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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 11-14 June 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 11-14 June 2018 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Amelia Cupelli as the new member for Italy, replacing Carmela Macchiarulo, and leaving the position of alternate vacant until further notice. In addition, the Chairperson welcomed Michal Radik as the new member for Slovakia, replacing Tatiana Magalova who became the alternate replacing Peter Koren. Moreover, the Chair noted that Karen Pernille Harg was the new alternate for Norway replacing Kristin Thorseng Kvande. Finally, the PRAC Chairperson announced that it was the last PRAC meeting for the current independent experts appointed by the European Commission: Marie-Louise (Marieke) de Bruin, Stephen Evans, Brigitte Keller-Stanislawski, Hervé Le Louet, Thierry Trenque and Lennart Waldenlind. The PRAC thanked all past delegates for their valuable contribution to the work of the PRAC.

1.2. Agenda of the meeting on 11-14 June 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 14-17 May 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 14-17 May 2018 were published on the EMA website on 09 July 2018 ([EMA/PRAC/394603/2018](https://www.ema.europa.eu/en/PRAC/394603/2018)).

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

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); piperimidic acid (NAP) - EMEA/H/A-31/1452

Applicant(s): Raptor Pharmaceuticals Europe BV (Quinsair), various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Martin Huber

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for quinolone- and fluoroquinolone-containing medicines for systemic and inhalational use, indicated for the treatment of bacterial infections, in particular those which are serious and life-threatening, in order to assess the persistence of side effects known to occur with quinolone and fluoroquinolone antibiotics, following reports of long-lasting side effects mainly affecting musculoskeletal and nervous systems. The ongoing review also assesses the need for adequate and consistent risk minimisation measures (RMMs) as well as the impact of this safety concern if confirmed on the overall benefit-risk balance of quinolones and fluoroquinolones for systemic and inhalational use, especially in authorised indications which are related to treatment of non-serious/non-severe infections. For further background, see [PRAC minutes February 2017](#), [PRAC minutes June 2017](#), [PRAC minutes October 2017](#), [PRAC](#)

[minutes November 2017](#), [PRAC minutes February 2018](#), [PRAC minutes March 2018](#) and [PRAC minutes May 2018](#).

Summary of recommendation(s)/conclusions

- The PRAC held a public hearing on 13 June 2018. Further information, including the agenda, written interventions, a summary report and the video recording are available on the [webpage dedicated to public hearings](#).

3.2.2. Radium (²²³Ra) dichloride - XOFIGO (CAP) - EMEA/H/A-20/1459

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Valerie Strassmann

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 Xofigo (radium-223 dichloride) to review the results of a phase 3 study (ERA 223¹) and assess their potential impact on the benefit-risk balance of Xofigo in the authorised indication of the treatment of castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. The review was started after analyses of uncleaned preliminary data from this clinical trial, evaluating Xofigo in combination with abiraterone acetate and prednisone/prednisolone in chemotherapy-naïve patients with asymptomatic or mildly symptomatic bone predominant metastatic castrate-resistant prostate cancer, found that the incidences of treatment emergent fractures and deaths were increased in the treatment arm (radium-223 dichloride plus abiraterone acetate and prednisone/prednisolone) compared to the control arm (placebo plus abiraterone acetate and prednisone/prednisolone). For further background, see [PRAC minutes December 2017](#), [PRAC minutes March 2018](#) and [PRAC minutes May 2018](#).

Summary of recommendation(s)/conclusions

- The PRAC adopted a second list of outstanding issues (LoOI), to be addressed by the MAH in accordance with a revised timetable ([EMA/PRAC/791811/2017 Rev. 2](#)).
- In addition, the PRAC adopted a list of experts (LoE) for the Inter-Committee Scientific Advisory Group (SAG) on Oncology ([SAG-O](#)) meeting scheduled on 19 June 2018.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures²

None

¹ Study 15396 (ERA-223) (NCT02043678): a phase 3, randomised, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

² Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

3.5. Others

None

4. Signals assessment and prioritisation³

4.1. New signals detected from other sources

See also Annex I 14.1.

4.1.1. Dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); liraglutide – VICTOZA (CAP)

Applicant(s): AstraZeneca AB (Bydureon, Byetta), Eli Lilly Nederland B.V. (Trulicity), Novo Nordisk A/S (Victoza)

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of diabetic ketoacidosis

EPITT 19237 – New signal

Lead Member State(s): IT, NL, SE

Background

Dulaglutide, exenatide and liraglutide are glucagon-like peptide-1 (GLP-1) analogues. Trulicity, a centrally authorised product containing dulaglutide, Bydureon and Byetta, centrally authorised products containing exenatide, and Victoza, a centrally authorised product containing liraglutide, are indicated in adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control, under certain conditions, in monotherapy and/or in add-on therapy with other glucose-lowering medicinal products including insulin.

The exposure for Trulicity (dulaglutide) is estimated to have been more than 812,000 patient-years worldwide, in the period from first authorisation in 2014 to 2017. The exposure for Bydureon and Byetta (exenatide) is estimated to have been more than 4.9 million patient-years worldwide, in the period from first authorisation in 2005 to 2018. The exposure for Victoza/Saxenda (liraglutide) is estimated to have been more than 121,395 patient-years worldwide, in the period from first authorisation in 2009 to 2017.

During routine signal detection activities, a signal of diabetic ketoacidosis (DKA) was identified by EMA, prompted by disproportionality and important medical event (IME) status. Italy confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the evidence from case reports in EudraVigilance and the literature, the PRAC agreed that the MAHs for dulaglutide-, exenatide- and liraglutide-containing products should provide a cumulative review of all cases of DKA as well as a discussion as to whether switching from other antidiabetic medicines (e.g. insulin) to GLP-1 receptor agonists may

³ 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

increase the risk of developing DKA and, if necessary, proposals for adequate measures to minimise this risk.

Depending on the outcome of the reviews, the MAHs should propose updates of the product information, risk management plan and other activities as appropriate.

The PRAC appointed Amelia Cupelli as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for dulaglutide-, exenatide- and liraglutide-containing products should submit to EMA, within 60 days, a cumulative review of all cases of DKA, including those from completed and ongoing clinical trials, with a discussion as to whether switching from other antidiabetic medicines (e.g. insulin) to GLP-1 receptor agonists may increase the risk of developing DKA and, if necessary, proposals for adequate measures to minimise this risk. Depending on the outcome of the reviews, the MAHs should additionally submit a proposal for amending the product information, risk management plan and other activities as appropriate.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. Xylometazoline (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of serious ventricular arrhythmia in patients with long QT syndrome

EPITT 19242 – New signal

Lead Member State(s): LV

Background

Xylometazoline is a sympathomimetic agent indicated for the symptomatic relief of nasal congestion, perennial and allergic rhinitis (including hay fever), and sinusitis.

Following the notification of a case of a patient who self-administered xylometazoline intranasally according to the instructions and afterwards experienced cardiac arrest and ventricular fibrillation, compatible with long QT syndrome (LQTS), a signal of serious ventricular arrhythmia in patients with long QT syndrome was identified by Finland, based in addition on 6 cases of MedDRA PT⁴ 'cardiac arrest', 27 cases of MedDRA PT 'loss of consciousness', 16 cases of MedDRA PT 'syncope', 4 cases of MedDRA PT 'ventricular fibrillation' and 3 cases of MedDRA PT 'ventricular tachycardia'. Latvia confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the PRAC agreed that the MAH GlaxoSmithKline should submit a cumulative review of all cases of ventricular cardiac arrhythmias and/or long QT interval associated with intranasal use of xylometazoline as well as a discussion on the need for any potential amendment to the

⁴ Medical dictionary for regulatory activities – Preferred Term

product information and/or the risk management plan and accordingly make a proposal for changes to the relevant sections within this discussion.

The PRAC appointed Zane Neikena as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for xylometazoline-containing product GlaxoSmithKline should submit to EMA, within 60 days, a cumulative review of the signal, including all cases reporting signs and symptoms of ventricular arrhythmias (including Torsade de Pointes) and long QT interval in association with the use of xylometazoline, and a proposal for amending the product information and/ or the risk management plan if deemed appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. Carbimazole (NAP); thiamazole (NAP)

Applicant(s): various

PRAC Rapporteur: Valerie Strassmann

Scope: New information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy

EPITT 19238 – New signal

Lead Member State(s): DE

Background

Carbimazole and thiamazole are imidazole derivatives indicated for therapy for hyperthyroidism under certain conditions.

