 20150136: an observational study measuring the safety and effectiveness of blinatumomab as well as utilisation and treatment practices

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

16.1.2. Idebenone – RAXONE (CAP) - EMEA/H/C/PSP/0034.1

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a revised PASS protocol for a non-interventional study of clinical experience in patients prescribed Raxone for the treatment of Leber's hereditary optic neuropathy (LHON)

16.2. Protocols of PASS non-imposed in the marketing authorisation(s)[41]

16.2.1. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/003718/MEA/006

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Draft protocol for pregnancy registry study OBS13436: an international Lemtrada pregnancy exposure cohort in multiple sclerosis

16.2.2. Dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/MEA/001.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: MAH's responses to MEA 001.1 [revised PASS protocol regarding the utilisation of dulaglutide in European countries: a cross-sectional, multi-country and multi-source drug utilisation study using electronic health record databases] as per request for supplementary information adopted in December 2015

16.2.3. Dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/MEA/002.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: MAH's responses to MEA 002.1 [revised PASS protocol on the utilisation and safety of dulaglutide in European countries: a modified prescription-event monitoring and network database study (multi-database collaborative research programme of observational studies)] as per request for supplementary information adopted in December 2015

16.2.4. Fenofibrate, pravastatin – PRAVAFENIX (CAP) - EMEA/H/C/001243/MEA/007.5

Applicant: Laboratoires SMB S.A.

PRAC Rapporteur: Isabelle Robine

Scope: Revised PASS protocol for a European, observational, three-year cohort comparative study on the safety of the fixeddose combination pravastatin 40 mg/fenofibrate 160 mg (Pravafenix) versus statin alone in real clinical practice (FENOPRA-IV-14-1)

[41] 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

16.3. Results of PASS imposed in the marketing authorisation(s)[42]

None

16.4. Results of PASS non-imposed in the marketing authorisation(s)[43]

16.4.1. Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS/0890 aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP) - EMEA/H/C/000964/WS/0890

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

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

16.4.2. Dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/II/0091/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of a group of variations containing 1) the final clinical study report (CSR) for study 1160.118: an observational cohort study to evaluate the safety and efficacy of switching from Lovenox (enoxaparin) 40 mg to Pradaxa (dabigatran etexilate) 220 mg in patients undergoing elective total hip or knee replacement surgery' and consequent update of the RMP and 2) update of the timeline for availability of study 1160.144 final report

16.4.3. Temozolomide – TEMODAL (CAP) - EMEA/H/C/000229/II/0075

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final results from study MK 7365-295: an observational PASS regarding Temodal and severe acute liver injury in brain cancer patients

16.4.4. Ticagrelor – BRILIQUE (CAP) - EMEA/H/C/001241/II/0031

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report for a drug utilisation study (DUS) to fulfil a post-authorisation measure (MEA 008): detailed description of patients who are prescribed ticagrelor for the first time and comparison with patients who are prescribed clopidogrel and prasugrel for the first time, with an estimation of the potential off-label use of ticagrelor. The study also aims to ascertain incident cases and estimate the crude incidence rate of selected safety outcomes among new users in the three cohorts of ticagrelor, clopidogrel and prasugrel

[42] In accordance with Article 107p-q of Directive 2001/83/EC
[43] 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

16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[44]

16.5.1. Exenatide – BYDUREON (CAP) - EMEA/H/C/002020/MEA/010.4

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Interim results of study H8O-MC-B016: a modified prescription event monitoring to identify possible cases of pancreatitis to be conducted in the UK, enrolling primary care patients with type 2 diabetes mellitus who receive prescription for exenatide once weekly

16.5.2. Influenza vaccine (split virion, inactivated) – IDFLU (CAP) - EMEA/H/C/000966/MEA/032.3; INTANZA (CAP) - EMEA/H/C/000957/MEA/032.3

Applicant: Sanofi Pasteur, Sanofi Pasteur MSD SNC

PRAC Rapporteur: Miguel-Angel Macia

Scope: Interim results of the enhanced passive safety surveillance for 2015-2016 campaign (study FLU07E)

