17 May 2018
EMA/PRAC/288660/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 09-12 April 2018

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

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

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

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006, Rev. 1).

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1. Introduction

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

The Chairperson opened the 09-12 April 2018 meeting by welcoming all participants.

Based on the declarations of interest submitted by the Committee members, alternates and experts as well as 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 Anette Kirstine Stark as the new alternate for Denmark. The Chair also announced that Guðrún Stefánsdóttir was the new member for Iceland, replacing Guðrún Kristín Steingrímsdóttir who became the alternate, replacing Hrefna Gudmundsdottir. In addition, the Chair announced that Anne-Cécile Vuillemin was the new alternate for Luxembourg replacing Nadine Petitpain. Finally, it was noted that Amy Tanti stepped down from her position of member for Malta.

1.2. Agenda of the meeting on 09-12 April 2018

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 05-08 March 2018

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 05-08 March 2018 were published on the EMA website on 08 May 2018 (EMA/PRAC/288259/2018).

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. Others

2.4.1. Hydroxyethyl starch (HES)[1] (NAP) - EMEA/H/A-107i/1457

Applicants: Fresenius Kabi Deutschland GmbH (Volulyte, Voluven), B. Braun Melsungen AG (Tetraspan, Venofundin), Seruwerk Bernburg AG (Hesra); various

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Ulla Wändel Liminga

Scope: Review of PRAC recommendation of a referral procedure under Article 107i of Directive 2001/83/EC adopted in January 2018, at the request of the European Commission

Background

The PRAC recommendation (see PRAC minutes January 2018), followed by the adoption by majority vote of the CMDh position in January 2018 (see EMA/35795/2018 corr. 1) for the referral procedure under Article 107i of Directive 2001/83/EC on hydroxyethyl starch (HES) solutions for infusion was transmitted to the European Commission (EC) for the adoption of a legally binding decision valid throughout the European Union (EU).

At its current plenary meeting, the PRAC was informed that the decision-making process at the level of the EC Standing Committee (SC) had been suspended as some Member States raised new questions of a scientific nature, in particular with regard to the impact of the suspension of HES-containing products on potential medical need and the feasibility and effectiveness of risk minimisation measures (RMM) (see S056176/01 (Summary record) in dossier CMTD(2018)0303 of the meeting of the 'EC SC on Medicinal Products for Human Use'). The EC referred back the PRAC recommendation and CMDh position to the respective Committee/Coordination Group for further consideration of these points.

Summary of recommendation(s)/conclusions

- The PRAC noted a letter from the EC addressed to the PRAC and CMDh asking for a review by the end of May 2018 of the PRAC recommendation and the CMDh position in the light of some questions of scientific nature.
- The PRAC discussed the request from the EC, the need for consultation of stakeholders on the points raised and the timelines for the revision of its recommendation. In relation to these questions, the PRAC considered that the feedback from the National Competent Authorities (NCAs) is required. No further stakeholder consultation was deemed necessary as stakeholders have already been consulted during the procedure and PRAC took into consideration the positions expressed by representative stakeholder groups.

[1] Solution for infusion

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

3.1. Newly triggered procedures

3.1.1. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP); NAP - EMEA/H/A-31/1463

Applicants: Therakind Limited (Jylamvo), Nordic Group B.V. (Nordimet), various

PRAC Rapporteur: Martin Huber; PRAC Co-rapporteur: Željana Margan Koletić

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

Background

Methotrexate is an antineoplastic and immunomodulating agent and folic acid analogue indicated for use in rheumatological and dermatological diseases (active rheumatoid arthritis, polyarthritic forms of active, severe juvenile idiopathic arthritis (JIA), and severe, treatment-refractory, disabling psoriasis under certain conditions) as well as in oncology for the maintenance treatment of acute lymphoblastic leukaemia (ALL).

The Spanish Agency on Medicines and Medical Devices [2] (AEMPS) sent a letter of notification dated 22/03/2018 of a referral under Article 31 of Directive 2001/83/EC for the review of methotrexate-containing medicines for oral use to assess the need for additional measures aimed at minimising the serious risk of overdose toxicity as a consequence of daily intake in error instead of weekly intake. As part of the recommendation of the PSUSA procedure (PSUSA/00002014/201706) finalised in March 2018, the PRAC requested the MAHs of methotrexate-containing medicines for oral use to submit within the next PSUR additional data analyses, consideration of further risk minimisation measures (RMMs) as well as means to measure their effectiveness (see PRAC minutes March 2018). Nevertheless, Spain considered there was a need to review thoroughly the data from all relevant sources and the RMMs taken nationally over recent years to fully elucidate the issue and to take appropriate measures.

Discussion

The PRAC noted the notification letter from the AEMPS and discussed a list of questions (LoQ) to the MAHs to be addressed during the procedure as well as a timetable for conducting the review. In addition, the PRAC discussed the possibility to extend the scope of the procedure to parenteral formulations. The PRAC also discussed the possibility of consulting with healthcare professional representative organisations and to collect further data at national level from the National Competent Authorities (NCA).

The PRAC appointed Martin Huber as Rapporteur and Željana Margan Koletić as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

- The Committee agreed to extend the scope of the procedure in order to review the issue for both oral and parenteral formulations

[2] Agencia Española de Medicamentos y Productos Sanitarios

- The Committee adopted a LoQ to the MAHs (EMA/PRAC/199743/2018) and a timetable for the procedure (EMA/PRAC/199744/2018).
- The Committee adopted a LoQ to healthcare professional representative organisations.
- The Committee agreed on the content of a non-urgent information request (NUI) to be distributed to the EU NCAs in order to collect information on the handling of medication errors associated with methotrexate and existing safety recommendations at national level.
- The PRAC discussed the option to conduct a public hearing in the context of the Article 31 procedure on medicinal products containing methotrexate, according to the pre-defined criteria set out in the rules of procedure[3] (EMA/363479/2015). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure as needed.

3.2. Ongoing procedures

3.2.1. Ulipristal acetate - ESMYA (CAP) - EMEA/H/A-20/1460

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur: Menno van der Elst

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Esmya (ulipristal acetate), a centrally authorised product indicated for pre-operative treatment as well as intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age, in order to investigate the risk of liver injury and assess its impact on the benefit-risk balance of the medicinal product. For further background, see PRAC minutes December 2017 and PRAC minutes February 2018.

Summary of recommendation(s)/conclusions

- The PRAC discussed a list of experts (LoE) for the ad-hoc experts meeting scheduled on 3 May 2018 and adopted a revised timetable (EMA/PRAC/791197/2017 Rev. 2) for the procedure accordingly.

Post meeting note: On 26 April 2018, the PRAC adopted the final LoE for the ad-hoc experts' meeting by written procedure.

3.3. Procedures for finalisation

None

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

3.4. Re-examination procedures[4]

None

3.5. Others

None

4. Signals assessment and prioritisation[5]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Lenograstim (NAP); lipegfilgrastim – LONQUEX (CAP); pegfilgrastim – NEULASTA (CAP)

Applicant(s): Amgen Europe B.V. (Neulasta), Sicor Biotech UAB (Lonquex), various

PRAC Rapporteur: Patrick Batty

Scope: Signal of pulmonary haemorrhage

EPITT 19181 – New signal

Lead Member State: UK

Background

Pegfilgastrim is a pegylated form of filgrastim, a granulocyte colony stimulating factor (G-CSF), indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

The cumulative exposure to medicines containing pegfilgrastim is estimated to have been approximately 1,720,001 person-years worldwide in the period from first authorisation in 2002 to 2016.

During routine signal detection activities, a signal of pulmonary haemorrhage was identified by the EMA, based on 10 cases of pulmonary haemorrhage, pulmonary alveolar haemorrhage and diffuse alveolar damage retrieved from EudraVigilance. The UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from EudraVigilance, including the temporal association and the likely class effect of G-CSF-containing products (i.e. filgrastim-containing products list haemoptysis (common) and pulmonary haemorrhage (uncommon) among other

[4] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[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

pulmonary adverse drug reactions (ADRs); lenograstim lists haemoptysis and pulmonary haemorrhage for healthy donors only as a warning), there is a reasonable possibility of a causal association for pegfilgrastim, lenograstim and pulmonary haemorrhage and haemoptysis. Therefore, the PRAC proposed that the MAHs for pegfilgrastim- and lenograstim-containing products update their product information to include these undesirable effects. Considering the biological plausibility that the G-CSF modulates the function of neutrophils including cytokine release, possibly inducing lung damage, the PRAC agreed to extend the scope of the recommendation and include the same wording in the product information of lipegfilgrastim-containing products.

The PRAC appointed Patrick Batty as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for pegfilgrastim-, lenograstim- and lipegfilgrastim-containing products should submit to EMA, within 15 days, comments on the proposed wording for amending the product information[6].

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Dienogest, ethinylestradiol (NAP)

Applicant(s): various

PRAC Rapporteur: Valerie Strassmann

Scope: New information on the known risk of venous thromboembolism with combined hormonal contraceptives (CHCs) containing dienogest and ethinylestradiol (DNG/EE)

EPITT 17409 – New signal

Lead Member State: DE

Background

Hormonal contraceptives are composed of steroid hormones. One of the two main types of formulations is the combined hormonal contraceptives (CHCs) that contain both a progestogen and an oestrogen. Dienogest is a progestogen and ethinylestradiol an oestrogen. Hormonal contraceptives are primarily used for the prevention of pregnancy.

In 2013, the EMA reviewed the risk of venous thromboembolism (VTE) with the different progestogens within a referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1356), and information about this risk was included in the product information of the medicines. The risks with different progestogens ranged between 5 and 12 cases of VTE per year for every 10,000 women taking the contraceptive (compared with 2 cases per year per 10,000 women not taking such medicines). At the time of this review, there was not enough information about the risk of VTE with products containing dienogest to quantify the risk.

[6] Proposed update of SmPC section 4.8

Following the recent submission by the MAH Bayer Vital GmbH of results of a meta-analysis of four prospective cohort studies[7] with identical study design on the risk of VTE associated with the use of CHC-containing dienogest/ethinylestradiol and levonorgestrel/ethinylestradiol performed following the completed referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1356), new information on the known risk of VTE with CHC-containing dienogest and ethinylestradiol (DNG/EE) was identified by Germany. The submitted meta-analysis combines data from over 228,000 women. The MAH preliminary analyses suggest that the risk with dienogest-containing contraceptives might be intermediate between the lowest and highest risk of available different progestogen-containing contraceptives pending further review of results. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the new information with regard to the known risk of VTE and the fact that the MAH of the originator dienogest/ethinylestradiol-combination containing products submitted a variation to update the product information accordingly, the PRAC agreed to close this signal procedure as the issue is to be addressed within the variation procedure.

The PRAC appointed Valerie Strassmann as the Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed to close the signal procedure. The signal will be assessed within the ongoing variation procedure.

4.2.2. Emicizumab – HEMLIBRA (CAP)

Applicant(s): Roche Registration Limited

PRAC Rapporteur: Amelia Cupelli

Scope: New information on the known risk of haemorrhagic events

EPITT 19214 – New signal

Lead Member State: IT

Background

Emicizumab is an antihemorrhagic agent. Hemlibra (emicizumab) is a centrally authorised medicine indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors.

Following the communication by the MAH of Hemlibra (emicizumab) recently sent to all investigators currently participating in clinical trials involving Hemlibra (emicizumab), together with the response to requests from the haemophilia community with respect to the number of fatalities in patients receiving emicizumab in the USA, Italy identified new information on the known risk of haemorrhagic events. The PRAC noted the complex medical histories of the reported cases. Italy confirmed that the signal needed initial analysis and prioritisation by the PRAC.

[7] LASS study: 'Long-term active surveillance study for oral contraceptives'; INAS-OC study: 'International active surveillance study of women taking oral contraceptives'; TASC study: 'Transatlantic active surveillance on cardiovascular safety of Nuvaring (etonogestrel/ethinylestradiol vaginal ring)', INAS-SCORE study: 'International active surveillance study – safety of contraceptives: role of estrogens'

Discussion

Following the recent public statement concerning five deaths occurring in patients treated with emicizumab and having considered the available evidence provided by the MAH on the fatal cases and data from EudraVigilance, the PRAC agreed that the MAH of Hemlibra (emicizumab) should submit, in the context of the next PSUR, supplementary information with responses to a list of questions (LoQ).

Summary of recommendation(s)

- The MAH for Hemlibra (emicizumab) should submit to EMA, within the next PSUR submission (data lock point (DLP): 15 May 2018), supplementary information with responses to the adopted LoQ.

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab – AMGEVITA (CAP), CYLTEZO (CAP), HUMIRA (CAP), IMRALDI (CAP), SOLYMBIC (CAP); infliximab – FLIXABI (CAP), INFLECTRA (CAP), REMICADE (CAP), REMSIMA (CAP)

Applicant(s): AbbVie Limited (Humira), Amgen Europe B.V. (Amgevita, Solymbic), Boehringer Ingelheim International GmbH (Cyltezo), Celltrion Healthcare Hungary Kft. (Remsima), Hospira UK Limited (Inflectra), Janssen Biologics B.V. (Remicade), Samsung Bioepis UK Limited (Flixabi, Imraldi)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of risk of lymphoma in patients with inflammatory bowel disease

EPITT 19121 – Follow-up to January 2018

Background

For background information, see PRAC minutes January 2018.

The publication by *Lemaitre M, et al.*[8] was assessed by the Rapporteur.

Discussion

Having considered the available evidence arising from the publication by *Lemaitre M, et al.* on the signal of the risk of lymphoma in patients with inflammatory bowel disease treated with tumour necrosis factor antagonists and considering that some methodological considerations in the study remain, the PRAC agreed to request the authors to provide additional clarifications on the study findings.

Summary of recommendation(s)

- The PRAC agreed a list of questions (LoQ) for the study authors to provide additional clarifications within 90 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

[8] Lemaitre M, Kirchgesner J, Rudnichi A, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA. 2017;318(17):1679–1686. doi:10.1001/jama.2017.16071

4.3.2. Amitriptyline (NAP)

Applicant(s): various

PRAC Rapporteur: Agni Kapou

Scope: Signal of dry eye

EPITT 19173 – Follow-up to March 2018

Background

For background information, see PRAC minutes March 2018.