Following the publications by *Song R, et al. 2017⁵*, *Khan I, et al. 2017⁶*, *Sachs C, et al. 2016⁷*, *Batra CM, et al. 2015⁸*, new information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy was identified by France. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from the literature, the PRAC agreed that the MAHs for originator thiamazole-containing products (Aspen pharma, Meda, Sandoz, Takeda, Sanóbia-centro de saúde e estética, Teofarma, Uni-pharma Kleon Tsetis) and originator carbimazole-containing products (Amdipharm) should provide cumulative reviews of cases reported with thiamazole and carbimazole related to the MedDRA SMQ⁹ pregnancy and neonatal topics, a comprehensive review of the scientific literature related to

⁵ Song R, Lin H, Chen Y, Zhang X, Feng W. 2017. Effects of methimazole and propylthiouracil exposure during pregnancy on the risk of neonatal congenital malformations: a meta-analysis. *PLoS One*. 2017 Jul 3; 12(7):e0180108

⁶ Khan I, Okosieme OE, Lazarus JH. 2017. Current challenges in the pharmacological management of thyroid dysfunction in pregnancy. *Expert Rev Clin Pharmacol*. 2017 Jan; 10(1):97-109

⁷ Sachs C, Tebacher-Alt M, Mark M, Cribier B, Lipsker D. 2016. Aplasia cutis congenita and antithyroid drugs during pregnancy: case series and literature review. *Ann Dermatol Venereol*. 2016 Jun-Jul; 143(6-7):423-35

⁸ Batra CM, Gupta V, Gupta N, Menon PS. 2015. Fetal hyperthyroidism: intrauterine treatment with carbimazole in two siblings. *Indian J Pediatr*. 2015 Oct; 82(10):962-4

⁹ Medical dictionary for regulatory activities – Standard Medical Query

thiamazole/carbimazole exposure during pregnancy, a discussion on whether new genotoxic, teratogenic, fetotoxic or pharmacological effects of thiamazole/carbimazole on the (unborn) child if administered during pregnancy have been identified or whether the characterisation of previously known risks has changed, as well as a discussion on the need for amendment of current risk minimisation measures and of further pharmacovigilance activities as appropriate.

The PRAC appointed Valerie Strassman as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs of originator thiamazole-containing products (Aspen pharma, Meda, Sandoz, Takeda, Sanóbia-centro de saúde e estética, Teofarma, Uni-pharma Kleon Tsetis) and originator carbimazole-containing products (Amdipharm) should submit to EMA, within 60 days, a cumulative review of cases reported with thiamazole and carbimazole related to the MedDRA SMQ¹⁰ pregnancy and neonatal topics, a comprehensive review of the scientific literature related to thiamazole/carbimazole exposure during pregnancy, a discussion on whether new genotoxic, teratogenic, fetotoxic or pharmacological effects of thiamazole/carbimazole on the (unborn) child if administered during pregnancy have been identified or whether the characterisation of previously known risks has changed, as well as a discussion on the need for amendment of current risk minimisation measures and of further pharmacovigilance activities as appropriate.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Nabumetone (NAP)

Applicant(s): various

PRAC Rapporteur: Sabine Straus

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

EPITT 19241 – New signal

Lead Member State(s): NL

Background

Nabumetone is a non-steroidal anti-inflammatory drug (NSAID) used to treat pain and inflammation and is indicated for relief of signs and symptoms of osteoarthritis and rheumatoid arthritis.

Following the publication of a fatal case of drug reaction with eosinophilia and systemic symptoms (DRESS) secondary to a short treatment with nabumetone in 'Reactions Weekly', a literature search and 4 further reports of DRESS identified in EudraVigilance, a signal of DRESS was identified by Sweden. The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence in EudraVigilance (i.e. well-documented post-marketing spontaneous cases) with regard to the risk of DRESS with nabumetone, the PRAC

¹⁰ Medical dictionary for regulatory activities – Standard Medical Query

agreed that the MAH(s) of nabumetone-containing medicinal product(s) should submit a variation to amend the product information to update the warning on serious skin reactions to include DRESS as well as to add severe cutaneous adverse reactions (SCARs) among the undesirable effects of with frequency 'very rare'.

The PRAC appointed Sabine Straus as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH(s) of nabumetone-containing medicinal product(s) should submit to the relevant national competent authorities of the MSs, within 60 days, a variation to amend the product information¹¹.

For the full PRAC recommendation, see [EMA/PRAC/397086/2018](#) published on 09/07/2018 on the EMA website.

4.3. Signals follow-up and prioritisation

4.3.1. Hydrochlorothiazide (NAP);

Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP)

Applicant(s): Actavis Group PTC ehf (Actelsar HCT), Bayer Pharma AG (Kinzalkomb, PritorPlus), Boehringer Ingelheim International (MicardisPlus), Krka, d.d. (Ifirmacombi, Tolucombi), Noden Pharma DAC (Rasilez HCT), Novartis Europharm Limited (Copalia HCT, Dafiro HCT), Sanofi-aventis groupe (Irbesartan Hydrochlorothiazide Zentiva, Karvezide), Sanofi Clir SNC (CoAprovel), Teva B.V. (Irbesartan/Hydrochlorothiazide Teva); various

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of skin cancer

EPITT 19138 – Follow-up to January 2018

Background

For background information, see [PRAC minutes January 2018](#).

The study authors (*Pottegard A, et al. 2017*¹² and *Arnsfang S, et al. 2017*¹³) replied to the request for information on the signal of skin cancer and the responses were assessed by the Rapporteur.

Discussion

Based on the assessment of the available data sources (i.e. literature, EudraVigilance), the PRAC considered there was a biologically plausible mechanistic model supporting the

¹¹ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

¹² Pottegard, A., Hallas, J., Olesen, M., Svendsen, M. T., Habel, L. A., Friedman, G. D. & Friis, S. 2017. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med*

¹³ Arnsfang, S., Gaist, D., Schmidt, S., LR., H., Friis, S. & Pottegard, A. 2017. Hydrochlorithiazide use and risk of non-melanoma skin cancer: a nationwide case- control study from Denmark. *Journal of the American Academy of Dermatology*

increased risk of non-melanoma skin cancer (NMSC) following higher cumulative dose of hydrochlorothiazide (HCTZ), and therefore that an update of the product information of HCTZ-containing products was warranted.

Summary of recommendation(s)

- The MAHs for HCTZ-containing medicinal products should submit to EMA, within 10 days, a proposal for amending the product information accordingly.
- A 15-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.2. Biotin (NAP)

Applicant(s): various

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of interference with clinical laboratory tests

EPITT 19156 – Follow-up to February 2018

Background

For background information, see [PRAC minutes February 2018](#).

The MAH Baxter replied to the request for information on the signal of interference of biotin with clinical laboratory tests and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence arising from EudraVigilance and other sources, the PRAC agreed that Essential Pharmaceuticals, Fresenius Kabi, Alfasigma, Baxter, Quiris Healthcare, Dr. Kleine Pharma, Krauterhaus Sanct Bernhard, Bio-H-Tin Pharma, FAR.G.IM and Bayer, MAHs of biotin-containing medicinal products, should submit a cumulative review of case reports, scientific literature as well as available pharmacokinetic data and should analyse the risk of interference with biotin-based immunoassays available in the EU for their products containing biotin. They should provide a discussion on relevant pharmacokinetic data for their products, through an in-depth analysis, including a discussion and proposal relating to relevant dosages of biotin and relevant product intake and washout periods and potential interruption of biotin intake needed to avoid the interference with clinical laboratory tests. Based on this review, the MAHs should provide a proposal for inclusion of relevant pharmacokinetic data in the product information.

Summary of recommendation(s)

- The MAHs of biotin-containing medicinal products, Essential Pharmaceuticals, Fresenius Kabi, Alfasigma, Baxter, Quiris Healthcare, Dr. Kleine Pharma, Krauterhaus Sanct Bernhard, Bio-H-Tin Pharma, FAR.G.IM and Bayer, should submit to EMA, within 60 days, a cumulative review of case reports, scientific literature as well as available pharmacokinetic data, an analysis of the risk of interference with biotin-based immunoassays available in the EU for all their products containing biotin, and a discussion on relevant pharmacokinetic data for their products as well as a proposal for inclusion of relevant pharmacokinetic data in the product information.

- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.3. Varenicline – CHAMPIX (CAP) – EMEA/H/C/000699/SDA/048

Applicant(s): Pfizer Limited

PRAC Rapporteur: Anette Stark

Scope: Signal of loss of consciousness

EPITT 19146 – Follow-up to February 2018

Background

For background information, see [PRAC minutes February 2018](#).

The MAH replied to the request for information on the signal of loss of consciousness 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 loss of consciousness, the PRAC agreed that the MAH for Champix (varenicline), Pfizer Limited, should submit a variation to amend the product information to include the information on the possible transient loss of consciousness with Champix (varenicline), with regards to the effects on ability to drive and use machines as well as to add transient loss of consciousness among the undesirable effects with frequency 'not known'.

Summary of recommendation(s)

- The MAH for Champix (varenicline), Pfizer Limited, should submit to EMA, within 60 days, a variation to amend the product information¹⁴.

For the full PRAC recommendation, see [EMA/PRAC/397086/2018](#) published on 09/07/2018 on the EMA website.

4.3.4. Dolutegravir – TIVICAY (CAP) – EMEA/H/C/002753/SDA/009; abacavir sulfate, dolutegravir sodium, lamivudine – TRIUMEQ (CAP); dolutegravir, rilpivirine – JULUCA (CAP)

Applicant(s): ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women

EPITT 19244 – Follow-up to May 2018

Background

For background information, see [PRAC minutes May 2018](#).