16.5.3. Insulin detemir – LEVEMIR (CAP) - EMEA/H/C/000528/MEA/045.4

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Second annual progress report (01 Nov 2014 to 31 Oct 2015) for a diabetes pregnancy registry (study NN304-4016): an international non-interventional prospective cohort study to evaluate the safety of treatment with Levemir (insulin detemir) in pregnant women with diabetes mellitus

16.6. Others

16.6.1. Panitumumab – VECTIBIX (CAP) - EMEA/H/C/000741/LEG 032.3

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Julie Williams

Scope: Annual update on the European Society of Pathology - (ESP) External Quality Assurance (EQA) programme in relation to KRAS testing

16.7. New Scientific Advice

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

16.8. Ongoing Scientific Advice

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

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

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

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

17. 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.

17.1. Annual reassessments of the marketing authorisation

17.1.1. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0013 (without RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

17.2. Conditional renewals of the marketing authorisation

None

17.3. Renewals of the marketing authorisation

17.3.1. Levetiracetam – LEVETIRACETAM ACCORD (CAP) - EMEA/H/C/002290/R/0012 (with RMP)

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

17.3.2. Levetiracetam – MATEVER (CAP) - EMEA/H/C/002024/R/0023 (without RMP)

Applicant: Pharmathen S.A.

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

17.3.3. Pramipexole – PRAMIPEXOLE ACCORD (CAP) - EMEA/H/C/002291/R/0010 (without RMP)

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

17.3.4. Telmisartan – TELMISARTAN TEVA PHARMA (CAP) - EMEA/H/C/002511/R/0014 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: 5-year renewal of the marketing authorisation

17.3.5. Varenicline – CHAMPIX (CAP) - EMEA/H/C/000699/R/0061 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

18. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 11-14 April 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
Marianne Lunzer	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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
Isabelle Robine	Member	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Melinda Palfi	Alternate - via telephone*	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
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
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Ingebjørg Buajordet	Member - via telephone*	Norway	No interests declared	Full involvement
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Leonor Chambel	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to this meeting	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Alternate - via telephone*	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Miguel-Angel Macia	Alternate - via telephone*	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 interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
		scientific expert	declared	
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Radim Tobolka	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Piere Demolis	Expert - in person*	France	No interests declared	Full involvement
Muriel Echemann	Expert - via telephone*	France	No interests declared	Full involvement
Claire Ferard	Expert - in person*	France	No interests declared	Full involvement
Nathalie Morgensztejn	Expert - via telephone*	France	No interests declared	Full involvement
Alexandre Moreau	Expert - in person*	France	No interests declared	Full involvement
Isabelle Yoldjian	Expert - via telephone*	France	No interests declared	Full involvement
Norbert Benda	Expert - in person*	Germany	No interests declared	Full involvement
Tania Meier	Expert - via telephone*	Germany	No interests declared	Full involvement
Elke Stahl	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Niamh Buckley	Expert - in person*	Ireland	No interests declared	Full involvement
Eleanor Carey	Expert - via	Ireland	No interests	Full

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	involvement
Anna Marie Coleman	Expert - via telephone*	Ireland	No interests declared	Full involvement
Negar Babae	Expert - in person*	Netherlands	No interests declared	Full involvement
Kora Doorduyn - van der Stoep	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Eirik Hagtvet	Expert - in person*	Norway	No interests declared	Full involvement
Natividad Galiana Llorca	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Consuelo Mejías Pavón	Expert - via telephone*	Spain	No interests declared	Full involvement
Eva A. Segovia	Expert - in person*	Spain	No interests declared	Full involvement
Jordi Bruix Tudo	Expert witness - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Kristina Dunder	Expert - via telephone*	Sweden	No interests declared	Full involvement
Annika Ekbom Schnell	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Karin Nylén	Expert - in person*	Sweden	No interests declared	Full involvement
Miriam Taekema	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jo Lynn Chooi	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Sarah Jane Mee	Expert - via telephone*	United Kingdom	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Martyn Ward	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.

19. 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

20. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse

event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation. PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/