The MAHs replied to the request for comments on the proposed amendment to the product information further to the signal of dry eye and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature with regard to the risk of dry eye associated with amitriptyline, as well as the MAHs' comments on the proposed update, the PRAC agreed that the MAHs of amitriptyline-containing medicinal products should amend the product information to add the undesirable effect 'dry eye' with a frequency not known.

Summary of recommendation(s)

- The MAHs for amitriptyline-containing medicinal products should submit to the relevant national competent authorities of the MSs, within 60 days, a variation to amend the product information[9].

For the full PRAC recommendation, see EMA/PRAC/211744/2018 published on 07/05/2018 on the EMA website.

4.3.3. Azithromycin (NAP)

Applicant(s): various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of increased rate of relapses of haematological malignancies and mortality in haematopoietic stem cell transplantation (HSCT) patients with azithromycin

EPITT 18907 – Follow-up to September 2017

Background

For background information, see PRAC minutes September 2017.

The MAH replied to the request for information on the signal of increased rate of relapses of haematological malignancies and mortality in haematopoietic stem cell transplantation (HSCT) patients with azithromycin and the responses as well as the additional information provided by the authors of the ALLOZITHRO study[10] were assessed by the Rapporteur.

[9] Recommendation to update SmPC section 4.8. The package leaflet is to be updated accordingly

[10] Bergeron et al. Effect of azithromycin on airflow decline-free survival after allogeneic hematopoietic stem cell transplant. The ALLOZITHRO randomized clinical trial. JAMA.2017;318(6):557-566

Discussion

Having considered the available evidence from the literature, the cumulative review provided by the MAH (Pfizer), and information from the authors of the ALLOZITHRO study, the PRAC agreed that long term azithromycin exposure subsequent to HSCT may be associated with an increased risk of relapse of haematological malignancies.

As azithromycin is used long-term in its approved long-term indications as well as off-label, specifically in long-term prophylactic management of a variety of chronic lung diseases including lung transplant, chronic obstructive pulmonary disease, cystic fibrosis, non-cystic fibrosis bronchiectasis, and asthma, the MAHs of systemic azithromycin-containing products should include in the next PSUR a cumulative review of post-marketing data, clinical trials and literature data regarding all types of cancers (not only haematological malignancies) with a main focus on long term treatment with azithromycin.

The PRAC recommended that the MAHs of systemic azithromycin-containing products collaboratively distribute a single direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the PRAC.

Summary of recommendation(s)

- The MAHs of systemic azithromycin-containing products should provide in the next PSUR a cumulative review of post-marketing data, clinical trials and literature data regarding all types of cancers (not only haematological malignancies) with a main focusing on long term treatment with azithromycin.
- In addition, the MAHs of systemic azithromycin-containing products should collaboratively distribute a single DHPC according to the text and communication plan agreed with the PRAC.

4.3.4. Dasatinib – SPRYCEL (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Signal of cytomegalovirus (CMV) reactivation

EPITT 19111 – Follow-up to December 2017

Background

For background information, see PRAC minutes December 2017.

The MAH of Sprycel (dasatinib) replied to the request for information on the signal of cytomegalovirus (CMV) reactivation and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of CMV infections, the PRAC agreed that the MAH of Sprycel (dasatinib) should amend the product information to include CMV infections among the herpes virus infections as an undesirable effect of common frequency.

Summary of recommendation(s)

- The MAH for Sprycel (dasatinib) should submit to EMA, within 60 days, a variation for amending the product information[11].

For the full PRAC recommendation, see EMA/PRAC/211744/2018 published on 07/05/2018 on the EMA website.

4.3.5. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP), HIZENTRA (CAP), HYQVIA (CAP), KIOVIG (CAP), PRIVIGEN (CAP); NAP

Applicant(s): Baxalta Innovations GmbH (HyQvia), Baxter AG (Kiovig), CSL Behring GmbH (Privigen, Hizentra), Instituto Grifols, S.A. (Flebogamma DIF), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of lupus-like syndrome and related terms

EPITT 19098 – Follow-up to December 2017

Background

For background information, see PRAC minutes December 2017.

The MAHs replied to the request for information on the signal of lupus-like syndrome and related terms and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the data submitted by the MAHs, the PRAC agreed that the views of the CHMP Blood Product Working Party (BPWP) on drug induced lupus erythematosus associated with immunoglobulins should be sought.

Summary of recommendation(s)

- The PRAC agreed that a list of questions (LOQ) should be addressed to the BPWP to seek their expertise on this matter.

4.3.6. Lapatinib – TYVERB (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of pulmonary hypertension

EPITT 19089 – Follow-up to December 2017

Background

For background information, see PRAC minutes December 2017.

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

Discussion

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of pulmonary arterial hypertension, the PRAC agreed that the MAH of Tyverb

[11] Recommendation to update SmPC section 4.8. The package leaflet is to be updated accordingly

(lapatinib) should amend the product information to include pulmonary arterial hypertension as undesirable effect with a frequency not known.

Summary of recommendation(s)

- The MAH for Tyverb (lapatinib) should submit to EMA, within 60 days, a variation to amend the product information[12].

For the full PRAC recommendation, see EMA/PRAC/211744/2018 published on 07/05/2018 on the EMA website.

4.3.7. Phenprocoumon (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

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

EPITT 18902 – Follow-up to December 2017

Background

For background information, see PRAC minutes December 2017.

The MAH replied to the request for information on the signal related to the risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal of treatment and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from a recent observational study, the PRAC agreed that the MAHs of phenprocoumon-containing medicinal products should amend the product information with regards to the risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal of treatment.

Summary of recommendation(s)

- The MAHs for phenprocoumon-containing medicinal products should submit to the relevant national competent authorities of the MSs, within 60 days, a variation to amend the product information[13].

For the full PRAC recommendation, see EMA/PRAC/211744/2018 published on 07/05/2018 on the EMA website.

4.3.8. Vortioxetine – BRINTELLIX (CAP)

Applicant(s): H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: Signal of angioedema and urticaria

[12] Recommendation to update SmPC section 4.8. The package leaflet is to be updated accordingly
[13] Recommendation to update of SmPC section 4.6. The package leaflet is to be updated accordingly – the entire sections should be updated for ease of implementation

EPITT 19099 – Follow-up to December 2017

Background

For background information, see PRAC minutes December 2017.

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

Discussion

Having considered the available evidence in EudraVigilance and Lundbeck's safety database, the PRAC has agreed that the MAH(s) of vortioxetine-containing products should amend the product information to add the undesirable effects angioedema and urticaria with a frequency not known.

Summary of recommendation(s)

- The MAH(s) for vortioxetine-containing products should submit to EMA, within 60 days, a variation to amend the product information[14].
- In the next PSUR (data lock point (DLP): 29 September 2018), the MAH of Brintellix (vortioxetine) should present a cumulative review of all cases of the MedDRA SMQ[15] 'anaphylactic reaction' associated with vortioxetine. The cumulative review should include a review of published literature, clinical trials and post-marketing data. The MAH should also discuss the need for any potential amendment to the product information and/or the RMP. Supportive cases (sufficiently documented, supportive time-relationship and/or physician judgment of causality) should be presented at case level.

For the full PRAC recommendation, see EMA/PRAC/211744/2018 published on 07/05/2018 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

5.1.1. Abemaciclib - EMEA/H/C/004302

Scope: Treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer

[14] Update of SmPC section 4.8. The package leaflet is updated accordingly
[15] Medical dictionary for regulatory activities – Standardised MedDRA Query (SMQ)

5.1.2. Adalimumab - EMEA/H/C/004429

Scope: Treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

5.1.3. Axicabtagene ciloleucel - EMEA/H/C/004480, Orphan

Applicant: Kite Pharma EU B.V., ATMP[16]

Scope: Treatment of diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL)

5.1.4. Fexinidazole Art 58[17]- EMEA/H/W/002320

Scope (accelerated assessment): Treatment of human African trypanosomiasis (HAT)

5.1.5. Lesinurad, allopurinol - EMEA/H/C/004412

Scope: Treatment of hyperuricaemia in gout patients

5.1.6. Patisiran - EMEA/H/C/004699, Orphan

Applicant: Alnylam UK Limited

Scope (accelerated assessment): Treatment of hereditary transthyretin-mediated amyloidosis

5.1.7. Trastuzumab - EMEA/H/C/004463

Scope: Treatment of metastatic and early breast cancer and metastatic gastric cancer (MGC)

5.1.8. Vigabatrin - EMEA/H/C/004534, PUMA[18]

Scope: Treatment in monotherapy of infantile spasms (West's syndrome) and resistant partial epilepsy in infants and children

5.1.9. Volanesorsen - EMEA/H/C/004538, Orphan

Applicant: Akcea Therapeutics UK Ltd.

Scope: Adjunct to diet for the treatment of patients with familial chylomicronemia syndrome (FCS)

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

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

See also Annex I 15.2.

5.2.1. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0027, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Updated RMP (version 4.0) in order to reclassify an imposed non-interventional PASS listed as a category 2 study in the RMP (specific obligation) to a study listed as a category 3 in the RMP (required additional pharmacovigilance activities). This study is an observational registry (DF-VOD2013-03-REG) aiming at recording safety and outcome data in patients diagnosed with severe veno-occlusive disease (VOD) following haematopoietic stem cell transplantation (HSCT) treated or not treated with Defitelio (defibrotide). Annex II of the product information is updated accordingly

Background

Defibrotide is an antithrombotic agent indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy in adults and in adolescents, children and infants over 1 month of age.

The PRAC is evaluating a variation procedure for Defitelio, a centrally authorised medicine containing defibrotide, to update the RMP in order to reclassify an observational registry study recording safety and outcome data in patients diagnosed with severe veno-occlusive disease (VOD) following haematopoietic stem cell transplantation (HSCT) treated or not treated with Defitelio (defibrotide) from an imposed to non-imposed PASS. 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. For further background, see PRAC minutes November 2017 and PRAC minutes February 2018

Summary of advice

- The RMP for Defitelio (defibrotide) in the context of the variation under evaluation could be considered acceptable provided that an update to RMP version 4.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- Taking into account the challenges in recruitment of controls due to ethical concerns and the fact that Defitelio (defibrotide) has become standard of care, the PRAC acknowledged that the study was no longer feasible in its current form. Nevertheless, the PRAC did not support the MAH's proposal to remove the study as a condition to the marketing authorisation(s). Alternatively, the PRAC advised amending the specific obligation (SO) by specifying that the report should also reflect on safety data collected during prophylactic treatment, and any potential safety differences between treatment *vs* prophylactic therapy. To this end, the MAH should provide appropriate objectives and the methodology for a systematic literature review as well as a detailed protocol including predefined objectives and methodologies for data analyses for review and approval prior study initiation.

  See also under I.8.3.1.

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

See also Annex I 15.3.

5.3.1. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/II/0015/G, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variations consisting of an update of sections 4.2, 4.3, 4.4, 4.5 and 5.2 of the SmPC based on the final data from: 1) study POP13777: an open-label pharmacokinetic and tolerability study of eliglustat tartrate given as a single dose in subjects with mild and moderate hepatic impairment, and in matched subjects with normal hepatic function (MEA003.3); and 2) study POP13778: an open-label two-stage pharmacokinetic and tolerability study of eliglustat tartrate given as a single dose in subjects with mild, moderate and severe renal impairment, and in matched subjects with normal renal function (MEA004.3). Annex II D, the package leaflet and the RMP (version 5.0) are updated accordingly

Background

Eliglustat is an inhibitor of glucosylceramide synthase indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6[19] poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).

The CHMP is evaluating a grouped variation application for Cerdelga, a centrally authorised product containing eliglustat, including updates to the key elements of the prescriber's guide and patient alert card (PAC) in relation to different stages of hepatic and renal impairments, based on the final data from studies POP13777 and POP13778, two open-label pharmacokinetic and tolerability studies of eliglustat tartrate in subjects with hepatic and renal impairment respectively. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure and the proposed changes to the key elements of the Annex II.D on additional risk minimisation measures. For further background, see PRAC minutes December 2017 and PRAC minutes February 2018.

Summary of advice

- The RMP for Cerdelga (eliglustat) in the context of the procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 5.1 and satisfactory responses to the request for supplementary information (RSI) are submitted to amend the risk minimisation measure (RMM) information in relation to the important potential risk of 'cardiac conduction disorders and arrhythmias'.
- The PRAC considered that the proposed updated key elements to the prescriber's guide and PAC including new information regarding use of Cerdelga (eliglustat) in different stages of hepatic impairment and the information on renal impairment for the PAC are acceptable in order to support safe and effective use of Cerdelga in the long-term treatment of adult patients.

[19] Cytochrome P450 2D6

5.3.2. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS1343/0036, REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS1343/0032

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the results of the Salford lung study (SLS)-asthma (HZA115150): an interventional post-authorisation safety category 1 open-label comparative study to further investigate the risk of pneumonia (ANX005). The RMP (version 9.2) is updated accordingly to reflect additional information following the completion of the study. In addition, the RMP is updated to amend the important identified risk of pneumonia with regards to findings from the study, and to provide a justification for the removal of the important potential risk of asthma-related intubations and deaths and a justification for removal of missing information related to long-term use in asthma (>1 year). Consequently, the Annex II condition of the product information is updated accordingly

Background

Fluticasone furoate is a synthetic corticosteroid and vilanterol is a selective, long-acting $beta_2$-receptor agonist. In combination, fluticasone furoate/vilanterol is indicated for the treatment of asthma in adults and adolescents aged 12 years and older when not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting $beta_2$-agonists, and for the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in the first second (FEV1) <70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

The CHMP is evaluating a worksharing variation application for Relvar Ellipta and Revinty Ellipta, centrally authorised products containing fluticasone furoate/vilanterol, consisting of the results of an interventional PASS imposed in the condition of the respective marketing authorisation(s) to investigate the risk of pneumonia (Salford lung study (SLS)-asthma). This results in a proposed update of the important identified risk of pneumonia and proposals for removing the important potential risk of asthma-related intubations and deaths and for removing missing information related to long-term use in asthma (>1 year). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Relvar Ellipta and Revinty Ellipta (fluticasone furoate/vilanterol) in the context of the procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 9.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed that the proposed changes to the RMP were overall acceptable. Nevertheless, the PRAC considered that the MAH should provide a detailed rationale for removing the targeted questionnaires on pneumonia (TFUQ) as a routine pharmacovigilance activity.