¹⁴ Update of SmPC sections 4.7 and 4.8. The package leaflet is to be updated accordingly

The MAH replied to the request for information on the preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the available evidence from the preliminary data on an observational study on birth outcomes in HIV-infected women – the Tsepamo study¹⁵ conducted in Botswana, as well as the additional data submitted by the MAH in relation to the safety of use of dolutegravir during pregnancy (from clinical trials, post-marketing experience and the literature).

While the PRAC noted the relevance of the data for the signal of neural tube defects in association with use of dolutegravir at the time of conception and the MAH's proposals for updates to the product information, it was considered that further information was needed in order to more fully evaluate the safety of use of dolutegravir during pregnancy.

The PRAC also noted the MAH's proposals regarding additional data sources and/or studies that could further inform the potential risk characterisation and agreed that further details are needed in addition to the preliminary data provided, in order to fully evaluate the adequacy of these proposals.

Summary of recommendation(s)

- The MAH for dolutegravir-containing products (single ingredient and fixed combinations) should submit to EMA, within 60 days, a further review of the safety of use of dolutegravir during pregnancy including new pregnancy information, after the data-lock point of the current evaluation, critically evaluating the cumulative data relating to the safety of use during pregnancy in the second and third trimesters and based on these data make proposals for the appropriate advice that could be included in the product information regarding the use during these periods. Moreover, the MAH should provide additional information on the further evaluation of the Brazil pregnancy cohort, including the planned chart review study, and submit for review the protocol for this study, as appropriate. Finally, the MAH should provide further detailed information on the proposals with respect to the non-clinical studies, including the results of the literature review to investigate risk factors for neural tube defects, investigations relating to the utility of the rat whole-embryo culture model and any proposals with regards to in vitro folate receptor binding research.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

¹⁵ Observational study capturing birth outcomes data at 8 government hospitals throughout Botswana (~45% of all deliveries) starting August 2014

authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

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

See also Annex I 15.1.

5.1.1. Damoctocog alfa pegol - EMEA/H/C/004054, Orphan

Applicant: Bayer AG

Scope: Treatment and prophylaxis of haemophilia A

5.1.2. Doravirine - EMEA/H/C/004747

Scope: Treatment of adults infected with human immunodeficiency virus 1 (HIV-1) without past or present evidence of viral resistance to treatment of adults to doravirine

5.1.3. Doravirine, lamivudine, tenofovir disoproxil - EMEA/H/C/004746

Scope: Treatment of adults infected with human immunodeficiency virus 1 (HIV-1) without past or present evidence of viral resistance to doravirine, lamivudine, or tenofovir

5.1.4. Lanadelumab - EMEA/H/C/004806, Orphan

Applicant: Shire Pharmaceuticals Ireland Limited

Scope (accelerated assessment): Routine prevention of angioedema attacks and control of symptoms of hereditary angioedema (HAE) in patients aged 12 years and older

5.1.5. Neratinib - EMEA/H/C/004030

Scope (re-examination procedure): Extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER2)-overexpressed, amplified breast cancer who are less than one year from the completion of prior adjuvant trastuzumab based therapy

Previous PRAC advice was provided in July 2017, see [PRAC minutes July 2017](#).

5.1.6. Pegfilgrastim - EMEA/H/C/004700

Scope: Treatment of neutropenia

5.2. Medicines already authorised – PRAC-led procedure

See also Annex I 15.2.

5.2.1. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/II/0023

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Caroline Laborde

Scope: Update of Annex II.D following the submission of the thirteenth and final study report for the digital ulcer outcome (DUO) registry (listed as a category 3 study in the RMP): a non-interventional post-approval safety study and additional risk minimisation measure in the bosentan EU RMP. The RMP (version 9.1) is updated accordingly

Background

Bosentan is a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (ETA and ETB) receptors. It is indicated, as Stayveer, for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO¹⁶ functional class III under certain conditions. Stayveer (bosentan) is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

The PRAC is evaluating a variation procedure for Stayveer, a centrally authorised medicine containing bosentan and duplicate of Tracleer (bosentan), evaluating the thirteenth and final study report for the digital ulcer outcome (DUO) registry: a multicentre, prospective, observational, non-interventional programme to document adherence to product information requirements for liver function and pregnancy testing. This registry study was imposed at the time of the approval of the extension of indication for Tracleer (bosentan) in 2007 to 'reduce the number of new digital ulcers (DU) in patients with systemic sclerosis and ongoing digital ulcer disease'. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for as Stayveer (bosentan) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 9.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the objectives of the DUO registry were met, in particular in the assessment of the compliance with liver function testing and contraceptive measures at the time of enrolment and over the time of patients' follow-up. The PRAC considered that the study was satisfactorily completed and therefore supported the proposed update of Annex II on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' to remove the obligation to conduct the study. The RMP should be adjusted accordingly.

5.2.2. [Bosentan - TRACLEER \(CAP\) - EMEA/H/C/000401/II/0086](#)

Applicant: Actelion Registration Limited

PRAC Rapporteur: Caroline Laborde

Scope: Update of Annex II.D following the submission of the thirteenth and final study report for the DUO registry (listed as a category 3 study in the RMP): a non-interventional PASS and additional risk minimisation measure in the bosentan EU RMP. The RMP (version 9.1) is updated accordingly

Background

¹⁶ World Health Organization

Bosentan is a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (ETA and ETB) receptors. It is indicated, as Tracleer, for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO¹⁷ functional class III under certain conditions. Tracleer (bosentan) is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

The PRAC is evaluating a variation procedure for a centrally authorised medicine containing bosentan, evaluating the thirteenth and final study report for the digital ulcer outcome (DUO) registry: a multicentre, prospective, observational, non-interventional programme to document adherence to product information requirements for liver function and pregnancy testing. This registry study was imposed at the time of the approval of the extension of indication in 2007 to 'reduce the number of new digital ulcers (DU) in patients with systemic sclerosis and ongoing digital ulcer disease'. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for as Tracleer (bosentan) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 9.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the objectives of the DUO registry were met, in particular in the assessment of the compliance with liver function testing and contraceptive measures at the time of enrolment and over the time of patients' follow-up. The PRAC considered that the study was satisfactorily completed and therefore supported the proposed update of Annex II on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' to remove the obligation to conduct the study. The RMP should be adjusted accordingly.

5.3. Medicines already authorised – CHMP-led procedure

See also Annex I 15.3.

5.3.1. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0020

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include the use of Lynparza (olaparib) tablets as monotherapy for the treatment of adult patients with BRCA-1/2-mutated human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting. 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 16) are updated accordingly

Background

¹⁷ World Health Organization

Olaparib is an inhibitor of human poly (adenosine diphosphate (ADP)-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), indicated, as Lynparza, as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian as well as relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) following platinum-based chemotherapy.

The CHMP is evaluating an extension of the therapeutic indication for Lynparza, a centrally authorised product containing olaparib, to include the use of Lynparza (olaparib) tablets as monotherapy for the treatment of adult patients with *BRCA*-1/2-mutated human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer who have previously been treated with chemotherapy. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP for as Lynparza (olaparib) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 16 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed that the important identified risk of anaemia should be removed from the list of safety concerns in line with revision 2 of GVP module V on 'risk management systems'. In addition, the wording of the important potential risk on medication errors as proposed by the MAH should be reworded as 'medication errors associated with dual availability of capsules and tablets'. The PRAC also agreed that missing information should be updated with 'long-term exposure to/potential toxicity of olaparib'.

6. Periodic safety update reports (PSURs)

6.1. Evaluation of PSUR procedures for centrally authorised products (CAPs)

See also Annex I 16.1.

6.1.1. Cabozantinib - CABOMETYX (CAP), COMETRIQ (CAP) - PSUSA/00010180/201711

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases (RTKs) indicated for the treatment of advanced renal cell carcinoma (RCC) under certain conditions. It is also indicated in the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cabometyx and Cometriq, centrally authorised medicines containing cabozantinib, 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 Cabometyx and Cometriq (cabozantinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of Cabometyx (cabozantinib) should be updated to include 'venous thrombosis' and 'arterial thrombosis' as undesirable effects with frequency 'common', and 'cerebrovascular accident' and 'myocardial infarction' with frequency 'not known'. In addition, the product information of Cometriq (cabozantinib) should be updated to include 'cerebrovascular accident' as an undesirable effect with frequency 'common' and 'myocardial infarction' with frequency 'not known'. Furthermore, 'transient ischaemic attack' with frequency 'uncommon' should be removed. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH should provide cumulative and literature reviews of cases of 'heart failure/ejection fraction decreased' reported with cabozantinib.

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. Etelcalcetide - PARSABIV (CAP) - PSUSA/00010533/201711

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Etelcalcetide is a synthetic peptide calcimimetic agent indicated for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Parsabiv, a centrally authorised medicine containing etelcalcetide, 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 Parsabiv (etelcalcetide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'hypersensitivity' as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.
- In the next PSUR, the MAH should provide detailed reviews of cases of 'gastrointestinal bleeding' as well as 'death' reported cases.