5.3.3. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/II/0169/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC to add the adverse drug reaction (ADR) 'gait disturbance' to address the CHMP recommendation from P46/085; 2) update of section 4.2 of the SmPC to add dysgeusia as a potential experience post administration and update of section 4.5 of the SmPC to remove drug interaction with methotrexate in accordance with the latest levetiracetam company core data sheet; 3) update of section 4.6 to add information on 'women of childbearing potential' and to update the pregnancy section to address the PRAC recommendation from LEG 084.1. The package leaflet and the RMP (version 8) are updated accordingly

Background

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

The CHMP is evaluating a grouped variation application for Keppra, a centrally authorised product containing levetiracetam, to reflect in particular safety data on pregnant women exposed to Keppra (levetiracetam) monotherapy. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes January 2018 and PRAC minutes March 2018.

Summary of advice

- The RMP version 8.1 for Keppra (levetiracetam) in the context of the procedure under evaluation by the CHMP is considered acceptable.
- The PRAC considered that the MAH's proposal to disseminate a direct healthcare professional communication (DHPC) was not warranted. As an alternative, the PRAC agreed that key messages and the supporting data outlined in the proposed DHPC can be used by National Competent Authorities (NCAs) to communicate at national level the product information update related to use of levetiracetam in pregnancy.

5.3.4. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0004, Orphan

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.8 of the SmPC to include new safety information related to hydrocephalus. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to correct some typographical errors in section 5.1 of the SmPC

Background

Nusinersen is an antisense oligonucleotide (ASO) indicated for the treatment of 5q spinal muscular atrophy (5q-SMA).

The CHMP is evaluating a variation application for Spinraza, a centrally authorised product containing nusinersen, consisting of an update of the product information proposing to add 'hydrocephalus' as an undesirable effect and a warning, following the development in a few infants of communicating hydrocephalus without signs of meningitis or bleeding, requiring a ventriculo-peritoneal shunt procedure. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes February 2018.

Summary of advice

- The RMP for Spinraza (nusinersen) in the context of the procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 7.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- Given that it may be difficult to identify clinical signs of hydrocephalus in the context of the impairments caused by SMA, the PRAC supported the distribution of a direct healthcare professional communication (DHPC) to relevant healthcare professionals (HCPs) to warn them of this risk. Therefore, the MAH is requested to provide a draft DHPC and communication plan for further review.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/201709

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Bedaquiline is an antimycobacterial diarylquinoline. Sirturo (bedaquiline) is indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be achieved for reasons of resistance or tolerability.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Sirturo (bedaquiline) 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 review in-depth, all new fatal cases given the safety issues potentially associated with bedaquiline in the context of its increasing use.
- The MAH should submit to EMA within 180 days a review, or a variation as applicable, on the most recent data on bedaquiline resistance together with a discussion on recommending the screening for bedaquiline resistance prior to bedaquiline therapy. In addition, the MAH should present what efforts are made around drug susceptibility testing (DST) assays (including rapid tests), and the current status of such efforts. The RMP should be updated as applicable.

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

6.1.2. Daclizumab beta – ZINBRYTA[20] – PSUSA/00010518/201711

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Discussion on a PSUSA procedure

Background

Daclizumab beta is an immunosuppressant, interleukin inhibitor. Zinbryta (daclizumab) was indicated[21] for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease-modifying therapies (DMTs) and for whom treatment with any other DMT is contraindicated or otherwise unsuitable.

In March 2018, the PRAC recommended, as provisional measures, to suspend the use and the marketing authorisation(s) for Zinbryta (daclizumab), and to recall all the batches of the medicinal product from the market up to the level of pharmacies and hospitals, without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004. For further background, see PRAC minutes March 2018. After the submission and start of the currently ongoing PSUSA procedure, the marketing authorisation(s) (MA) was withdrawn at the MAH's request and a European Commission (EC) decision was issued on 27 March 2018. In line with the 'Guidance on handling of PSUR procedures for suspended or withdrawn/non-renewed/revoked marketing authorisations' (EMA/576230/2015) (see PRAC minutes January 2016), the PRAC discussed the need to request the submission of a further/ad-hoc PSUR.

Discussion

- The PRAC agreed on completing the ongoing PSUSA assessment with finalisation planned in June 2018. The PRAC also agreed that a further PSUR should be submitted to the EMA 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.

[20] European Commission (EC) decision on the MA withdrawal of Zinbryta dated 27 March 2018
[21] European Commission (EC) decision on the MA withdrawal of Zinbryta dated 27 March 2018

6.1.3. Daptomycin - CUBICIN (CAP) - PSUSA/00000931/201709

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Daptomycin is an antibacterial for systemic use. Cubicin (daptomycin) is indicated for the treatment of adult and paediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI), adult patients with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus,* as well as for adult and paediatric patients (1 to 17 years of age) with *Staphylococcus aureus* bacteraemia (SAB).
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 benefit-risk balance of Cubicin (daptomycin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include thrombocytopenia as an undesirable effect of unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should provide a cumulative review of cases of interstitial lung disease received to date and any reports received in the next reporting interval, and propose updates to the product information as necessary, as well as a detailed discussion of any new cases of neutropenia and leukopenia.

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. Denosumab[23] - PROLIA (CAP) - PSUSA/00000954/201709

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Denosumab is a human monoclonal antibody (immunoglobulin (Ig)G2) affecting bone structure and mineralisation. Prolia (denosumab) is indicated for the treatment osteoporosis in postmenopausal women and in men at increased risk of fractures as well as for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

[22] 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
[23] Indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer

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 benefit-risk balance of Prolia (denosumab) 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 review of cases of 'paraesthesia' and discuss the need to update the product information.
- The US database study to assess whether there is an increased risk of myocardial infarction and stroke with the use of Prolia (denosumab) among osteoporosis patients in real-world clinical practice should be included in the RMP as a category 3 study and the RMP updated at the next regulatory opportunity. The study proposal is overall accepted, although certain points in relation to a more detailed study design need further assessment.

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. Denosumab[24] - XGEVA (CAP) - PSUSA/00009119/201709

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Denosumab is a human monoclonal antibody (immunoglobulin (Ig)G2) affecting bone structure and mineralisation. Xgeva (denosumab) is indicated for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours as well as for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xgeva, a centrally authorised medicine containing denosumab, and issued a recommendation on its marketing authorisation(s). At the current meeting, an oral explanation by the MAH took place.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Xgeva (denosumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add information regarding the risk of 'new primary malignancy' in the course of Xgeva (denosumab) treatment as

[24] Indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone

an undesirable effect of common frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[25].

- In addition, the PRAC agreed on the need for a direct healthcare professional communication (DHPC) to inform healthcare professionals (HCPs) about this new 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.

Post-meeting note: On 19 April 2018, the PRAC adopted by written procedure the PRAC assessment report and recommendation and agreed the content of the DHPC together with a communication plan.

6.1.6. Dulaglutide - TRULICITY (CAP) - PSUSA/00010311/201709

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Dulaglutide is a blood glucose lowering long-acting glucagon-like peptide 1 receptor agonist. Trulicity (dulaglutide) is indicated for the treatment of adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control as monotherapy and add-on therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Trulicity (dulaglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add the undesirable effects cholelithiasis and cholecystitis with a frequency uncommon. Therefore, the current terms of the marketing authorisation(s) should be varied[26].

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

6.1.7. Eftrenonacog alfa - ALPROLIX (CAP) - PSUSA/00010499/201709

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

Scope: Evaluation of a PSUSA procedure

Background

Eftrenonacog alfa is a long-acting, fully recombinant, fusion protein. Alprolix (eftrenonacog alfa) is indicated for the treatment and prophylaxis of bleeding in all-age-groups patients with haemophilia B (congenital factor IX deficiency).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Alprolix (eftrenonacog alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be amended to update the information on hypersensitivity and anaphylaxis as a warning and as an undesirable effect. Therefore the current terms of the marketing authorisation(s) should be varied[27].

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

6.1.8. Eltrombopag - REVOLADE (CAP) - PSUSA/00001205/201709 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Eltrombopag is an antihaemorrhagic systemic haemostatic. Revolade (eltrombopag) is indicated for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP) in patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins), for the treatment of thrombocytopenia in adult patients with chronic hepatitis C virus (HCV) infection, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy as well as for the treatment of adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pre-treated and are unsuitable for haematopoietic stem cell transplantation.

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

Summary of recommendation(s) and conclusions

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

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

- Nevertheless, the product information should be updated to add a warning on potential laboratory test interference with total bilirubin and creatinine testing. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide summaries of reviews for cataract and neutropenia in paediatric populations and should closely monitor cases of pancreatitis.

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. Insulin aspart - FIASP (CAP), NOVOMIX (CAP), NOVORAPID (CAP) - PSUSA/00001749/201709

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Insulin aspart is a rapid-acting insulin analogue indicated for the treatment of diabetes mellitus under certain conditions.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Fiasp, NovoMix, and NovoRapid, centrally authorised medicines containing insulin aspart, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Fiasp, NovoMix and NovoRapid (insulin aspart) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The PRAC agreed on the content of communication letters to be disseminated to patients and healthcare professionals, to re-emphasise key handling aspects of the Accu-Chek Insight insulin pump system, in order to minimise the risk of leakage when changing a pre-filled insulin cartridge.
- In the next PSUR, the MAH should discuss reports of medication errors defined as incorrect product storage and the related potential risk minimisation. Moreover, the MAH should discuss the potential causes for lack of efficacy associated with use of Fiasp via the pump system and perform a review of the cases related to serious systemic allergic reactions associated with Fiasp, with a proposal for an update of the product information, if applicable, in line with the product information for NovoRapid.

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.

[28] Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.10. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/201709

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Naltrexone is a mu-opioid antagonist and bupropion is an inhibitor of neuronal dopamine and norepinephrine reuptake. Mysimba (naltrexone/bupropion) is indicated for the management of weight in adult patients (≥18 years) with an initial body mass index (BMI) of ≥30 kg/m^2 (obese), or ≥27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g. type 2 diabetes, dyslipidaemia, or controlled hypertension).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Mysimba (naltrexone/bupropion) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add urticaria as an undesirable effect for the naltrexone/bupropion fixed-dose combination with the frequency uncommon. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH should provide separate, detailed reviews of medication errors, off-label use and misuse. If any safety issue is observed based on adverse reactions pertaining to use outside the approved product information, the need for risk minimisation measures should be discussed. Additionally, the MAH should provide an in-depth analysis of cases related to nervous system disorders and psychiatric disorders in elderly patients taking naltrexone/bupropion, including a causality assessment. Moreover, the MAH should provide a cumulative review of somnolence cases related to the naltrexone/bupropion fixed-combination as well as of cases reported with long–term use of naltrexone/bupropion / chronic use beyond 1 year under the MedDRA SOC[30] 'musculoskeletal and connective tissue disorders'.

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

6.1.11. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201709

Applicant: The Medicines Company UK Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

[29] 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
[30] Medical dictionary for regulatory activities – System Organ Class (SOC)

Background

Oritavancin is a glycopeptide antibacterial for systemic use. Orbactiv (oritavancin) is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Orbactiv (oritavancin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the occurrence of 'red man syndrome' as well as to add 'red man syndrome' as an undesirable effect of rare frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[31].

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

6.1.12. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201709

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Pembrolizumab is a humanised monoclonal antibody and antineoplastic agent. Keytruda (pembrolizumab) is indicated as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, for the first line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) under certain conditions, for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 under certain conditions, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) under certain conditions as well as for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy or who are not eligible for cisplatin-containing chemotherapy.

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

Summary of recommendation(s) and conclusions

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

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

- Nevertheless, the product information should be updated to add pericarditis and pericardial effusion as undesirable effects of uncommon frequency and to include additional information on the existing undesirable effect of myasthenic syndrome to indicate the inclusion of myasthenia gravis. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH should provide a cumulative review of sepsis, a review of the risk of cholangitis sclerosis, a discussion on the cases of exacerbation of pre-existing myasthenia gravis and the related need for a warning on the risk of exacerbation of the symptoms of myasthenia gravis and new onset of myasthenia gravis and myasthenia syndrome. In addition, the MAH should include a discussion and/or review of the risk of tumour lysis syndrome from all sources with a proposal to update the product information if applicable. Moreover, the MAH should provide a review of organising pneumonitis, use in patients with pre-existing autoimmune diseases and aplasia pure red cell or erythroblastopenia.

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

6.1.13. Regorafenib - STIVARGA (CAP) - PSUSA/00010133/201709

Applicant: Bayer AG

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Regorafenib is an antineoplastic protein kinase inhibitor. Stivarga (regorafenib) is indicated as monotherapy for the treatment of adult patients with metastatic colorectal cancer (CRC) under certain conditions, with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on, or are intolerant to, prior treatment with imatinib and sunitinib, and with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Stivarga (regorafenib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include peripheral neuropathy as an undesirable effect of common frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[33].

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

- The MAH should submit to EMA within 60 days a cumulative review of necrotising fasciitis taking into account all sources of information (study, literature, post-marketing reporting).

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

6.1.14. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/201709

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Rivaroxaban is a direct factor Xa inhibitor. Xarelto (rivaroxaban) is indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery as well as for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults. Finally, Xarelto (rivaroxaban), co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

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 benefit-risk balance of Xarelto (rivaroxaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include ‘drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome’ in the dermatological reactions warning, to include information on the interactions with clarithromycin, erythromycin and fluconazole, as well as to add DRESS syndrome and anaphylactic reactions including anaphylactic shock as undesirable effects with a frequency very rare. Therefore, the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAH should present a cumulative tabulation of all cases where the diagnosis of vasculitis has been confirmed by biopsy or other reliable method of diagnosis, including a temporal relationship and information on dechallenge/rechallenge, medical history and concomitant medications, with a detailed discussion and analysis of the cases. In addition, the MAH should include a review of new cases of hepatic failure and new cases of medically confirmed esophagitis.

[34] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

6.1.15. Teriflunomide - AUBAGIO (CAP) - PSUSA/00010135/201709

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Teriflunomide is selective immunosuppressant. Aubagio (teriflunomide) is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Aubagio (teriflunomide) 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 present a review of any new information relating to malignancies in general and lymphoma in particular. The MAH should also closely monitor cases of progressive multifocal leukoencephalopathy (PML) and take immediate action as soon as any new case of PML with teriflunomide becomes known.
- The MAH is requested to submit to EMA a variation within 60 days to provide the final study report for study LTS6050[35] and to discuss within that report whether the results of the study warrant changes to the product information. The MAH is also asked specifically to discuss whether any frequencies of undesirable effects listed in the product information should be updated according to the results of the study (e.g. those currently listed with frequency unknown) and whether additional undesirable effects should be included, especially taking into account colitis and pulmonary hypertension.