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

¹⁹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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.

Considering the possible clinical consequences leading to severe hypocalcaemia when Parsabiv (etelcalcetide) is co-administered with cinacalcet-containing product(s), the PRAC advised to request the MAH of the originator cinacalcet-containing product to submit to EMA, within 90 days, a detailed review on the wash-out period for switching patients from etelcalcetide- to cinacalcet-containing product(s).

6.1.3. Fondaparinux - ARIXTRA (CAP) - PSUSA/00001467/201712

Applicant: Aspen Pharma Trading Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Fondaparinux is a synthetic and selective inhibitor of activated factor X (Xa) indicated for the prevention of venous thromboembolic events (VTE) under certain conditions. Fondaparinux is also indicated for the treatment of acute symptomatic spontaneous superficial vein thrombosis (SVT) of the lower limbs without concomitant deep vein thrombosis (DVT) as well as for the treatment of unstable angina (UA), ST segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI) under certain conditions. In addition, it is indicated for the treatment of DVT and treatment of acute pulmonary embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Arixtra, a centrally authorised medicine containing fondaparinux, 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 Arixtra (fondaparinux) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the warning on patients with heparin induced thrombocytopenia (HIT) due to the potential cross-reactivity of fondaparinux to sera. Therefore, the current terms of the marketing authorisation(s) should be varied²⁰.
- In the next PSUR, the MAH should provide a thorough assessment on the implementation of follow-up questionnaires and their effectiveness in relation to the use of fondaparinux during pregnancy.

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.

²⁰ Update of SmPC sections 4.4 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.4. Ibrutinib - IMBRUVICA (CAP) - PSUSA/00010301/201711

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK) indicated in monotherapy for the treatment of adults with relapsed or refractory mantle cell lymphoma (MCL), for the treatment of previously untreated adults with chronic lymphocytic leukaemia (CLL) as well as for the treatment of adults with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. In addition, ibrutinib is indicated in monotherapy or in combination with bendamustine and rituximab (BR) for the treatment of adults with CLL who have received at least one prior therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Imbruvica (ibrutinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'peripheral neuropathy' as an undesirable effect with frequency 'common'. In addition, the product information should be updated to refine the frequency of dose reductions and discontinuations due to adverse drug reactions. Therefore, the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should review cases of infection and fatal cases from study PCYC-1139-CA²². In addition, the MAH should perform a review of cases of 'hepatic failure' on the entire population cumulatively enrolled in monotherapy trials. Moreover, the MAH should include reviews of cases of alopecia, organising pneumonia, invasive fungal infection and cases of psychiatric disorders. The MAH should discuss the need to update the product information accordingly 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.

6.1.5. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/201711 (with RMP)

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

²¹ 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

²² Clinical study with ibrutinib with bortezomib and dexamethasone in relapsed refractory multiple myeloma

Background

Lumacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) corrector and ivacaftor is a CFTR potentiator. In combination, they are indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Orkambi, a centrally authorised medicine containing lumacaftor/ivacaftor, 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 Orkambi (lumacaftor/ivacaftor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information related to false positive urine tests for tetrahydrocannabinol (THC). Therefore the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAH should discuss the findings related to respiratory events during treatment initiation described by Walayat *et al.*²⁴ and Richards *et al.*²⁵. In addition, the MAH should provide a discussion on cases of depression in patients under 18 years and whether younger patients are at higher risk of experiencing depression while being treated with Orkambi (lumacaftor/ivacaftor). Finally, the MAH is requested to confirm whether additional information regarding use of Orkambi (lumacaftor/ivacaftor) while breastfeeding is available and to discuss whether amendment to the product information is warranted.

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

6.1.6. Pixantrone - PIXUVRI (CAP) - PSUSA/00009261/201711

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Pixantrone is a cytotoxic aza-anthracenedione indicated for the treatment of adults with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL).

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

²³ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁴ Walayat S, Hussain N, Patel J, Hussain F, Patel P, Dhillon S, Drug-induced dyspnoea versus cystic fibrosis exacerbation: a diagnostic dilemma *Int Med Case Rep J.* 2017; 10(243-46)

²⁵ Richards C, Sicilian L, Neuringer I, Decline and recovery of lung function with the initiation and cessation of lumacaftor-IVA *Am. J. Respir Crit Care Med* 2017; 195(-): A1508

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Pixuvri (pixantrone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'hepatotoxicity' as an undesirable effect with frequency 'uncommon'. Therefore the current terms of the marketing authorisation(s) should be varied²⁶.
- In the next PSUR, the MAH should provide an overview of cases in the PIXreal²⁷ study and any other available sources of non-interventional data where doses were omitted rather than modified or delayed, including details of the reasons for dose omission and details of patients' outcomes following treatment. The MAH should also present any data on the efficacy of treatment after doses have been omitted and discuss ways to investigate this. In addition, the MAH should discuss whether the information on dose modifications in the product information is sufficient to minimise any risks from omission of doses.

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

6.1.7. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201712

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) NS5B ribonucleic acid (RNA)-dependent RNA polymerase indicated for the treatment of chronic hepatitis C (CHC) in adults and in adolescents.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sovaldi, a centrally authorised medicine containing sofosbuvir, 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 Sovaldi (sofosbuvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the warning of cardiac arrhythmias with co-administration of sofosbuvir-containing regimens and amiodarone. In addition, the product information should be updated to include 'Stevens-Johnson

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

²⁷ An observational, multicentre, open-label study of pixantrone 50mg/m² given on days 1, 8, and 15 of each 28-day cycle for up to 6 cycles for the treatment of adult patients with multiply relapsed or refractory aggressive B-cell non-Hodgkin lymphomas

syndrome' (SJS) as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.

- In the next PSUR, the MAH should provide a discussion on reactivation of hepatitis delta (HDV) following direct acting antiviral (DAA) therapy for HCV described by *Childs et al.*²⁹ and should provide a cumulative review on HDV reactivation following initiation of DAA treatment and any potential clinical impact.

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 PRAC considered that the above recommendation updating the product information of Sovaldi (sofosbuvir) is relevant to the other sofosbuvir-containing products. Therefore, the PRAC advised that the MAH(s) should be requested to submit to EMA, within 60 days, a variation to implement the respective updates for these medicinal products.

6.1.8. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/201711

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Vedolizumab is a humanized monoclonal gut-selective antibody indicated for the treatment of adults with moderately to severely active ulcerative colitis as well as for adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alfa (TNFa) antagonist.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Entyvio, a centrally authorised medicine containing vedolizumab, 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 Entyvio (vedolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'anaphylactic reaction' and 'anaphylactic shock' as undesirable effects with frequency 'very rare'. Therefore the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH should provide cumulative reviews of cases of liver injury and cases of herpes zoster infection.

²⁸ 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

²⁹ Childs K, Cannon M, Byrne R, Bruce M, Tylor C, Carey I, et al. Reactivation of hepatitis delta (HDV) following directly acting antiviral (DAA) therapy for hepatitis C (HCV) in a man with quadruple infection (hepatitis B virus (HBV)/HCV/HDV/human immunodeficiency virus (HIV)). Abstract 24. International Conference on Viral Hepatitis (ICVH) - IAPAC 2017 Oct 9-10; Chicago

³⁰ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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. Venetoclax - VENCLYXTO (CAP) - PSUSA/00010556/201712

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Venetoclax is a selective inhibitor of B-cell lymphoma (BCL)-2 indicated for the treatment of chronic lymphocytic leukaemia (CLL) for adults who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Venclyxto, a centrally authorised medicine containing venetoclax, 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 Venclyxto (venetoclax) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'sepsis' as a warning and as an undesirable effect with frequency 'common'. Therefore the current terms of the marketing authorisation(s) should be varied³¹.
- In the next PSUR, the MAH should provide a cumulative review on cases of hepatobiliary 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.

6.2. Evaluation of PSUR procedures for centrally authorised products (CAPs) and nationally authorised products (NAPs)

See Annex I 16.2.

6.3. Evaluation of PSUR procedures for nationally authorised products (NAPs)

See also Annex I 16.3.

6.3.1. Atorvastatin (NAP) - PSUSA/00010347/201710

Applicant(s): various

PRAC Lead: Valerie Strassmann

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

Scope: Evaluation of a PSUSA procedure

Background

Atorvastatin is a synthetic lipid-lowering agent indicated for the prevention of cardiovascular diseases as well as for the treatment of hypercholesterolaemia under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing atorvastatin 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 atorvastatin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the effect of co-administration of atorvastatin with elbasvir/grazoprevir as well as the maximum dose recommended for atorvastatin in this situation. In addition, the product information should be updated to reflect a contraindication with glecaprevir/pibrentasvir, and to highlight the elimination pathway information for atorvastatin so that healthcare providers have all the information available as regards future interactions with atorvastatin-containing products. Therefore, the current terms of the marketing authorisation(s) should be varied³².
- In the next PSUR, MAHs should provide a cumulative review of cases of 'spontaneous abortion' due to suspected paternal-mediated exposure. In addition, the MAHs should include the data from the study by *McLean et al.*³³ entitled 'statin interaction with influenza vaccine, leading to reduced vaccine immune response'.
- The PRAC considered that the safety concerns of 'systemic lupus erythematosus/lupus erythematosus/lupus-like syndrome' and 'muscle rupture/torn muscle' needed to be further assessed. Further consideration is to be given at the level of the CMDh.