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

6.1.16. Trabectedin - YONDELIS (CAP) - PSUSA/00003001/201709

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Doris Stenver

[35] Long-term extension of the multinational, double-blind, placebo controlled study EFC6049 (HMR1726D/3001) to document the safety of two doses of teriflunomide (7 and 14 mg) in patients with multiple sclerosis with relapses. NCT00803049. EudraCT number: 2006-003361-14

Scope: Evaluation of a PSUSA procedure

Background

Trabectedin is an antineoplastic agent indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents, and for the treatment of patients with relapsed platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin (PLD).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Yondelis (trabectedin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add additional information to the warning on capillary leak syndrome (CLS) and include CLS as an undesirable effect. Therefore, the current terms of the marketing authorisation(s) should be varied[36].
- In the next PSUR, the MAH should comment on the missing information 'genetic polymorphism' and 'use in patients of different racial/ethnic origin' and should the spontaneous reports not be considered suitable for obtaining information about genetic polymorphisms, the MAH should discuss alternative measures that could be initiated to retrieve further information on the topic of genetic polymorphisms.

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 single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

See also Annex I 16.2.

6.2.1. Pantoprazole - CONTROLOC CONTROL (CAP), PANTOLOC CONTROL (CAP), PANTOZOL CONTROL (CAP), SOMAC CONTROL (CAP); NAP - PSUSA/00002285/201708

Applicants: Takeda GmbH, various

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Pantoprazole is a proton pump inhibitor for acid-related disorders indicated for the short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

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

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Controloc Control, Pantoloc Control, Pantozol Control, Somac Control, centrally authorised medicines containing pantoprazole, and nationally authorised medicines containing pantoprazole, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of pantoprazole-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add paraesthesia and hypocalcaemia as undesirable effects with a frequency not known. Therefore, the current terms of the marketing authorisations should be varied[37].
- In the next PSUR, the MAH should provide more details regarding pregnancy cases, in particular the number of reports of normal births, spontaneous abortions, and congenital malformations as well as cumulative reviews of DRESS, rhabdomyolysis, and gastrointestinal premalignant disorders.

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

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

See also Annex I 16.3.

6.3.1. Alprostadil[38] (NAP) - PSUSA/00000111/201707

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Alprostadil is a prostaglandin E1 (PGE1) indicated for the treatment of erectile dysfunction in adult males.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of alprostadil-containing medicinal product(s) in the approved indication(s) remains unchanged.

[37] 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
[38] Indicated in peripheral arterial occlusive diseases only

- Nevertheless, the product information should be updated to include gastrointestinal haemorrhage. Therefore, the current terms of the marketing authorisation(s) should be varied[39].
- In the next PSUR, the MAHs Recordati and UCB should update safety concerns and add gastrointestinal haemorrhage as an important identified risk, as well as closely monitor cases of haemorrhage.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC is not required and the EURD list should be updated accordingly.

6.3.2. Dexamfetamine (NAP) - PSUSA/00000986/201709

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Dexamfetamine is a centrally acting sympathomimetic with central stimulant and anorectic activity, indicated in narcolepsy. It is also indicated for children with refractory hyperkinetic states under the supervision of a physician specialising in child psychiatry.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of dexamfetamine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include Raynaud's phenomenon as an undesirable effect with a frequency not known. Therefore, the current terms of the marketing authorisation(s) should be varied[40].
- In the next PSUR, the MAHs should provide a detailed review of all adverse drug reactions that could be related to the occurrence of serotonin syndrome in patients taking dexamfetamine.

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.

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

6.3.3. Finasteride (NAP) - PSUSA/00001392/201708

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Finasteride is a testosterone-5-alpha reductase inhibitor indicated for the treatment of benign prostatic hyperplasia as the 5µg formulation and for the treatment of androgenetic alopecia in men as the 1mg formulation.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of finasteride-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include anxiety as an undesirable effect with a frequency not known. Therefore, the current terms of the marketing authorisation(s) should be varied[41].
- In the next PSUR, the MAH(s) should present the case narratives and a thorough analysis of muscle-related cases. The MAH(s) should also closely monitor the events of persistent psychiatric disorders and any new cases should be discussed. Furthermore, the MAH(s) should perform a careful literature review and discuss publications of relevance for the safety of finasteride.

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. Leuprorelin (NAP) - PSUSA/00001844/201707

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Leuprorelin is a synthetic gonadotropin-releasing hormone analogue indicated for the treatment of hormone-responsive cancers such as prostate cancer and breast cancer. It may also be used for oestrogen-dependent conditions such as endometriosis or uterine fibroids. It may be used for the treatment of precocious puberty in both males and females, and to prevent premature ovulation in cycles of controlled ovarian stimulation for in vitro fertilisation (IVF).

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of leuprorelin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add interstitial lung disease, as undesirable effect with a frequency not known. Therefore, the current terms of the marketing authorisation(s) should be varied[42].
- In the next PSUR, the MAH should perform a comprehensive review of the cases of facial paralysis (and related terms) including data from the literature, clinical trial and post marketing data, and provide a discussion on the need to update the product information accordingly.

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. Naproxen (NAP) - PSUSA/00002125/201708

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Naproxen is a propionic acid derivative and non-steroidal anti-inflammatory non-selective cyclooxygenase 1-2 (COX1-2) inhibitor drug (NSAID) used to treat a variety of inflammatory conditions and symptoms that are due to excessive inflammation, such as pain and fever (naproxen has fever-reducing or antipyretic properties in addition to its anti-inflammatory activity). Inflammatory sources of pain that may respond to naproxen's anti-inflammatory activity are conditions such as migraine, osteoarthritis, kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps, tendinitis, and bursitis.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of naproxen-containing medicinal products in the approved indication(s) remains unchanged.

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

- Nevertheless, the product information should be updated to add the information on interaction with low dose acetylsalicylic acid. Therefore, the current terms of the marketing authorisation(s) should be varied[43].
- In the next PSUR, the MAHs should keep under monitoring the increased risk of thromboembolism in patients with atrial fibrillation and the drug interaction with pemetrexed. In addition, the MAH Bayer should submit the number of medical errors PTs[44] associated or not with adverse events, information on the number of cases related to these PTs, categorised by those associated or not with adverse events, and provide a calculation of the reporting rate of medication errors and associated adverse events for those terms more frequently reported, and assess if an imbalance in the rates occurred in comparison to the previous interval periods, with a critical discussion of the possible reasons, in case of an imbalance.

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

6.3.6. Permethrin (NAP) - PSUSA/00002355/201707

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Permethrin is a pyrethrine ectoparasiticide indicated as topical use for the treatment of head lice (*Pediculus capitis*), of scabies (caused by *Sarcoptes scabiei*) and of treatment of crab lice infection (caused by *Pthirus pubis*).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of permethrin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include warnings on hypersensitivity reactions to chrysanthemums (a type of flowering plants) and on the need for close medical supervision in young children as well as to add paraesthesia as an undesirable effect of frequency common for the 5% topical formulation and not known for the 1% and 0.43% topical formulations. Therefore, the current terms of the marketing authorisation(s) should be varied[45].

[43] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[44] Medical dictionary for regulatory activities – Preferred Term (PT)
[45] 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

- In the next PSUR, the MAHs should present a detailed review on permethrin resistance especially when used for the treatment of head lice/nits, and discuss the possibilities to further evaluate the carcinogenic/mutagenic potential of their medicinal products. The MAHs should also discuss whether, as a precautionary measure taking into account that treatment alternatives for head lice based on a physical mechanism of action are available, a warning should be included in the product information (PI) stating that the treatment of head lice with permethrin in pregnant women should only constitute a second line treatment to physically acting treatment alternatives. In addition, the MAHs should submit a cumulative review of all serious and non-serious cases of alopecia and dizziness and review the potential effects in developing infants exposed to permethrin via breast feeding with a discussion on whether a statement regarding interruption of breastfeeding should be included in the PI.

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

6.3.7. Quetiapine (NAP) - PSUSA/00002589/201707

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Quetiapine is an antipsychotic indicated for the treatment of schizophrenia, the treatment of moderate to severe manic episodes in bipolar disorder, the treatment of major depressive episodes in bipolar disorder and for the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment. Prolonged release quetiapine-containing medicinal products are additionally indicated for add-on treatment of major depressive episodes in patients with major depressive disorder (MDD) who have had sub-optimal response to antidepressant monotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of quetiapine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add for all quetiapine-containing products ‘drug reaction with eosinophilia and systemic symptoms (DRESS)’ as an undesirable effect with a frequency not known. In addition, ‘delayed peak sedation and peak pulse’ observed with the prolonged release formulations should be added to the product information section on overdose for quetiapine prolonged release

formulations. Therefore, the current terms of the marketing authorisation(s) should be varied[46].

- In the next PSUR, the MAH for the originator quetiapine-containing product is requested to provide a cumulative review with a detailed discussion on intraoperative floppy iris syndrome (IFIS), including a proposal for updating the product information (PI) if considered relevant. In addition, cumulative analyses on confusion and on nystagmus, and cumulative data with regard to congenital malformations, should be included.

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 16.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[47]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[48]

See also Annex I 17.2.

7.2.1. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 007.1

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 007 [protocol for study SB2-G41-AS; SB2-G42-CD: a prospective observational cohort study in ankylosing spondylitis (AS) and Crohn's disease (CD) for two years to observe safety, efficacy and immunogenicity of Flixabi with active comparator in AS and CD] as per the request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

Background

Flixabi is a centrally authorised medicine containing infliximab, a tumour necrosis factor alfa (TNF-α) inhibitor indicated in rheumatoid arthritis in combination with methotrexate under conditions, in adult Crohn's disease (CD) under conditions, in paediatric CD under conditions,

[46] Update of SmPC sections 4.8 (for all quetiapine-containing medicinal products) and 4.9 (for quetiapine prolonged release formulation only). The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[47] In accordance with Article 107n of Directive 2001/83/EC
[48] 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

in ulcerative colitis under conditions, in ankylosing spondylitis (AS) under conditions, in psoriatic arthritis under conditions and in psoriasis under certain conditions.

As part of the RMP for Flixabi (infliximab), the MAH was required to conduct prospective observational cohort study(ies) of Flixabi (infliximab) in AS and CD for 2 years in order to investigate immunogenicity, serum sickness (delayed hypersensitivity reactions), serious infusion reactions during a re-induction regimen following disease flare, and acute hypersensitivity reactions including anaphylactic shock. In June 2017 the MAH submitted two study protocols, versions 1.0 respectively, for the two above-mentioned cohort studies (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) which were assessed by the Rapporteur. The PRAC considered that the revised protocols should be resubmitted within 60 days and a 60 day-timetable was to be followed. For further background see PRAC minutes November 2017. In January 2018 the MAH submitted the revised protocols which were assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC noted the assessment of the PRAC Rapporteur and had a preliminary discussion. The PRAC agreed that further discussion on the most appropriate way forward was needed at the PRAC meeting in May 2018.

7.3. Results of PASS imposed in the marketing authorisation(s)[49]

None

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

See also Annex I 17.4.

7.4.1. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0070/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report from the LUMINOUS study (CRFB002A2406): an observational, multicentre study to assess the long-term safety and effectiveness of ranibizumab in routine clinical practice, in fulfilment of the post-authorisation measures MEA 036, MEA 048 and MEA 054 - the RMP is updated accordingly; 2) submission of an updated RMP (version 17.0) to include changes not consequential to LUMINOUS study. In addition, the MAH is proposing the removal of the use of educational materials and targeted follow-up checklists listed in Annex II-D of the product information

Background

Lucentis is a centrally authorised medicine containing ranibizumab, an anti-neovascularisation ophthalmological agent. Lucentis (ranibizumab) is indicated for the

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

treatment of adults with neovascular (wet) age-related macular degeneration (AMD), with visual impairment due to choroidal neovascularisation (CNV), with visual impairment due to diabetic macular oedema (DME), as well as with visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).

The MAH for Lucentis (ranibizumab) conducted an observational, multicentre study (CRFB002A2406)[51] to assess the long-term safety and effectiveness of ranibizumab in routine clinical practice, in fulfilment of post-authorisation measures (MEA 036, MEA 048 and MEA 054). The Rapporteur assessed the MAH's final study report submitted by the MAH in November 2017.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC considered that supplementary information is warranted. The post-authorisation measures in relation to the LUMINOUS study are considered fulfilled, however further changes to the RMP are needed. Finally, the removal of the educational material for the prescriber as a risk minimisation measure is endorsed as the safety messages of the educational materials are well-known by HCPs and are all included in the product information. However, the patient educational material is an important risk minimisation measure to ensure that the individual patient receives adequate information on key signs and symptoms of adverse events, and guidance on when to seek urgent attention from a healthcare provider. Thus, the PRAC agreed that this should be maintained.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

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

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

None

[51] The LUMINOUS study

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

8.3.1. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/R/0032 (without RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

Background

Defitelio is a centrally authorised medicine containing defibrotide, an antithrombotic agent, authorised in 2013. Defitelio (defibrotide) is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.

The MAH submitted an application for renewal of the marketing authorisation(s) for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Taking into account the available pharmacovigilance data for Defitelio (defibrotide) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) was warranted on the basis of pharmacovigilance grounds given the current status of outstanding specific obligations (SO).

  See also under 5.2.1.

8.3.2. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/R/0028 (without RMP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

Background

Imnovid is a centrally authorised medicine containing pomalidomide, an immunomodulating agent, authorised in 2013. Imnovid (pomalidomide) in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

The MAH submitted an application for renewal of the marketing authorisation(s) for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Imnovid (pomalidomide) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds as presented in Annex IV of the opinion, relating to the slower recruitment than expected in the category 1 PASS conducted to better characterise the risks of the treatment with Imnovid (pomalidomide) in clinical practice (i.e. haemorrhage, thromboembolic events and serious infections).
- The PRAC concluded that no relevant safety concerns had arisen from the assessment of this first renewal procedure. The PRAC recommended that the MAH continue to submit yearly PSURs.

8.3.3. Radium (^{223}Ra) dichloride - XOFIGO (CAP) - EMEA/H/C/002653/R/0030 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

Background

Xofigo is a centrally authorised medicine containing radium dichloride, a therapeutic alfa particle-emitting radiopharmaceutical, authorised in 2013. Xofigo (radium-223 dichloride) is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

The MAH submitted an application for renewal of the marketing authorisation(s) for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Xofigo (223-radium dichloride) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds relating to the ongoing review conducted under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1459). This is without prejudice to the final conclusions of this referral procedure.
- The PRAC concluded that no other relevant safety concerns had arisen from the assessment of this first renewal procedure. The PRAC recommended that the MAH continue to submit yearly PSURs.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC working group - Best practice guide – recommendations on efficiency of plenary meetings - implementation

PRAC lead: Martin Huber, Ulla Wändel Liminga, Menno van der Elst, Tatiana Magálová, Albert van der Zeijden, Ghania Chamouni, Jan Neuhauser

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016), the PRAC was updated at the organisational matters teleconference held on 26 April 2018 on quantitative measures collected for the PRAC meetings in the last quarter of 2017 and first quarter of 2018 .

12.2. Coordination with EMA Scientific Committees or CMDh-v

12.2.1. EMA Scientific Committees – Timing for chair elections

The EMA Secretariat informed the PRAC on the timing for Chair's and vice-Chair's elections for 2018. The PRAC Chair election is scheduled in July 2018 and the PRAC vice-Chair election in September 2018.

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

12.3.1. Working Party with Healthcare Professionals' Organisations (HCPWP) - work plan 2018-2019

The PRAC endorsed the HCPWP work plan for 2018-2019 and welcomed the opportunities for further dialogue and interaction with representatives of healthcare professionals, academia and learned societies.

12.3.2. Working Party with Patients' and Consumers' Organisations (PCWP) – work plan 2018-2019

The PRAC endorsed the PCWP work plan for 2018-2019 and fully endorsed the value of the strengthened involvement of patient and consumer organisations in a wide array of EMA activities, including PRAC activities where appropriate.

12.3.3. Blood Products Working Party - Haemophilia registries – workshop

The PRAC was updated on the organisation of a workshop on Haemophilia Registries to be held on 8 June 2018 at the EMA and was presented with a draft agenda. The current revision of the factor VIII (FVIII) guideline (consultation ended in January 2018) includes the proposed removal of the requirement to perform specific pre-marketing studies in previously untreated patients (PUPs) (in line with paediatric investigation plan (PIP) requirements) and instead to request these data to be generated through registries. This multi-stakeholder meeting is organised to discuss and agree on the implementation of this new requirement as well as requirements for novel therapies.

12.4. Cooperation within the EU regulatory network

12.4.1. Brexit: preparedness of the regulatory network and capacity increase

The topic was deferred to May 2018.

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 – Q1 2018 and predictions

The topic was deferred to May 2018.

12.8.2. PRAC workload statistics – Q1 2018

The EMA secretariat presented, at the organisational matters teleconference held on 26 April 2018, quarterly and cumulative figures to estimate the evolution of the workload of the PRAC, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. See previous update, PRAC minutes March 2018.

12.9. Pharmacovigilance audits and inspections

12.9.1. Good Pharmacovigilance Practices (GVP) module I on 'Pharmacovigilance systems and their quality systems' - revision

The PRAC was informed that the Pharmacovigilance Inspectors Working Group (PhV IWG) was working on a proposal to revise the 'Good Pharmacovigilance Practices (GVP) module I on 'Pharmacovigilance systems and their quality systems'. Once the proposal is drafted, a review by PRAC will be conducted.

12.9.2. Pharmacovigilance systems and their quality systems

None

12.9.3. Pharmacovigilance inspections- Template for sharing assessor's information – launch of pilot phase

Further to the presentation at the March 2018 meeting of the finalised template for sharing of information between 'Assessors and Inspectors' on pharmacovigilance matters, which had been developed by the Pharmacovigilance Inspectors Working Group (PhV IWG)-PRAC subgroup and consolidated further to PRAC comments, the EMA Secretariat presented to PRAC the launch of a pilot phase. For further background, see PRAC minutes October 2017 and PRAC minutes March 2018.

12.9.4. Pharmacovigilance inspections - Union procedure on follow-up of pharmacovigilance inspections

Further to previous discussion on the draft 'Union procedure on the follow-up of pharmacovigilance inspections' (see PRAC minutes November 2017 and PRAC minutes January 2018), the PRAC adopted the finalised 'Union procedure on the follow-up of pharmacovigilance inspections'.

12.9.5. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports single assessment (PSUSA) – update on follow-up procedures (PSUFU) for nationally approved products (NAPs) and CMDh table on other considerations

PRAC lead: Menno van der Elst

The PRAC was updated on the PSUR follow-up procedures from CMDh and on the CMDh interaction table on the 'other considerations' section.

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the progress made including the update on the EURD tool (a tool that supports the decision making on changing PSUR frequencies).

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list, version April 2018, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of April 2018, the updated EURD list was adopted by the CHMP and CMDh at their April 2018 meetings and published on the EMA website on 08/05/2018, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the SMART Working Group (SMART WG) meeting held on 9 April 2018. With regards to the paracetamol pilot (run between August 2017 and January 2018), the PRAC was updated on the WG agreement to handle the follow-up information for previously confirmed signals through a non-urgent information request (NUI). In addition, the SMART WG discussed possible challenges for communication at national level.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on 26/04/2018 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. EMA relocation - update

The PRAC was updated on the status and plans for the EMA relocation to Amsterdam (NL). A tracking tool has been published on the EMA website.

12.20.2. Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population-specific considerations IV: 'Paediatric pharmacovigilance'

The topic was deferred to May 2018.

13. Any other business

Next meeting on: 14-17 May 2018

14. Annex I – Signals assessment and prioritisation[52]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[53].

14.1.1. Alemtuzumab – LEMTRADA (CAP)

Applicant(s): Genzyme Therapeutics Ltd

PRAC Rapporteur: Anette Stark

Scope: Signal of cytomegalovirus (CMV) infection

EPITT 19193 – New signal

Lead Member State: DK

14.1.2. Belimumab – BENLYSTA (CAP)

Applicant(s): Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of lupus nephritis

EPITT 19174 – New signal

Lead Member State: SE

14.1.3. Daratumumab – DARZALEX (CAP)

Applicant(s): Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of encephalopathy

EPITT 19176 – New signal

Lead Member State: PT

14.1.4. Dimethyl fumarate – TECFIDERA (CAP)

Applicant(s): Biogen Idec Ltd

[52] [52] 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

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

PRAC Rapporteur: Martin Huber

Scope: Signal of immune thrombocytopenic purpura, thrombocytopenia

EPITT 19192 – New signal

Lead Member State: DE

14.1.5. Parathyroid hormone – NATPAR (CAP)

Applicant(s): Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Almath Spooner

Scope: Signal of nephrolithiasis

EPITT 19177 – New signal

Lead Member State: IE

14.1.6. Sitagliptin – JANUVIA (CAP), RISTABEN (CAP), TESAVEL (CAP), XELEVIA (CAP); sitagliptin, metformin hydrochloride – JANUMET (CAP), EFFICIB (CAP), RISTFOR (CAP), VELMETIA (CAP) Angiotensin-converting-enzyme (ACE)-inhibitors: benazepril (NAP); captopril (NAP); cilazapril (NAP); delapril (NAP); enalapril (NAP); fosinopril (NAP); imidapril (NAP); lisinopril (NAP); moexipril (NAP); perindopril (NAP); quinapril (NAP); ramipril (NAP); spirapril (NAP); trandolapril (NAP); zofenopril (NAP); zofenopril, hydrochlorothiazide (NAP)

Applicant(s): Merck Sharp & Dohme Limited, various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of potential drug interaction between sitagliptin and angiotensin-converting-enzyme (ACE)-inhibitors leading to an increased risk of angioedema

Action: For adoption of PRAC recommendation

EPITT 17608 – New signal

Lead Member State: NL

14.1.7. Tocilizumab – ROACTEMRA (CAP)

Applicant(s): Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of hypofibrinogenaemia

EPITT 19179 – New signal

Lead Member State: DE

14.2. New signals detected from other sources

14.2.1. Duloxetine – ARICLAIM (CAP), CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP); NAP

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

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of interstitial lung disease

EPITT 19175 – New signal

Lead Member State: ES

14.2.2. Olanzapine – ZALASTA (CAP), ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP); NAP

Applicant(s): Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), KRKA d.d. (Zalasta), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of somnambulism

EPITT 19202 – New signal

Lead Member State: FI

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

None

15.2. Medicines in the post-authorisation phase – PRAC-led procedure

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the variation procedure for the below mentioned medicine(s).

15.2.1. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/II/0004

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Updated RMP (version 2.1) in order to indicate changes in the distribution method for the Imraldi patient alert card (PAC) from its inclusion in Annex IIIa of the product

information to be provided to patients by healthcare professionals by including the PAC in the physician educational material. Annex IIIa is updated accordingly

15.2.2. Ceftazidime, avibactam - ZAVICEFTA (CAP) - EMEA/H/C/004027/II/0008

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Updated RMP (version 2.0) in order to incorporate data from the REPROVE study (already submitted in procedure II/02), align the RMP with the current EU template, and add current post-marketing experience relative to the RMP data lock point (DLP): 24/8/2017. REPROVE is a phase 3 randomized, multicentre, double-blind, double-dummy, parallel group comparative study to determine the efficacy, safety and tolerability of ceftazidime/avibactam (CAZ-AVI) (2,000 mg ceftazidime/500 mg avibactam) *vs* meropenem (1,000 mg) in the treatment of nosocomial pneumonia (NP), including ventilator associated pneumonia (VAP), in hospitalised adults 18 years of age or older

15.2.3. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS1342/0034; ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS1342/0041

Applicant: AbbVie Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Updated RMP (version 4) to incorporate changes requested by PRAC (in procedures PSUSA/00010363/201701 and PSUSA/00010367/201701 finalised in September 2017): addition of a new potential risk of depression and suicide as newly identified safety concerns; removal of off-label use and medication error as potential risks; renaming of the potential risk of development of resistance to lack of efficacy/risk of development of resistance. In addition, the commitment dates for four ongoing studies (on-going and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan) have been revised

15.2.4. Follitropin alfa - BEMFOLA (CAP) - EMEA/H/C/002615/II/0016

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Menno van der Elst

Scope: Updated RMP (version 2) based on a phase 3 multicentre study conducted to compare the efficacy and safety of two recombinant human follicle stimulating hormone (r-hFSH) formulations in normal ovulatory women 35 to 42 years of age undergoing in-vitro fertilisation (IVF) (CSR FIN3002)

15.2.5. Follitropin alfa, lutropin alfa - PERGOVERIS (CAP) - EMEA/H/C/000714/II/0055

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Julie Williams

Scope: Updated RMP (version 5.1) in order to revise the epidemiology section based on the recent literature data, to revise the non-clinical part of the safety specification section with the data available from recombinant human follicle stimulating hormone (r-hFSH), recombinant human luteinizing hormone (r-hLH) and Pergoveris (follitropin alfa/lutropin alfa) as well as to revise the clinical trial section for clinical studies for r-hFSH/r-hLH for ovulation induction (OI) and assisted reproductive technologies (ART). In addition, the patient exposure data is updated and a reference is added to the recently approved pharmaceutical forms (solution for injection in pre-filled pen (300IU/150IU, 450IU/225IU and 900IU/450IU)). Finally, the RMP is aligned with GVP module V on 'Risk management systems', revision 1

15.2.6. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0092, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Updated RMP (version 21.0) in order to delete 'myelosuppression' as an important identified risk and to reclassify 'cardiac failure' from an important potential to an important identified risk. In addition, changes in the definition of the identified risks 'hepatotoxicity' and 'fluid retention' have been implemented

15.2.7. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0144

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Updated RMP (version 16.0) to remove the additional risk minimisation measure of educational outreaches for the important identified risk of 'infusion related reactions' and 'acute infusion related reactions' (IRR)

15.2.8. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/WS1357/0063, RISTABEN (CAP) - EMEA/H/C/001234/WS1357/0055, TESAVEL (CAP) - EMEA/H/C/000910/WS1357/0063, XELEVIA (CAP) - EMEA/H/C/000762/WS1357/0067; sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/WS1357/0089, JANUMET (CAP) - EMEA/H/C/000861/WS1357/0089, RISTFOR (CAP) - EMEA/H/C/001235/WS1357/0076, VELMETIA (CAP) - EMEA/H/C/000862/WS1357/0092

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Updated RMP (version 10) in order to remove 'theoretic carcinogenic potential' currently classified as missing information from the list of safety concerns

15.3. Medicines in the post-authorisation phase – CHMP-led procedure

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the updated versions of the RMP for the below mentioned medicine(s).