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

6.3.2. Deoxycholic acid (NAP) - PSUSA/00010525/201710

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Deoxycholic acid is an endogenous bile acid indicated for the treatment of moderate to severe convexity or fullness associated with submental fat (SMF) in adults when the presence of SMF has a psychological impact for the patient.

³² Update of SmPC sections 4.2, 4.3, 4.4, 4.5 and 5.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³³ McLean et al. Effect of statin use on influenza vaccine effectiveness; *J Infect Dis.* 2016 Oct 15;214(8):1150-8

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing deoxycholic acid 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 deoxycholic acid-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'injection site hypoaesthesia' as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAHs should discuss cases of 'lymphadenopathy', 'ear pain', 'hypoaesthesia oral' and 'neck pain'.

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.

6.3.3. Epinastine (NAP) - PSUSA/00001231/201710

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Epinastine is a histamine H1-receptor antagonist indicated for the treatment and/or prevention of the signs and symptoms of seasonal conjunctivitis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing epinastine 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 epinastine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'hypersensitivity reaction' including symptoms or signs of eye allergy and extra-ocular allergic reactions, including angioedema, skin rash and redness as well as eye swelling and/or eyelid oedema with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁵.

³⁴ 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

³⁵ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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. Morphine (NAP); morphine, cyclizine (NAP) - PSUSA/00010549/201710

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Morphine is an opioid receptor agonist and cyclizine is a histamine H1 receptor antagonist of the piperazine class. Morphine and morphine/cyclizine are indicated for the relief of severe pain.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing morphine and morphine/cyclizine 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 morphine and morphine/cyclizine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on 'acute chest syndrome' in patients with sickle cell disease, a warning on 'adrenal insufficiency', on 'hypogonadism', on 'hyperalgesia', on interaction with benzodiazepines and other sedative medicines, and a warning on morphine abuse, overdose and risk factors. In addition, the product information should be updated to include 'anaphylactoid reaction', 'allodynia', 'hyperalgesia', 'hyperhidrosis', and 'dry mouth' as undesirable effects with frequency 'not known', and to include 'dysphoric mood' and 'anxiety' as drug withdrawal symptoms. Furthermore, the product information should be updated to include information on reduced fertility and risk of chromosomal damage, and on the risk of neonatal abstinence syndrome in newborns of mothers treated with opioids. Lastly, the product information of morphine sulfate-containing products authorised for injection/infusion should be updated to include information on incompatibility of morphine sulfate and 5-fluorouracil. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.
- In the next PSUR, the MAHs should provide a cumulative analysis of cases of 'serotonin syndrome' in patients who had already received serotonergic medicines, but only developed serotonin syndrome within a relevant time after addition of morphine. In addition, MAHs should include detailed cumulative reviews of cases of deafness, deep vein thrombosis (DVT) and pulmonary embolism associated with morphine use in DVT, interaction with antiplatelet agents as well as myocardial infarction or acute coronary syndrome.

³⁶ Update of SmPC sections 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.3 and 6.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- The PRAC considered that the risk of interaction between morphine and rifampicin is relevant to be included in the product information of medicinal products containing rifampicin. Further consideration is to be given at the level of the CMDh.

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. Prulifloxacin (NAP) - PSUSA/00002569/201710

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Prulifloxacin is a fluoroquinolone antibiotic indicated for the treatment of certain types of urinary tract infections (UTI), for the treatment of acute exacerbation of chronic bronchitis, and for the treatment of acute bacterial rhinosinusitis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing prulifloxacin 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 prulifloxacin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on 'exacerbation of myasthenia gravis' as well as to include it as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁷. This recommendation is without prejudice to the final conclusions of the ongoing referral procedure under Article 31 of Directive 2001/83/EC for fluoroquinolones and quinolones for systemic and inhalation use (EMA/H/A-31/1452). See under 3.2.1.

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

6.3.6. Treprostinil (NAP) - PSUSA/00003013/201711

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

³⁷ 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

Treprostinil is a prostacyclin analogue indicated for the treatment of primary pulmonary arterial hypertension to improve exercise tolerance and symptoms of the disease in patients classified as NYHA³⁸ class III.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing treprostinil 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 treprostinil-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'pain in extremity' with frequency 'common' and 'high output cardiac failure' with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁹.

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 procedures

See Annex I 16.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁴⁰

See also Annex I 17.1.

7.1.1. Cerliponase alfa – BRINEURA (CAP) - EMEA/H/C/PSP/S/0063

Applicant: BioMarin International Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Protocol for study 190-504 (previously known as study 190-501): a non-interventional PASS in order to evaluate the long-term safety of cerliponase alfa, including the occurrence of serious hypersensitivity reactions and anaphylaxis in patients with neuronal ceroid lipofuscinosis type 2 (CLN2)

Background

Brineura is a centrally authorised medicine containing cerliponase alfa, an alimentary tract and metabolism product. Brineura (cerliponase alfa) is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

³⁸ New York Heart Association

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

Since Brineura (cerliponase alfa) has been approved under exceptional circumstances, pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete as a post authorisation measure a non-interventional PASS: study 190-501, based on an adequate source of data deriving from a registry of patients with CLN2, in order to evaluate the long-term safety of cerliponase alfa, including the occurrence of serious hypersensitivity reactions and anaphylaxis. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH BioMarin International Limited submitted on 29 March 2018 a PASS protocol version 1.0 to EMA for Brineura (cerliponase alfa). The evaluation procedure started on 16 April 2018.

Of note, the original protocol (study 190-501) submitted as part of the initial marketing authorisation application was designed as an observational disease study. However, the MAH proposes to change the design of the study to an observational drug study focusing mainly on safety. The main reasons for the MAH to switch to an observational drug study are related to feasibility issues since the proposed disease registry study would compete with an already existing disease registry (DEM-CHILD⁴¹). The MAH stated its commitment to continuing the collaboration with DEM-CHILD and in an effort to do so proposes to enrol only patients treated with cerliponase alfa into the newly proposed protocol for study 190-504 with the primary objective of evaluating the long-term safety of cerliponase alfa in patients with neuronal CLN2 disease.

Endorsement/Refusal of the protocol

- The PRAC, having reviewed the PASS protocol 190-504 version 1.0, dated 13 April 2018, and in accordance with Article 107n of Directive 2001/83/EC, considered that the PASS protocol for Brineura (cerliponase alfa) could be endorsed, provided that satisfactory clarifications are provided regarding the feasibility of conducting an observational disease study with the possibility of collecting safety data in collaboration with DEM-CHILD, as well as that the number of potentially eligible patients for the study is at least estimated.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 day-assessment timetable will be applied.

7.1.2. [Dexketoprofen, tramadol \(NAP\) - EMEA/H/N/PSP/S/0062](#)

Applicant: Menarini International Operations Luxembourg S.A. (Dextradol, Enanplus, Lenizak, Takudex)

PRAC Rapporteur: Eva Segovia

Scope: PASS protocol for a drug utilisation study (DUS) on dexketoprofen-tramadol (DKP-TRAM) fixed combination to evaluate the pattern of prescriptions of DKP-TRAM and assess the risk of adverse events (AE) (e.g. nausea, vomiting, diarrhoea, vertigo) in DKP-TRAM vs. tramadol monotherapy (including tramadol-paracetamol combinations) users, with a special focus on patients 75 years old and over

Background

⁴¹ Treatment oriented research project of neuronal ceroid lipofuscinoses (NCL) disorders as a major cause of dementia in childhood

Dexketoprofen trometamol is a non-steroidal anti-inflammatory drug (NSAID). Tramadol is a weak opioid with central analgesic activity and long-lasting effect. Dexketoprofen trometamol plus tramadol hydrochloride (25 mg/75 mg) (DKP-TRAM) is a pharmacological fixed-dose combination with analgesic activity indicated in the symptomatic short-term treatment of moderate to severe acute pain in adult patients.

This study was imposed as a condition of the marketing authorisation during procedure ES/H/0317-0318/001/DC to address concerns regarding the safety and tolerability of this high dose fixed combination of tramadol and dexketoprofen in the general population including the frail-elderly and very elderly patients in the approved indication. The drug utilisation study (DUS) and PASS on the fixed combination DKP-TRAM, is a category 1, imposed, cohort, population-based study, part of the approved RMP (version 2.2 dated 21 December 2017). In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH, Menarini International Operations Luxembourg S.A. submitted on 3 April 2018 a PASS protocol version 01 to EMA for the fixed combination DKP-TRAM. The evaluation procedure started on 16 April 2018.