15.3.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0037, Orphan

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include a new population: children from 2 to less than 5 years of age. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.1) are updated accordingly

15.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0004

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of section 4.8 of the SmPC in order to update the safety information based on the primary results from study IMvigor211 in order to fulfil ANX 002 (submission of the final clinical study report (CSR) is listed as an imposed post-authorisation efficacy study (PAES) in Annex II.D). This is a phase 3, open-label, multicentre, randomized study to investigate the efficacy and safety of atezolizumab (anti-programme death-ligand 1 (PD-L1) antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to implement some editorial changes throughout the product information

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

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

15.3.4. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/II/0111

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of section 5.1 of the SmPC to reflect the phase II outcome results from the ‘global registry on long-term oral antithrombotic treatment in patients with atrial

fibrillation' (GLORIA-AF) with the main objective 'to collect real-world data on important outcome events of antithrombotic treatments for the prevention of stroke' for patients taking Pradaxa (dabigatran etexilate). In addition, the results of the Medicare study (P14-15648) are proposed to be included in section 5.1 with further information on the effectiveness and safety of Pradaxa in patients with non-valvular atrial fibrillation (NVAF) in a real-world setting. The RMP (version 35.0) is updated accordingly

15.3.5. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/II/0003/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of an update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to reflect the week-48 results from two studies listed as category 3 studies in the RMP, namely: 1) study TMC114FD2HTX3001: evaluation of the efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed-dose combination regimen versus a regimen consisting of darunavir/cobicistat (DRV/COBI) fixed dose combination (FDC) co-administered with emtricitabine/tenofovir alafenamide (FTC/TDF) FDC in antiretroviral (ARV) treatment-naïve human immunodeficiency virus 1 (HIV-1) infected subjects; 2) study TMC114IFD3013: evaluation of switching to a D/C/F/TAF once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor combined with FTC/TDF in virologically-suppressed, HIV-1 infected subjects. The RMP (version 2.0) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to make minor editorial revision in the product information

15.3.6. Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/X/0056/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Grouped application consisting of: 1) extension application (line extension) to introduce a new pharmaceutical form (powder for oral suspension) associated with a new strength (10 mg/mL); 2) extension of indication to include the treatment of children and adolescents aged 1 year to 18 years with Philadelphia chromosome-positive (Ph+) chronic phase in chronic myeloid leukaemia (CML). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, to add a warning on effects on growth and development in the paediatric population and to update the safety information. The package leaflet and the RMP (version 15.0) are updated accordingly

15.3.7. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0026, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the frequencies of

adverse reactions included in the tabulated list of adverse reactions and to update the clinical efficacy and safety information based on the results from study 2006-05 (listed as a category 3 in the RMP): a phase 3, open-label expanded access study designed to provide access to defibrotide as an investigational new drug to patients with severe hepatic veno-occlusive disease. The package leaflet and the RMP (version 3.4) are updated accordingly. In addition, the MAH took the opportunity to bring the SmPC in line with the latest QRD template (version 10), to update the list of local representatives in the package leaflet and to correct a translation error in the Polish, Finnish, Danish and Latvian versions

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.9. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0059

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information and to revise the special warnings, precautions for use and undesirable effects based on cases of clinically significant hypercalcemia following discontinuation of denosumab in patients with growing skeletons (i.e. adolescent subject with giant-cell tumour of bone (GCTB) in study 20062004: an open label, multicentre, phase 2 study of denosumab in subjects with GCTB) and in post-marketing reports of paediatric patients treated with denosumab for GCTB or for unapproved indications previously determined as an important identified risk. The package leaflet and the RMP (version 30) are updated accordingly

15.3.10. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/II/0026

Applicant: Orion Corporation

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include the ‘sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation’ for Dexdor (dexmedetomidine). As a consequence, section

4.1, 4.2, 4.4, 4.6, 4.7, 4.8 and 5.1 of the SmPC are updated. In addition, the package leaflet and the RMP (version 7.0) are updated accordingly

15.3.11. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/X/0048/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form (prolonged-release suspension for injection (in autoinjector)); 2) variation to align the product information for the approved Bydureon formulations (powder and solvent for prolonged-release suspension for injection, powder and solvent for prolonged-release suspension for injection in pre-filled pen) with the product information proposed for the new pharmaceutical form (prolonged-release suspension for injection (in autoinjector)). In addition, the MAH took the opportunity to introduce minor editorial changes in the SmPC. The RMP (version 28) is updated accordingly

15.3.12. Human normal immunoglobulin - PRIVIGEN (CAP) - EMEA/H/C/000831/II/0129

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.3 of the SmPC to remove the contraindication on hyperprolineamia based on a comprehensive data survey of data from all available sources. The package leaflet and RMP (version 6.0) are updated accordingly

15.3.13. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0212

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 to include a warning recommending adult patients to be brought up to date with all vaccinations if possible prior to initiating Remicade (infliximab) therapy, in line with the current warning for children, and to clarify that patients on infliximab may receive concurrent vaccinations, except for live vaccines. The package leaflet and the RMP (version 15.1) are updated accordingly. The MAH took the opportunity to include minor editorial changes in the product information

15.3.14. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0054

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.1 of the SmPC to update the overall survival data of ipilimumab 3mg/kg monotherapy pooled across studies based on the final results of study CA184332 and CA184338 (listed as category 3 studies in the RMP), in order to fulfil MEA 035 and MEA 030.1 respectively. Study CA184332 is a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab as first line therapy in a community practice setting and study CA184438 is a

multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab as first line therapy. The RMP (version 18.4) is updated accordingly

15.3.15. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0055

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in adults in combination with nivolumab for Yervoy (ipilimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 20.0) are updated accordingly. In addition, the MAH took the opportunity to update the contact details of the Irish local representative in the package leaflet

15.3.16. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0098, Orphan

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Update of Annex II to amend the key elements of the risk minimisation programme with information on prescription duration and to revise due dates of two post-authorisation non-interventional, safety studies CC-5013-MDS-10 and CC-5013-MDS-1 on patients with myelodysplastic syndromes (MDS) treated with lenalidomide to gather safety data on the use of lenalidomide in MDS patients and monitor off-label use. Section 4.4 of the SmPC is updated accordingly. The RMP (version 35) is updated in line with GVP module V on 'Risk management systems' revision 1, in order to reclassify and/or rename known safety concerns associated with the use of Revlimid (lenalidomide). As a consequence, Annex IID is updated

15.3.17. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0039

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer after two or more prior systemic therapies, based on data from study ONO-4538-12: a Phase 3 study, multicentre, double-blind, randomized study in patients with unresectable advanced or recurrent gastric cancer. As a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. Annex II, package leaflet and the RMP (version 11.0) are updated accordingly

15.3.18. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0041

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include adjuvant treatment of adults and adolescents of 12 years of age and older with completely resected stage III and IV melanoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from pivotal study CA209238: a phase 3, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab after complete resection of stage IIIb/c or stage IV melanoma in subjects who are at high risk for recurrence. The package leaflet and the RMP (version 12.0) are updated in accordingly. The MAH also took the opportunity to revise the due dates for two category 4 studies, namely study CA209172: a single-arm, open-label, multicentre clinical trial with nivolumab for subjects with histologically confirmed stage III (unresectable) or stage IV melanoma progressing post prior treatment containing an anti-cytototoxic T lymphocyte-associated antigen (CTLA-4) monoclonal antibody; and study CA209171: an open-label, multicentre clinical trial with nivolumab monotherapy in subjects with advanced or metastatic squamous cell (Sq) non-small cell lung cancer (NSCLC) who have received at least one prior systemic regimen for the treatment of stage IIIb/IV SqNSCLC. In addition, the MAH took the opportunity to make minor editorial changes to the product information

15.3.19. Octocog alfa - ADVATE (CAP) - EMEA/H/C/000520/II/0091

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.2 of the SmPC in order to remove a statement mentioning that 'the use of the 2 mL presentation has not been documented for paediatric subjects below 2 years of age'. This update follows the final results from study 061101 (listed as a category 3 study in the RMP): a prospective, non-interventional, post-marketing surveillance study that assessed the safety and efficacy of Advate (octocog alfa) reconstituted in 2 mL of sterile water for injection during routine clinical practice in the EU. The package leaflet and the RMP (version 15.1) are updated accordingly

15.3.20. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0019

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations, based on data from FLAURA study (D5160C00007): a phase 3, double-blind, randomised study to assess the efficacy and safety of osimertinib versus a standard of care epidermal growth factor receptor-tyrosine kinase inhibitor as first-line treatment in patients with epidermal growth factor receptor mutation-positive, locally-advanced or metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8) are updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and package leaflet. As part of this application, the MAH requested an additional year of market protection

15.3.21. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0042

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include treatment as monotherapy of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) on or after platinum-containing chemotherapy based on the results from KEYNOTE-040 (KN040) with supportive data from two additional single arm studies (KEYNOTE-012: a phase Ib multi-cohort study of pembrolizumab on subjects with advanced solid tumours; KEYNOTE-055: a phase II clinical trial of single agent pembrolizumab in subjects with recurrent or metastatic head). KN040 is a randomized, multicentre, pivotal phase 3 study investigating Keytruda (pembrolizumab) as a monotherapy versus standard treatment (methotrexate, docetaxel or cetuximab) in patients with recurrent or metastatic HNSCC who have previously progressed on prior platinum. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 15.1) are updated accordingly. In addition, the MAH took the opportunity to include in SmPC section 5.2 the description of pembrolizumab pharmacokinetic (PK) results on time-dependent change in clearance using a time-dependent pharmacokinetic (TDPK) model structure rather than the static PK model structure

15.3.22. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/II/0034

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication for Perjeta (pertuzumab) in combination with trastuzumab and chemotherapy for the adjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. The submission is based on the primary analysis of efficacy and safety data from the pivotal phase 3 study BIG-4-11/BO25126/TOC4939g (APHINITY): a randomized multicentre, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Annex II-D (fulfilment of the obligation to include a neoadjuvant indication), the package leaflet and the RMP (version 10.0) are updated accordingly

15.3.23. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) - PREVENAR 13 (CAP) - EMEA/H/C/001104/II/0161

Applicant: Pfizer Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final study report from effectiveness study B1851041: a phase 4 post marketing study to determine 'national trends in ambulatory care visits for otitis media in children under the age of five in the United States'. The RMP (version 12) is updated accordingly

15.3.24. Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/WS1335/0010; RIXIMYO (CAP) - EMEA/H/C/004729/WS1335/0010

Applicant: Sandoz GmbH

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final clinical study reports (CSR) for: 1) study GP13-302: a randomized, double-blind, parallel-group safety study with the aim to specifically address a potential safety risk of a switch from treatment with originator rituximab containing product to treatment with GP2013 (biosimilar rituximab containing products); 2) study GP13-201: a 52-week multicentre, randomized, double-blind, parallel-arm, comparative study in patients with active rheumatoid arthritis (RA) refractory or intolerant to standard disease modifying anti-rheumatic drugs (DMARDs) and one or up to three anti-tumour necrosis factor (TNF) therapies. The RMP (version 3.0) is updated accordingly

15.3.25. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/II/0052, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Almath Spooner

Scope: Update of section 4.4 of the SmPC to add a warning regarding gastritis and update of section 4.8 to add the following adverse events regarding gastrointestinal tract and respiratory irritation: oropharyngeal pain, oesophageal pain, dyspepsia, nausea, gastritis and pharyngitis. The package leaflet and the RMP (version 13.0) are updated accordingly

15.3.26. Siltuximab - SYLVANT (CAP) - EMEA/H/C/003708/II/0026/G, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of an update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the product information following final results from: 1) study CNTO328MCD2001: a randomized, double blind, placebo controlled study to assess the efficacy and safety of siltuximab plus best supportive care compared with best supportive care in subjects with multicentric Castleman's disease; 2) study CNTO328MCD2002: an open-label, multicentre study to evaluate the safety of long-term treatment with siltuximab in subjects with multicentric Castleman's disease, both listed as imposed obligations in Annex II. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.27. Sirolimus - RAPAMUNE (CAP) - EMEA/H/C/000273/II/0164

Applicant: Pfizer Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of patients with lymphangioleiomyomatosis. As a consequence, section 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 6.0) are updated

accordingly. In addition, the MAH took the opportunity to make very minor formatting changes in the labelling

15.3.28. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0006

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include treatment of adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy, based on data from study A3921091: a phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of tofacitinib or adalimumab in subjects with active psoriatic arthritis; study A3921092: a long term, open label extension study of tofacitinib for the treatment of psoriatic arthritis; study A3921125: a phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of tofacitinib in subjects with active psoriatic arthritis and an inadequate response to at least one tumour necrosis factor (TNF) inhibitor. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to update Annex II with minor editorial changes

15.3.29. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/II/0009

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication based on the results of a completed post-authorisation efficacy study (PAES), study 156-13-210: a phase 3b, multicentre, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the efficacy and safety of tolvaptan (45 to 120 mg/day, split-dose) in subjects with chronic kidney disease (CKD) between late stage 2 to early stage 4 due to autosomal dominant polycystic kidney disease. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC and Annex II are updated. The package leaflet and the RMP (version 13.2) are updated accordingly. The MAH took the opportunity to introduce minor editorial changes to the product information

15.3.30. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0008, Orphan

Applicant: AbbVie Limited

PRAC Rapporteur: Patrick Batty

Scope: Extension of indication to include Venclyxto (venetoclax) in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. This is based on the results from the MURANO study: a multicentre, phase 3, open-label, randomised study in relapsed/refractory patients with CLL to evaluate the benefit of venetoclax plus rituximab compared with bendamustine plus rituximab. Annex II, the package leaflet and the RMP (version 3.0) are updated

accordingly

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

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

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

16.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only

16.1.1. Afatinib - GIOTRIF (CAP) - PSUSA/00010054/201709

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.2. Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/201709

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Anette Stark

Scope: Evaluation of a PSUSA procedure

16.1.3. Alirocumab - PRALUENT (CAP) - PSUSA/00010423/201709

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.4. Aliskiren - RASILEZ (CAP); aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - PSUSA/00000089/201709

Applicant: Noden Pharma DAC

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.5. Azilsartan medoxomil - EDARBI (CAP) - PSUSA/00000280/201708

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.6. Aztreonam[54] - CAYSTON (CAP) - PSUSA/00000283/201709

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.7. Bivalirudin - ANGIOX (CAP) - PSUSA/00000421/201709

Applicant: The Medicines Company UK Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.8. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/201709

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.9. Cholic acid[55] - KOLBAM (CAP) - PSUSA/00010182/201709

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.10. Cholic acid[56] - ORPHACOL (CAP) - PSUSA/00010208/201709

Applicant: Laboratoires CTRS

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

[54] For inhalation use only
[55] Treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7α-hydroxylase (CYP7A1) deficiency indications only
[56] Treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency or Δ4-3-oxosteroid-5β-reductase indications only

16.1.11. Ciclosporin[57] - IKERVIS (CAP) - PSUSA/00010362/201709

Applicant: Santen Oy

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.12. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/201709

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.13. Dapagliflozin - EDISTRIDE (CAP), FORXIGA (CAP) - PSUSA/00010029/201710

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.14. Deferiprone - FERRIPROX (CAP) - PSUSA/00000940/201708 (with RMP)

Applicant: Apotex Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.15. Dexamethasone[58] - NEOFORDEX (CAP) - PSUSA/00010480/201709

Applicant: Laboratoires CTRS

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.16. Dibotermin alfa - INDUCTOS (CAP) - PSUSA/00001034/201709

Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.17. Eculizumab - SOLIRIS (CAP) - PSUSA/00001198/201710

Applicant: Alexion Europe SAS

[57] For topical use only
[58] Centrally authorised product(s) indicated in symptomatic multiple myeloma

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.18. Eluxadoline - TRUBERZI (CAP) - PSUSA/00010528/201709

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - PSUSA/00010514/201708

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.20. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/201710

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.21. Etravirine - INTELENCE (CAP) - PSUSA/00001335/201709

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.1.22. Ferric citrate coordination complex - FEXERIC (CAP) - PSUSA/00010418/201709