Endorsement/Refusal of the protocol

- The PRAC, having reviewed the PASS protocol version 01, dated 26 March 2018, and in accordance with Article 107n of Directive 2001/83/EC, considered that the PASS protocol for DKP-TRAM could be endorsed, provided that satisfactory responses are provided regarding the definition of the daily dose, the selection of comparators, the justification of the sample size calculation and explanations on how data will be managed when a patient receives different treatment courses of DKP-TRAM during the 3-month follow-up period.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

Post-meeting note: Further to a request from the MAH, the PRAC agreed on 10/07/2018 by written procedure to extend by additional 60 days the timelines for submission to EMA of the requested revised PASS protocol.

7.1.3. Nonacog beta pegol – REFIXIA (CAP) - EMEA/H/C/PSP/S/0059

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a non-interventional PASS in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate safety of N9-GP during long term routine use

Background

Refixia is a centrally authorised medicine containing nonacog beta pegol, an antihæmorrhagic blood coagulation factor IX. Refixia (nonacog alfa) is indicated for the treatment and prophylaxis of bleeding in patients aged 12 years and above with haemophilia B (congenital factor IX deficiency).

The authorisation of Refixia (nonacog alfa) is subject to the obligation to conduct, as a post-authorisation measure, a non-interventional post-authorisation safety study (PASS) deriving from a registry of haemophilia patients according to an agreed protocol in order to

investigate the potential effects of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and other tissues/organs. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n of Directive 2001/83/EC, the MAH, NovoNordisk, submitted on 14 March 2018 a PASS protocol version 1.11 to EMA for Refixia (nonacog beta pegol).

The evaluation procedure started on 16 April 2018.

Endorsement/Refusal of the protocol

- The PRAC, having reviewed the PASS protocol version 1.16, dated 12 June 2018, and in accordance with Article 107n of Directive 2001/83/EC, considered that the PASS protocol for Refixia (nonacog beta pegol) could be endorsed.

7.1.4. Prasterone – INTRAROSA (CAP) - EMEA/H/C/PSP/S/0061

Applicant: Endoceutics Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a non-interventional PASS: a drug utilisation study (DUS) to describe the baseline characteristics and utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa (prasterone) and to assess whether EU prescribers abide by the contraindications stated in the EU SmPC

Background

Intrarosa is a centrally authorised medicine containing prasterone, a precursor steroid. Intrarosa (prasterone) is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

The authorisation of Intrarosa (prasterone) is subject to the obligation to conduct, as a post-authorisation measure, a non-interventional PASS - drug utilisation study (DUS) to describe the baseline characteristics, utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa (prasterone) and to assess whether EU prescribers abide by the contraindications stated in the EU SmPC. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n of Directive 2001/83/EC, the MAH, Endoceutics Ltd. submitted on 28 March 2018 a PASS protocol version 1.0 to EMA for Intrarosa (prasterone).

The evaluation procedure started on 16 April 2018.

Endorsement/Refusal of the protocol

- The PRAC, having reviewed the PASS protocol version 1.0, dated 26 March 2018, and in accordance with Article 107n of Directive 2001/83/EC, considered that the PASS protocol for Intrarosa (prasterone) could be endorsed, provided that satisfactory responses are provided regarding the proposed milestones, data sources, study size, data analysis and potential missing information on indication and contraindications in all proposed EU databases.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴²

See Annex I Error! Reference source not found.

7.3. Results of PASS imposed in the marketing authorisation(s)⁴³

See also Annex I 17.3.

7.3.1. Alanine, arginine, aspartic acid, calcium chloride dihydrate, cysteine, glucose anhydrous, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, magnesium acetate tetrahydrate, methionine, olive oil refined, ornithine, phenylalanine, potassium acetate, proline, serine, sodium chloride, sodium glycerophosphate hydrated, soya bean oil refined, taurine, threonine, tryptophan, tyrosine, valine (NAP) - EMEA/H/N/PSR/S/0017

Applicant: Baxter Healthcare Ltd. (Numeta)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: PASS results for a multicentre, non-interventional, uncontrolled, open-label, observational study in children (up to age 24 months) to generate descriptive data for serum magnesium (Mg) levels in full-term, new born infants and children up to 24 months of age following dosing with Numeta G16%E; to observe the following parameters in subjects who receive parenteral nutrition (PN) with Numeta G16%E: 1) actual infused Numeta G16%E intake (mL/kg/day); 2) actual nutritional intake (total calories from oral, enteral, and parenteral sources other than Numeta); 3) adverse events (AEs) and serious adverse events (SAEs), including clinically significant (CS) abnormal laboratory results and CS abnormal vital signs

Background

Numeta G16%E emulsion for infusion is a nationally authorised product that was subject to a referral procedure under Article 107i of Directive 2001/83/EC, which concluded in September 2013 (see [EMA/564255/2013](#)). The conclusion of the referral requested (see [Annex V](#)) a prospective non-interventional post-authorisation safety study to further evaluate magnesium levels observed in term newborn infants and children up to two years of age treated with Numeta G16%E in routine clinical practice. A protocol dated 3 July 2014 for study 7032-001 was endorsed by the PRAC on 10 July 2014. For further background, see [PRAC minutes February 2014](#), [PRAC minutes May 2014](#), [PRAC minutes, June 2014](#) and [PRAC minutes July 2014](#).

The final study report was submitted to EMA by MAH Baxter with an update of the RMP and the product information (PI) resulting from the data presented in this PASS final study report. The PRAC discussed the final study results. For further background, see [PRAC minutes March 2018](#).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the PASS entitled 'a multicentre, non-interventional, uncontrolled, open-label, observational study in children (up to age 24

⁴² 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

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

months) to evaluate serum Mg levels associated with the intake of Numeta G16%E' version dated 31 October 2017, the PRAC considered that the benefit-risk balance of medicinal products containing the active substances alanine/arginine/aspartic acid/calcium chloride dihydrate/cysteine/glucose anhydrous/glutamic acid/glycine/histidine/isoleucine/leucine/lysine/magnesium acetate tetrahydrate/methionine/olive oil refined/ornithine/phenylalanine/potassium acetate/proline/serine/sodium chloride/sodium glycerophosphate hydrated/soya bean oil refined/taurine/threonine/tryptophan/tyrosine/valine concerned by the PASS final report is subject to a request for supplementary information before a recommendation can be made.

- The MAH should submit to EMA within 60 days complementary analyses of serum Mg levels, a description of the proportion of subjects in the study that had $\geq 70\%$ of their nutritional need covered by Numeta for at least 5 consecutive days, for 6-10 days, and for >10 days, a clarification on the rationale for classifying four cases as hypermagnesemia with verification that correct normal ranges have been provided, a discussion as to whether the data provided can identify any risk factors predicting a rapid increase in serum Mg and presentation of the data on actual intake of Numeta as mL/kg/day. A 60 day-assessment timetable will be applied.

7.3.2. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/PSR/S/0014

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: PASS results for an observational study to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis

Background

Kalydeco (ivacaftor) is a respiratory system product, potentiator of the CFTR⁴⁴ protein, indicated for the treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. The MAH was required as a condition to the marketing authorisation ([Annex II-D](#)) to set up a PASS⁴⁵ in the form of a 5-year long-term observational study with ivacaftor in patients with cystic fibrosis, including microbiological and clinical endpoints (e.g. exacerbations), according to a protocol agreed with the CHMP.

The final study report was submitted to EMA by MAH Vertex on 11 December 2017 with an update of the RMP and the product information (PI) resulting from the data presented in this PASS final study report. The PRAC discussed the final study results. For further background, see [PRAC minutes March 2018](#).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'an observational study to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis', the PRAC considered that the benefit-risk balance of Kalydeco (ivacaftor)

⁴⁴ Cystic fibrosis transmembrane conductance regulator

⁴⁵ EUPAS4270. An Observational Study to Evaluate the Long-term Safety of Ivacaftor in Patients With Cystic Fibrosis

remains unchanged. As a consequence, the PRAC recommended that the terms of the marketing authorisation(s) for Kalydeco (ivacaftor) should be varied to remove the PASS as an 'obligation to conduct a post-authorisation measure' from Annex II on 'conditions or restrictions with regard to the safe and effective use of the medicinal product'.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁶

See Annex I 17.4.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation⁴⁷

See also Annex I 17.5.

7.5.1. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 013.5

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 013.4 [annual interim report from an observational database-assisted comparative cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma ISN 9463-CL-140: a multicentre cohort study of the short and long-term safety of micafungin and other parenteral antifungal agents (MYCOS)] as per the request for supplementary information (RSI) adopted at the September 2017 PRAC meeting

Background

Mycamine is a centrally authorised medicine containing micafungin, an antimycotic for systemic use, indicated in adults, adolescents ≥ 16 years of age and elderly patients, for the treatment of invasive candidiasis, the treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate and the prophylaxis of Candida infection in patients undergoing allogeneic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/ μ l) for 10 or more days. Mycamine (micafungin) is also indicated in children (including neonates) and adolescents <16 years of age for the treatment of invasive candidiasis, and for the prophylaxis of Candida infection in patients undergoing allogeneic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/ μ l) for 10 or more days.