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.23. Glycopyrronium[59] - SIALANAR (CAP) - PSUSA/00010529/201709

Applicant: Proveca Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

[59] For centrally authorised product(s) indicated for the treatment of severe siallorrhea

16.1.24. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/201709

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.25. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/201709

Applicant: Bio Products Laboratory Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.26. Idebenone[60] - RAXONE (CAP) - PSUSA/00010412/201709

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.27. Indacaterol, glycopyrronium bromide - ULTIBRO BREEZHALER (CAP), ULUNAR BREEZHALER (CAP), XOTERNA BREEZHALER (CAP) - PSUSA/00010105/201709 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.28. Indinavir - CRIXIVAN (CAP) - PSUSA/00001733/201709

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.29. Insulin degludec - TRESIBA (CAP); insulin degludec, insulin aspart - RYZODEG (CAP) - PSUSA/00010036/201709

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

[60] Centrally authorised product(s) only

16.1.30. Insulin degludec, liraglutide - XULTOPHY (CAP) - PSUSA/00010272/201709

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.31. Insulin human[61] - INSUMAN (CAP) - PSUSA/00010107/201709

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.32. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201709

Applicant: Basilea Medical Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.33. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/201709 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.34. Mecasermin - INCRELEX (CAP) - PSUSA/00001942/201708

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.35. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201709

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.36. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/201709

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

[61] Intraperitoneal route of administration only

Scope: Evaluation of a PSUSA procedure

16.1.37. Pandemic influenza vaccine (H5N1) (whole virion, vero cell derived, inactivated) - PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP); prepandemic influenza vaccine (H5N1) (whole virion, vero cell derived, inactivated) - VEPACEL (CAP) - PSUSA/00002282/201708

Applicant: Nanotherapeutics UK Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.38. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/201709

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.39. Pitolisant - WAKIX (CAP) - PSUSA/00010490/201709

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.40. Raltegravir - ISENTRESS (CAP) - PSUSA/00010373/201709

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.41. Retigabine - TROBALT (CAP) - PSUSA/00002624/201709

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.42. Riociguat - ADEMPAS (CAP) - PSUSA/00010174/201709

Applicant: Bayer AG

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.43. Rolapitant - VARUBY (CAP) - PSUSA/00010592/201708

Applicant: Tesaro UK Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.44. Sirolimus - RAPAMUNE (CAP) - PSUSA/00002710/201709

Applicant: Pfizer Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.45. Tasonermin - BEROMUN (CAP) - PSUSA/00002850/201708

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.46. Telavancin - VIBATIV[62] - PSUSA/00002879/201709

Applicant: Theravance Biopharma Ireland Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.47. Tobramycin[63] - VANTOBRA (CAP) - PSUSA/00010370/201709

Applicant: PARI Pharma GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.48. Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/201709

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.49. Vernakalant - BRINAVESS (CAP) - PSUSA/00003109/201708

Applicant: Cardiome UK Limited

[62] European Commission (EC) decision on the MA withdrawal of Vibativ dated 23 March 2018
[63] Nebuliser solution, centrally authorised product(s) only

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.50. Vortioxetine - BRINTELLIX (CAP) - PSUSA/00010052/201709

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Anagrelide - XAGRID (CAP); NAP - PSUSA/00000208/201709

Applicants: Shire Pharmaceutical Contracts Limited (Xagrid), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.2.2. Duloxetine - ARICLAIM (CAP), CYMBALTA (CAP), DULOXETINE LILLY (CAP), XERISTAR (CAP), YENTREVE (CAP); NAP - PSUSA/00001187/201708

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

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.2.3. Leflunomide - ARAVA (CAP), LEFLUNOMIDE MEDAC (CAP), LEFLUNOMIDE WINTHROP (CAP); NAP - PSUSA/00001837/201709

Applicants: Medac Gesellschaft fur klinische Spezialpraparate mbH (Leflunomide medac), Sanofi-Aventis Deutschland GmbH (Arava, Leflunomide Winthrop), various

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.2.4. Zoledronic acid[64]- ZOLEDRONIC ACID HOSPIRA (CAP), ZOLEDRONIC ACID MEDAC (CAP), ZOMETA (CAP); NAP - PSUSA/00003149/201708

Applicants: Hospira UK Limited (Zoledronic acid Hospira), Medac Gesellschaft fur klinische Spezialpraparate mbH (Zoledronic acid medac), Novartis Europharm Limited (Zometa), various

[64] Indicated for cancer and fractures only

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

16.3.1. Aciclovir, hydrocortisone (NAP) - PSUSA/00009004/201707

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Adenosine (NAP) - PSUSA/00000062/201708

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.3. Anastrozole (NAP) - PSUSA/00000210/201708

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.4. Buprenorphine (NAP) - PSUSA/00000459/201707

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.5. Clindamycin phosphate, tretinoin (NAP) - PSUSA/00010080/201707

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.3.6. Diphtheria, tetanus, poliomyelitis (inactivated) vaccine (adsorbed, reduced antigens(s) content) (NAP) - PSUSA/00001127/201708

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.7. Ethinylestradiol, gestodene[65] (NAP) - PSUSA/00010145/201708

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.3.8. Ethinylestradiol, norethisterone (NAP) - PSUSA/00001312/201708

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.9. Etoposide (NAP) - PSUSA/00001333/201708

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.10. Fenofibrate (NAP) - PSUSA/00001362/201707

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.11. Fludarabine (NAP) - PSUSA/00001406/201708

Applicant(s): various

PRAC Lead: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.3.12. Fluocinolone acetonide[66] (NAP) - PSUSA/00010224/201708

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

[65] Transdermal application only
[66] Intravitreal implant in applicator only

16.3.13. Fluvoxamine (NAP) - PSUSA/00001458/201707

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.14. Human tetanus immunoglobulin (NAP) - PSUSA/00002909/201708

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.15. Ketoprofen[67] (NAP) - PSUSA/00001809/201707

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.16. Norethisterone (NAP) - PSUSA/00002188/201708

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.17. Pilocarpine[68] (NAP) - PSUSA/00002409/201707

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.18. Quinagolide (NAP) - PSUSA/00002590/201707

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.19. Suxamethonium (NAP) - PSUSA/00002834/201708

Applicant(s): various

[67] All formulations except topical
[68] All formulations except ophthalmic

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.20. Triazolam (NAP) - PSUSA/00003023/201707

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.21. Typhoid polysaccharide vaccine (NAP) - PSUSA/00003065/201708

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/LEG 027

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review of cases of headache, dizziness, and abdominal pain/gastrointestinal (GI) pain from all available sources (post marketing cases, clinical trial data and literature) as requested in the conclusions of PSUSA/00000226/201705 adopted at the December 2017 PRAC

16.4.2. Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/LEG 009

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Cumulative review of cases of hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions from all available sources (post marketing cases, clinical trial data and literature) as requested in the conclusions of PSUSA/00009118/201705 adopted at the December 2017 PRAC

16.4.3. Ibritumomab tiuxetan - ZEVALIN (CAP) - EMEA/H/C/000547/LEG 046

Applicant: Spectrum Pharmaceuticals B.V.

PRAC Rapporteur: Doris Stenver

Scope: Detailed review of cases of myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), analysis of types of multiple cytogenetic abnormalities at individual patient level in order to identify whether specific abnormalities are present in relation to

treatment with Zevalin (ibritumomab tiuxetan), number of patients who, in addition to complex cytogenetics, have cytogenetic abnormalities normally associated with poor prognostic groups or therapy-related MDS/AML as well as a detailed review on whether these patient characteristics differ between treatment and control groups, as requested in the conclusions of PSUSA/00001704/201702 adopted at the October 2017 PRAC

16.4.4. Meningococcal group A, C, W135 and Y conjugate vaccine - MENVEO (CAP) - EMEA/H/C/001095/LEG 037

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Detailed review investigating the root cause of the observed peak in reconstitution errors reporting within the EU, including proposals for appropriate measures as applicable as part of routine risk minimisation as requested in the conclusions of PSUSA/00001969/201703 adopted at the November 2017 PRAC

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[69]

17.1.1. Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Daclatasvir – DAKLINZA (CAP); dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir – ZEPATIER (CAP); glecaprevir, pibrentasvir – MAVIRET (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, peritepreviir, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatasvir – EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir - VOSEVI - EMEA/H/C/PSA/J/0028

Applicant(s): AbbVie Limited (Exviera, Maviret, Viekirax), Bristol-Myers Squibb Pharma EEIG (Daklinza), Gilead Sciences International Ltd (Epclusa, Harvoni, Sovaldi, Vosevi), Janssen-Cilag International NV (Olysio), Merck Sharp & Dohme Limited (Zepatier)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Substantial amendment to the previously agreed joint protocol in January 2018 for a non-interventional imposed PASS on early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAAV) therapy in order to estimate the risk of early HCC recurrence (within 24 months after the first HCC-free image) associated with DAAV therapy exposure relative to no DAAV therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of

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

Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[70]

17.2.1. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 006.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol amendment to study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTI) and evaluating severe complications of UTI [final clinical study report (CSR) due in 2019]

17.2.2. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 007.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol amendment to study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2019]

17.2.3. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 008.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol amendment to study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2019]

17.2.4. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 009.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol amendment to study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

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

17.2.5. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 001.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol amendment to study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTI) and evaluating severe complications of UTI [final clinical study report (CSR) due in 2019]

17.2.6. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 002.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol amendment to study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2019]

17.2.7. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 003.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol amendment to study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2019]

17.2.8. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 004.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol amendment to study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

17.2.9. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 005.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Protocol amendment to study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTI) and evaluating severe complications of UTI [final clinical study report (CSR) due in 2019]

17.2.10. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 006.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Protocol amendment to study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2019]

17.2.11. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 007.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Protocol amendment to study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2019]

17.2.12. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 008.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Protocol amendment to study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

17.2.13. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 008.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Protocol amendment to study MB102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology study assessing the risk of severe complications of urinary tract infections (UTI) and evaluating severe complications of UTI [final clinical study report (CSR) due in 2019]

17.2.14. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 009.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Protocol amendment to study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure and evaluating the risk of acute kidney injury [final clinical study report (CSR) due in 2019]

17.2.15. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 010.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Protocol amendment to study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure and evaluating the risk of acute liver injury [final clinical study report (CSR) due in 2019]

17.2.16. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 011.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Protocol amendment to study MB102-118 ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology study assessing the risk of cancer [final clinical study report (CSR) due in 2024]

17.2.17. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/MEA 003

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Protocol for study R668-AD-1639 pregnancy registry: a safety study to monitor pregnancy and infant outcomes following administration of dupilumab during planned or unexpected pregnancy in North America

17.2.18. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/MEA 005.1

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 005 [protocol for a non-imposed, non-interventional PASS safety study: a drug utilisation study (DUS) of Intuniv (guanfacine extended release) in European countries (DUS-database) and protocol for a prescriber survey (DUS-survey) conducted in European countries] as per the request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

17.2.19. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol for study A-LUT-T-E02-402 (SALUS) (a category 3 study in the RMP): an international post-authorisation safety registry to assess the long-term safety of Lutathera (lutetium (^{177}Lu) oxodotreotide) for unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NET) [final report expected in December 2025] (from initial opinion/MA)

17.2.20. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.1

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response complementing MEA 001 [PASS protocol A-LUT-T-E02-402 (SALUS study, listed as a category 3 study in the RMP): an international post-authorisation safety registry to assess the long-term safety of Lutathera for unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs)]

17.2.21. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 009.2

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 009.1 [protocol for PASS study 178-PV-002: a drug utilisation study (DUS) of Betmiga (mirabegron) using real-world healthcare databases from the Netherlands, Spain, United Kingdom and Finland] as per the request for supplementary information (RSI) adopted in January 2018

17.2.22. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.4

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.3 [protocol synopsis for an observational retrospective database study based on secondary data analysis using existing databases, as suitable] as per the request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

17.2.23. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 004.5

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 004.4 [PASS protocol for study NB-452: a cross-sectional survey to evaluate the effectiveness of the physician prescribing checklist (PPC) among physicians in the EU] as per the request for supplementary information (RSI) adopted in January 2018

17.2.24. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 007

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Protocol for a non-interventional PASS study A3921298 evaluating the effectiveness of additional risk minimisation measures (aRMM) for Xeljanz (tofacitinib) in the European Union via a survey of healthcare professionals (HCPs) considered as an additional pharmacovigilance activity in the RMP (listed as a category 3 study in the RMP)

17.2.25. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/MEA 026.4

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 026.3 [protocol for study 6621 049-00 (SPECTRUM): a prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant intravenous (IV) sterile concentrate]

17.3. Results of PASS imposed in the marketing authorisation(s)[71]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[72]

17.4.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0039

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final report for PASS study 16526 (listed as a category 3 study in the RMP): an observational study to evaluate the physician and patient knowledge of safety and safe use information for aflibercept in Europe as stated in the EU educational material of Eylea (aflibercept)

17.4.2. Azilsartan medoxomil - EDARBI (CAP) - EMEA/H/C/002293/II/0021

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from a drug utilisation study (DUS) (listed as a category 3 study in the RMP): a retrospective non-interventional cohort study using a patient level electronic medical records database in Germany aimed to describe the prescription of Edarbi (azilsartan medoxomil) in patients with essential hypertension and those prescribed Edarbi (azilsartan medoxomil) for other reasons. The RMP (version 5.0) is updated accordingly

[71] In accordance with Article 107p-q of Directive 2001/83/EC
[72] 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

17.4.3. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0047/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report for study IM103061 (listed as a category 3 study in the RMP): an epidemiological study on pregnancy outcome among belatacept users in the US; 2) submission of the final report for study IM103089 (listed as a category 3 study in the RMP): evaluation of retrospective data to assess the association between belatacept and the risk of post-transplant lymphoproliferative disorder (PTDL) in renal transplant recipients in Europe. The RMP (version 15) is updated accordingly

17.4.4. Dronedarone - MULTAQ (CAP) - EMEA/H/C/001043/II/0039/G

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) submission of the final report from study DRONE_C_05917 (listed as a category 3 study in the RMP): a non-interventional epidemiological study aimed for the surveillance of serious liver injuries/diseases (SLD) with the use of dronedarone using multiple databases in the US, including the addendum on surveillance of interstitial lung disease (ILD); 2) submission of the final report from study DRONE_C_05911 (listed as a category 3 study in the RMP): a non-interventional epidemiological study aimed at studying the concomitant use of dronedarone and digoxin (or statins) and the risk of digitalis intoxication (or rhabdomyolysis and myopathy). The RMP (version 11.0) is updated accordingly