The MAH, Astellas Pharma Europe B.V., committed to conduct post-authorisation an observational database-assisted comparative cohort study entitled 'a multicentre cohort study of the short and long-term safety of micafungin and other parenteral antifungal agents (MYCOS)' to investigate the risk of hepatotoxicity and hepatocellular carcinoma (HCC). The study protocol has two time points for analysis. The first analysis is performed on the results obtained 30 days after hospital discharge following the first in-hospital treatment with a parenteral antifungal agent. The second analysis time point is defined as the 'late analysis' which is assessed after linkage of the patient data with the US 'National Death Index' (NDI) to obtain reliable numbers on death caused by HCC on a long-term basis (up to 13 years; 2005 through 2017) and to analyse the risk of liver cancer as a function of antifungal agent

⁴⁶ 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

⁴⁷ In line with the revised variations regulation for any submission before 4 August 2013

used and of other patient characteristics. The first time point '30-day analysis' was completed in November 2014. An updated report was submitted by 20 August 2015 and was assessed by PRAC. For further background, see [PRAC minutes December 2015](#), [PRAC minutes June 2016](#), [PRAC minutes January 2017](#), and [PRAC minutes September 2017](#).

Summary of advice

- The PRAC acknowledged that given the low HCC mortality event rates within the study, further extension of the study for additional 2 years as per protocol would not sufficiently increase the power regarding detection of any differences in event rates. Therefore, even after study extension, the study would not allow for meaningful analyses of the primary HCC mortality endpoint and it was also acknowledged that further increasing the patient numbers would be challenging. In the context of the submission of the final report through a variation, the MAH is requested to further discuss the initial assumptions on incidence rates and sample size calculation of the study.
- The post-authorisation measure is not considered fulfilled and the MAH should provide, by November 2018, the final report on a revised analysis of liver injury incorporating transaminase in combination with bilirubin thresholds as described in the common terminology criteria for adverse events (CTCAE) v4.0 and proposed by the MAH as well as the the final mortality report (late analysis report), and further discuss the initial assumptions on incidence rates and sample size calculation. Deviations from the initial assumptions and reasons for the lower incidence rates within the study should be discussed including the suitability of study design and data sources to identify relevant cases to derive incidence rates. In particular the possibility that HCC is under-ascertained through the NDI should be examined. The MAH should also discuss in the final report other more frequent causes of death ascertained within the study and should provide data on all-cause mortality.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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)

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 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. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/R/0079 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

Background

Influenza vaccine (live attenuated, nasal) is indicated for the prophylaxis of influenza in children and adolescents from 24 months to less than 18 years of age.

Fluenz Tetra, a centrally authorised influenza vaccine (live attenuated, nasal) containing antigens for four influenza virus strains (an A/(H1N1) strain, an A/(H3N2) strain, and two B strains)) was authorised in 2013.

The MAH submitted an application for renewal of the marketing authorisation 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 Fluenz Tetra (influenza vaccine (live attenuated, nasal)) and the CHMP Rapporteur's assessment report, the PRAC considered that the MAH should be requested to propose a study plan for estimating the effectiveness of quadrivalent live attenuated influenza vaccine (Q/LAIV) against A/H1N1pdm09 for at least two influenza seasons to demonstrate that the issues associated with the signal 'lower than expected vaccine effectiveness' against A/H1N1pdm09 are addressed. In addition, the MAH should compare the 'risk of hypersensitivity reactions in subjects vaccinated with Q/LAIV to the same risk associated to other vaccines and should discuss whether the concern associated with hypersensitivity reactions should be further reviewed. Moreover, safety information collected via cases of accidental exposure to Q/LAIV of pregnant and lactating women or exposure of children with active wheezing or severe asthma, or new safety data related to exposure of children with severe chronic diseases should be discussed in future 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 minutes.

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

11.1.1. Dienogest, ethinylestradiol (NAP) - DE/H/xxxx/WS/534

Applicant: Bayer (Celimona, Celimone, Maxim, Valette)

PRAC Lead: Valerie Strassmann

Scope: PRAC consultation on a worksharing variation assessing the risk of venous thromboembolism with combined hormonal contraceptives (CHCs) containing

dienogest/ethinylestradiol (DNG/EE) compared to levonorgestrel/ethinylestradiol-containing CHCs

Background

In 2013, the EMA reviewed the risk of venous thromboembolism (VTE) with different progestogen-containing combined hormonal contraceptives (CHCs) 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. At the time of this review, there was not enough information about the risk of VTE with products containing dienogest to quantify the risk. However, information has been included in the product information for dienogest/ethinylestradiol (DNG/EE)-containing CHCs that 'limited epidemiological data suggest that the risk of VTE with dienogest-containing CHCs may be similar to the risk with levonorgestrel-containing CHCs', which have the lowest VTE-risk among the CHCs.

Following the recent submission by the MAH Bayer Vital GmbH of results of a meta-analysis of four prospective cohort studies⁴⁸ with identical study design on the risk of VTE associated with the use of CHCs containing DNG/EE 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 DNG/EE was identified by Germany. For further background, see [PRAC minutes April 2018](#). In the context of the evaluation of a worksharing type II variation procedure DE/H/xxxx/WS/534 to evaluate the risk of VTE associated with DNG/EE compared to levonorgestrel (LNG)/EE based on the assessment of the results of a meta-analysis of 4 prospective cohort studies with identical study design to investigate the VTE risk in women taking a CHC containing DNG/EE versus the VTE risk in women taking a CHC containing LNG/EE and further update the product information accordingly, Germany requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported to request the MAH to provide further data, a discussion and analysis regarding the results of the meta-analysis to further evaluate the following main issues: the difference in numbers of VTE cases and exposure data in different study reports, excluded VTE cases and exposure time based on restricting the comparator cohort to women receiving LNG combination containing 30 µg only and further information on sensitivity analysis, regression model and chosen data model (continuous versus categorical variables), TASC sensitivity analysis, and handling of risk factor variables and missing data.
- In addition, pending assessment of the further data to be provided as part of the MAH's responses to the request for supplementary information (RSI) and confirmation of the robustness of the meta-analysis results, the PRAC supported the update of the product information for the CHCs containing DNG/EE, in line with the outcome of the referral procedure under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1356](#)) to reflect the medium VTE risk for these products.

⁴⁸ 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'

- Moreover, the PRAC supported a communication to inform healthcare professionals about the medium VTE risk of CHCs containing DNG/EE in accordance with national needs and requirements, at the discretion of the national competent authorities of the Member States. Finally, the PRAC suggested that the reference Member State for the worksharing procedure, Germany, requests further advice from PRAC on their updated assessment and conclusions regarding the MAH's responses to the request for supplementary information (RSI).

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 on using PRAC plenary time efficiently and effectively – recommendations, implementation plan and goals

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

Following the 2018 PRAC work plan ([EMA/PRAC/139104/2018](#)) and activity to 'monitor the adherence to the principles of the 'Best Practice Guide on using PRAC plenary time efficiently and effectively' and taking into account two years of experience with the current BPG, the PRAC working group identified some areas for improvement and prepared revisions of the current 'BPG' as well as of the 'implementation plan and goals'.

At the current meeting, the working group presented to PRAC the draft revisions of the BPG and the implementation goals for endorsement. The PRAC adopted revision 1 of the BPG and revision 1 of the implementation goals, coming into effect immediately. The PRAC expressed its thanks to the working group for all their work and for the positive impact it has had.

12.2. Coordination with EMA scientific committees or CMDh-v

None

12.3. Coordination with EMA working parties/working groups/drafting groups

None

12.4. Cooperation within the EU regulatory network

12.4.1. European Network Training Centre (EU NTC) - operation of pharmacovigilance in the EU training needs and priorities - plan for trainings 2018 – 2020

The EMA Secretariat updated the PRAC on the training opportunities being made available to the European regulatory network through the European Network Training Centre (EU NTC) and specifically on the EU NTC learning management system. Currently, all EMA committees

are requested to consider priority areas for training for the coming years and to work with experts to develop and deliver training in these priority areas. PRAC members were reminded of the adopted PRAC implementation plan and of the deadlines for delivery of trainings. PRAC members were also requested to update on progress made at National Competent Authorities (NCA) and network levels in this area with the aim of confirming trainings to be delivered in 2018 and plans for 2019 taking into account Brexit- and relocation-related activities. The PRAC will be kept informed on a regular basis.

12.4.2. Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Further to the discussion at the October 2017 PRAC meeting (see [PRAC minutes October 2017](#)), the EMA Secretariat presented to PRAC the outcome of the three-month public consultation on the reflection paper on the 'use of extrapolation in the development of medicines for paediatrics'. PRAC delegates were invited to send written comments by 2 July 2018. A further update will follow in July 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

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list. In addition, the PRAC was presented with the functionalities of the EURD tool under development, aiming to support decision-making on changing PSUR frequencies. The EURD tool will make use of EudraVigilance data as well as other safety related data.