17.4.5. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/II/0087

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for study GS-EU-236-0141 (listed as a category 3 study in the RMP, in fulfilment of a MEA 006): an observational drug utilisation study (DUS) of Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil) in adults with human immunodeficiency virus 1 (HIV-1) infection

17.4.6. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS1283/0035; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS1283/0031

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final report for study 205052 (PRJ2214): a drug utilisation study (DUS) to identify the extent of any off-label prescribing fluticasone furoate/vilanterol (FF/VI) in any dose in children less than 12 years of age; and prescribing of FF/VI 200/25 mcg in patients with a diagnosis of chronic obstructive

pulmonary disease (COPD) considering the presence of a concurrent diagnosis of asthma. The RMP (version 9.1) is updated accordingly

17.4.7. Glycopyrronium bromide - ENUREV BREEZHALER (CAP) - EMEA/H/C/002691/WS1299/0025; SEEBRI BREEZHALER (CAP) - EMEA/H/C/002430/WS1299/0025; TOVANOR BREEZHALER (CAP) - EMEA/H/C/002690/WS1299/0028

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final study report for study CNVA237A2402T (a category 1 study in the RMP and marketing authorisations): a multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled glycopyrronium bromide (NVA237) in Europe. As a consequence, Annex II is updated. In addition, the additional monitoring list is to be updated by removing Enurev Breezhaler, Seebri Breezhaler, Tovanor Breezhaler (glycopyrronium bromide). As a consequence, Annex I and IIIB are updated. The MAH also took this opportunity to update the local representatives. The RMP (version 8) is also updated accordingly

17.4.8. Indacaterol, glycopyrronium - ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/WS1340/0022; ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/WS1340/0022; XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/WS1340/0025

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report for study CQVA149A2401: a multinational, multi-database drug utilisation study (DUS) of indacaterol/glycopyrronium bromide (QVA149) in Europe with the objective to estimate the use of QVA149 off-label and in the subpopulations with missing information mentioned in the RMP

17.4.9. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/001252/II/0031, Orphan

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report of a survey on healthcare professionals (listed as a category 3 study in the RMP): a final survey aimed at measuring the effectiveness of the educational materials at 6 months post-launch and 6 months post-redistribution of the revised healthcare professional leaflet. The RMP (version 7.0) is updated accordingly

17.4.10. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/II/0035

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report for the online survey for EU PAS register number

EUPAS13634 measuring the effectiveness of the Mycamine prescriber checklist in the EU. The RMP (version 18.0) is updated accordingly

17.4.11. Prucalopride - RESOLOR (CAP) - EMEA/H/C/001012/II/0042

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final clinical study report (CSR) for the post-authorisation drug utilisation study (DUS) SHP555-804 (in fulfilment of MEA 006.11): a DUS to examine characteristics of patients prescribed Resolor (prucalopride) and a pharmacoepidemiological study of the occurrence of major cardiovascular events, pregnancy, and pregnancy outcomes in the UK clinical practice research datalink (CPRD) database. The RMP (version 14.0) is updated accordingly

17.4.12. Radium (^{223}Ra) dichloride - XOFIGO (CAP) - EMEA/H/C/002653/II/0031

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final clinical study report (CSR) for study 17399 (listed as category 4 study in the RMP): an observational PASS to evaluate the use of radium-223 dichloride in patients in Sweden with a diagnosis of castration-resistant prostate cancer (CRPC) with bone metastases (mCRPC) and patients in whom radium-223 dichloride may have been potentially used off-label

17.4.13. Somatropin - NUTROPINAQ (CAP) - EMEA/H/C/000315/II/0069/G

Applicant: Ipsen Pharma

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of: 1) submission of the final report from the international cooperative growth study (iNCGS) Post marketing surveillance programme for NutropinAq (somatropin): a study collecting long-term safety and effectiveness data on NutropinAq during treatment of paediatric growth disorders for which growth hormone is indicated; 2) submission of an updated RMP (version 3.0) in order to include updates from the PASS iNCGS post marketing surveillance programme for NutropinAq. In addition, the RMP has been formatting in accordance with the new RMP template

17.4.14. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0009

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final clinical study report (CSR) for study A3921024 (listed as a category 3 study in the RMP (MEA 003)): a long term, non-interventional, open label follow-up study to evaluate the long-term safety of patients on 5 mg twice a day (BID) of Xeljanz (tofacitinib) with a secondary objective of evaluating sustained efficacy in patients with rheumatoid arthritis

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[73]

17.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.8

Applicant: Genzyme Europe BV

PRAC Rapporteur: Caroline Laborde

Scope: Annual report for the Pompe registry: a global, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.9

Applicant: Genzyme Europe BV

PRAC Rapporteur: Caroline Laborde

Scope: Annual report 2017 for the Pompe registry: a global, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease, focussing on data on patients with renal or hepatic insufficiency

17.5.3. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: First interim report for study ALIROC07997: a PASS using healthcare databases, in order to monitor the safety of Praluent (alirocumab) in patients affected with the human immunodeficiency virus (HIV) (from initial opinion/MA)

17.5.4. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 002.1

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Patrick Batty

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

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

17.5.5. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 003.1

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Patrick Batty

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

17.5.6. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 004.1

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Patrick Batty

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

17.5.7. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 005.1

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Patrick Batty

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

17.5.8. Florbetaben (^{18}F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.5

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Patrick Batty

Scope: Interim report for study FBB-01-03-13 (PASS2): a non-interventional prospective observational multicentre, multinational registry to observe usage pattern, safety and tolerability of NeuraCeq (florbetaben (^{18}F)) in clinical practice, including off-label use [final clinical study report: Q2 2020]

17.5.9. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/MEA 045.8

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Fourth annual progress report for diabetes pregnancy registry (NN304-4016): an international non-interventional prospective cohort study to evaluate the safety of treatment with insulin detemir in pregnancy women with diabetes mellitus

17.5.10. Ivabradine - CORLENTOR (CAP) - EMEA/H/C/000598/ANX 027.2

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study CLE-16257-107: a multinational, retrospective, drug utilisation study (DUS) in select European countries aimed at describing the characteristics of ivabradine users, as well as describing the patterns of use of ivabradine, and the effectiveness of risk minimisation measures (RMM) as required in the conclusions of the safety referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMA/H/A20/1404) finalised in 2014 and agreed protocol (EMEA/H/C/PSP/j/0019.1.A.1) dated May 2016

17.5.11. Ivabradine - IVABRADINE ANPHARM (CAP) - EMEA/H/C/004187/ANX 002.1

Applicant: Anpharm Przedsiebiorstwo Farmaceutyczne S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study CLE-16257-107: a multinational, retrospective, drug utilisation study (DUS) in select European countries aimed at describing the characteristics of ivabradine users, as well as describing the patterns of use of ivabradine, and the effectiveness of risk minimisation measures (RMM) as required in the conclusions of the safety referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMA/H/A20/1404) finalised in 2014 and agreed protocol (EMEA/H/C/PSP/j/0019.1.A.1) dated May 2016

17.5.12. Ivabradine - PROCORALAN (CAP) - EMEA/H/C/000597/ANX 027.2

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study CLE-16257-107: a multinational, retrospective, drug utilisation study (DUS) in select European countries aimed at describing the characteristics of ivabradine users, as well as describing the patterns of use of ivabradine, and the effectiveness of risk minimisation measures (RMM) as required in the conclusions of the safety referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMA/H/A20/1404) finalised in 2014 and agreed protocol (EMEA/H/C/PSP/j/0019.1.A.1) dated May 2016

17.5.13. Meningococcal group B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 017.5

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report for study V72_36OB: a post-licensure observational safety study after Bexsero (meningococcal B vaccine 4CMenB) vaccination in routine UK care [final report due date: 31/12/2019]

17.5.14. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.4

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Progress report for study D3820R00009 (EVM-17123): an observational PASS of Moventig (naloxegol) conducted amongst patients aged 18 years and older treated with opioids chronically for non-cancer and cancer pain (from initial opinion/MA)

17.5.15. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 009.1

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Annual progress study report for study D3820R00008: a US post-marketing, comparative, observational study in order to evaluate the cardiovascular safety of naloxegol in patients with non-cancer pain in comparison to other treatments for opioid induced constipation [final study report: December 2023]

17.5.16. Octocog alfa - HELIXATE NEXGEN (CAP) - EMEA/H/C/000276/MEA 085.6

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Eighth annual report for the European Haemophilia Safety Surveillance (EUHASS) registry in order to evaluate cases with adverse events (AEs) of special interest

17.5.17. Octocog alfa - KOGENATE BAYER (CAP) - EMEA/H/C/000275/MEA 086.6

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Eighth annual report for the European Haemophilia Safety Surveillance (EUHASS) registry in order to evaluate cases with adverse events (AEs) of special interest

17.5.18. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Eighth annual report for epidemiological study 14149 conducted within the European Haemophilia Safety Surveillance (EUHASS) registry in order to evaluate cases with adverse events (AEs) of special interest

17.5.19. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/MEA 004.2

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 004.1 [annual progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date: 2020]] as per the request for supplementary information (RSI) adopted at the December 2017 PRAC meeting

17.5.20. Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/MEA 004.1

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 004 [annual progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date: 2020]] as per the request for supplementary information (RSI) adopted at the December 2017 PRAC meeting

17.5.21. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.13

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Annual report for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics

17.6. Others

17.6.1. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 011.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 011 [revised statistical analysis plan (SAP) and submission of protocol (version 1.0) for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI

including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted at the September 2017 PRAC meeting

17.6.2. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 003.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 003 [revised statistical analysis plan (SAP) and submission of protocol (version 1.0) for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted at the September 2017 PRAC meeting

17.6.3. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 007.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 007 [revised statistical analysis plan (SAP) and submission of protocol (version 1.0) for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important

potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted at the September 2017 PRAC meeting

17.6.4. Trastuzumab - HERCEPTIN (CAP) - EMEA/H/C/000278/LEG 100

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Assessment (drug safety report (DSR) 1083135) of cardiac monitoring practices in patients treated with Herceptin (trastuzumab) in order to assess the effectiveness of risk minimisation measures following the distribution of a direct healthcare professional communication (DHPC) a requested in the conclusions of variation EMEA/H/C/000278/II/135 adopted at the October 2017 PRAC and CHMP

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0019 (without RMP)

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Annual reassessment of the marketing authorisation

18.1.2. Anagrelide - XAGRID (CAP) - EMEA/H/C/000480/S/0081 (without RMP)

Applicant: Shire Pharmaceutical Contracts Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS (CAP) - EMEA/H/C/002801/R/0010 (without RMP)

Applicant: MolMed SpA, ATMP[74]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0041 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/R/0020 (with RMP)

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Anette Stark

Scope: 5-year renewal of the marketing authorisation

[74] Advanced therapy medicinal product

18.3.2. Esomeprazole - NEXIUM CONTROL (CAP) - EMEA/H/C/002618/R/0021 (without RMP)

Applicant: Pfizer Consumer Healthcare Limited

PRAC Rapporteur: Simona Kudeliene

Scope: 5-year renewal of the marketing authorisation

18.3.3. Human fibrinogen, human thrombin - EVICEL (CAP) - EMEA/H/C/000898/R/0054 (without RMP)

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.4. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/R/0056 (without RMP)

Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.5. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/R/0047 (without RMP)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.6. Levodopa, carbidopa, entacapone - CORBILTA (CAP) - EMEA/H/C/002785/R/0015 (with RMP)

Applicant: Orion Corporation

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 09-12 April 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence Defays	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
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Anette Kirstine Stark	Alternate	Denmark	No restrictions applicable to this meeting	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
Ghania Chamouni	Member	France	No restrictions applicable to this meeting	Full involvement
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Rhea Fitzgerald	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	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
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	4.2.1. Dienogest, ethinylestradiol (NAP) 6.1.53. Regorafenib - STIVARGA (CAP) - PSUSA/00010133/201709 6.1.56. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/201709 6.3.20. Naproxen (NAP) - PSUSA/00002125/201708 8.3.9. Radium (223Ra) dichloride - XOFIGO (CAP) - EMEA/H/C/002653/R/0030 (without RMP)
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate - via telephone*	Portugal	No interests declared	Full involvement
Roxana Dondera	Alternate	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No participation in final deliberations and voting on:	6.3.24. Quetiapine (NAP) - PSUSA/00002589/201707

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Jens Piero Quartarolo	Expert - in person*	Denmark	No participation in discussion, final deliberations and voting on:	4.3.1. Adalimumab – AMGEVITA (CAP), CYLTEZO (CAP), HUMIRA (CAP), IMRALDI (CAP), SOLYMBIC (CAP); infliximab – FLIXABI (CAP), INFLECTRA (CAP), REMICADE (CAP), REMSIMA (CAP) 6.3.19. Leuprorelin (NAP) - PSUSA/00001844/201707 8.3.8.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/R/0028 (without RMP)
Alexandre Moreau	Expert - in person*	France	No interests declared	Full involvement
Christine Diesinger	Expert - via telephone*	Germany	No interests declared	Full involvement
Nils Lilienthal	Expert - via telephone*	Germany	No interests declared	Full involvement
Walburga Lütkehermölle	Expert - via telephone*	Germany	No interests declared	Full involvement
Ronan Grimes	Expert - in person*	Ireland	No interests declared	Full involvement
Marcel Kwa	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Monika Trojan	Expert - via telephone*	Poland	No interests declared	Full involvement
Pilar Rayón Iglesias	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - in person*	Sweden	No interests declared	Full involvement
Rickard Ljung	Expert - in person*	Sweden	No participation in discussion, final deliberations and voting on:	4.2.1. Dienogest, ethinylestradiol (NAP) 5.1.7. Trastuzumab - TRAZIMERA (CAP MAA) - EMEA/H/C/004463 8.3.3. Esomeprazole - NEXIUM CONTROL (CAP) - EMEA/H/C/002618/R/0021 (without RMP)
Elina Rönnemaa	Expert - via telephone*	Sweden	No interests declared	Full involvement
Dominik Karres	Expert - in person*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Representatives from the Medicines Evaluation Board (the Netherlands) visited the Committee				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

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: http://www.ema.europa.eu/ema/