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 dated June 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 June 2018, the updated EURD list was adopted by the CHMP and CMDh at their June 2018 meetings and published on the EMA website on 04/07/2018, 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 SMART working group meeting was cancelled in June 2018 due to rescheduling of the current PRAC plenary meeting to accommodate the public hearing. The next meeting will take place in July 2018.

12.12. Adverse drug reactions reporting and additional monitoring

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 27/06/2018 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 - EudraVigilance stakeholder change management plan: integration with the identity and access management (IAM2) project deliverables

The EMA Secretariat presented to PRAC the Agency's identity and access management (IAM2) project aiming at simplifying the registration and management of EudraVigilance organisations and users from a business process and technology point of view. The PRAC was also presented with a change management plan describing the changes impacting on the EudraVigilance organisation and user management process and how EudraVigilance stakeholders will register, administer and maintain their registration details at organisation and user level. The PRAC noted this information.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

12.14.2. Risk management plan for centrally authorised biological products – Guideline on safety specification – prioritisation strategy

PRAC lead: Doris Stenver, Menno van der Elst, Patrick Batty, Sabine Straus, Ulla Wändel Liminga

Following the adoption of revision 2 of GVP module V on 'Risk management systems' ([EMA/838713/2011 Rev 2*](#)) in 2017, the EMA Secretariat together with a subset of PRAC delegates working as a drafting group further elaborated on the handling of safety specifications for biological- and biosimilar-containing products. At the current meeting, the EMA Secretariat presented to PRAC a draft guidance document on reviewing safety

specification of centrally approved biological products. The aim of the guidance is to establish a strategy to ensure that RMPs are critically reviewed, including their list of safety concerns, at relevant time point(s) when sufficient data are gathered. PRAC delegates were invited to provide written comments by 27 July 2018. Further discussion will take place in due course.

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public 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. Good Pharmacovigilance Practices (GVP) – GVP revisions during 2018 revision cycle

The PRAC was provided with an overview of the GVP module status, including an update on

the ongoing or planned work on new or revised GVP modules together with their scope, and proposed timelines for 2018 for PRAC discussion and adoption.

12.20.2. Type II variations – PRAC and CHMP involvement

In line with the 2018 PRAC work plan ([EMA/PRAC/139104/2018](#)) on the activity on 'optimal role of PRAC for safety related variations', the EMA Secretariat presented to PRAC a proposal for creating a working group composed of PRAC and CHMP delegates to work on a proposal to rationalise CHMP and PRAC involvement in type II variations in line with the expertise and legal mandates of the two committees. PRAC delegates were invited to express interest in joining the working group by 30 June 2018. Further discussion will follow in due course.

13. Any other business

Next meeting on: 09-12 July 2018

14. Annex I – Signals assessment and prioritisation⁴⁹

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 timetables⁵⁰.

14.1.1. Nivolumab – OPDIVO (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of keratoacanthoma

EPITT 19250 – New signal

Lead Member State(s): DE

14.1.2. Rivaroxaban – XARELTO (CAP)

Applicant(s): Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of acquired haemophilia

EPITT 19240 – New signal

⁴⁹ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

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

Lead Member State(s): SE

14.1.3. Tacrolimus⁵¹ – ADVAGRAF (CAP), ENVARSUS (CAP), MODIGRAF (CAP), TACFORIUS (CAP), NAP

Applicant(s): Astellas Pharma Europe B.V. (Advagraf, Modigraf), Chiesi Farmaceutici S.p.A. (Envarsus), Teva B.V. (Tacforius); various

PRAC Rapporteur: Almath Spooner

Scope: Signal of hepatitis E infection

EPITT 19246 – New signal

Lead Member State(s): IE

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

15.1.1. Silodosin - EMEA/H/C/004964

Scope: Treatment of prostatic hyperplasia (BPH)

15.1.2. Ulipristal acetate - EMEA/H/C/005017

Scope: Treatment of uterine fibroids

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

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 4.0) in order to re-classify an imposed non-

⁵¹ Systemic formulations only

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 with Defitelio (defibrotide). Annex II of the product information is updated accordingly

15.2.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/II/0030, Orphan

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 2.10) in order to revise the risk re-categorisation justifications and lay language wording, as well as to add clarifications to the described additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures and set up date of EU network of laboratories, as requested by PRAC following the assessment of the annual renewal procedure completed in February 2018

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

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Julie Williams

Scope: Update of the 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 (300 IU/150 IU, 450 IU/225 IU and 900 IU/450 IU)). Finally, the RMP is aligned with GVP module V on 'Risk management systems', revision 1

15.2.4. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0022

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of the RMP (version 9) in order to remove PASS D5165C00001 (listed as a category 3 study in the RMP): 'a phase 3, multicentre, open label, randomized study to assess the efficacy and safety of osimertinib (AZD9291) in combination with durvalumab (MEDI4736) versus osimertinib monotherapy in patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have received prior EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy (CAURAL)' from the pharmacovigilance plan

15.2.5. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0023

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of the RMP (version 9) in order to remove PASS D5160C00022 (listed as a category 3 study in the RMP): 'an open label, multinational, multicentre, real world treatment study of single agent osimertinib for patients with advanced/metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have received prior therapy with an EGFR tyrosine kinase inhibitor (EGFR-TKI) (ASTRIS)' from the pharmacovigilance plan

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. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0045

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to add information related to earlier treatment extension and related increment intervals based on the final study results of study ALTAIR: an interventional, randomized, open-label phase 4 study evaluating the efficacy and safety of repeated doses of intravitreal (IVT) aflibercept with variable treatment intervals in Japanese subjects with neovascular age-related macular degeneration (AMD). The package leaflet and the RMP (version 24.1) are updated accordingly

15.3.2. Ambrisentan - VOLIBRIS (CAP) - EMEA/H/C/000839/II/0054, Orphan

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.2 and 5.2 of the SmPC based on results of GSK1325760 study: a juvenile nonclinical toxicology study to further investigate the respiratory function following oral dosing from postnatal days 7 through 36, including an assessment of recovery. The RMP (version 7.5) is updated accordingly. In addition, the MAH took the opportunity to correct typographical errors including the frequency of the adverse drug reaction 'rash' in section 4.8 of the SmPC as well as the date of renewal. The MAH also proposed to introduce a minor update in the Braille section. Moreover, the MAH took the opportunity to propose a combined version of the SmPCs for the different authorised strengths

15.3.3. 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: 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. This fulfils ANX 002 (submission of the final clinical study report (CSR) listed as an imposed post-authorisation efficacy study (PAES) in Annex II.D). In addition, the MAH took the opportunity to implement some editorial changes throughout the product information

15.3.4. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0006

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of section 4.8 of the SmPC in order to include pneumonia as an adverse drug reaction with a frequency 'common' as requested in the final PRAC recommendation dated February 2018 for the signal on pneumonia (EPITT - 18950). The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.5. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRIMBOW (CAP) - EMEA/H/C/004257/II/0002

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Extension of indication to include all adult patients with moderate or severe chronic obstructive pulmonary disease (COPD). As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated in order to add the results of two phase 3 studies, namely: 1) study Triple 7 (CCD-05993AA1-07): a multinational, multicentre, randomised, open-label, active-controlled, 26-week, 2-arm, parallel group study to evaluate the non-inferiority of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pressurised metered dose inhaler (pMDI) (CHF 5993) vs fixed combination of fluticasone furoate plus vilanterol administered via dry powder inhaler (DPI) (Relvar) plus tiotropium bromide (Spiriva) for the treatment of patients with COPD; 2) study Triple 8 (CCD-05993AA1-08): a 52-week, double blind, double dummy, randomized, multinational, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pMDI (CHF 5993) versus indacaterol/glycopyrronium (Ultibro) via DPI in patients with COPD (TRIBUTE). The package leaflet and the RMP (version 5.0) are updated accordingly

15.3.6. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0018, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include children aged one month and older to the authorised population for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to include the new population, update the posology and the safety information. The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.7. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0005

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of advanced hepatocellular carcinoma in adults following prior systemic therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated with safety and efficacy information. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.8. Choriogonadotropin alfa - OVITRELLE (CAP) - EMEA/H/C/000320/II/0073/G

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC in order to indicate that thromboembolism can also occur without the presence of ovarian hyperstimulation syndrome (OHSS). The package leaflet and risk management plan (RMP) (version 5.1) are updated accordingly; 2) update of the RMP to extend the important potential risk of 'misuse' to 'weight loss and anabolic growth promoting effect'. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet, to make editorial changes in the product information and in the Annex A (list of authorised presentations). The MAH also took the opportunity to make some minor revisions in the RMP

15.3.9. 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'. 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

15.3.10. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/II/0102, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Submission of the clinical study report (CSR) of study C11-003 (listed as a category 3 study in the RMP): an observational, multicentre, multinational long term follow up study of atypical haemolytic uremic syndrome (aHUS) patients treated with eculizumab in a prior clinical study. The RMP (version 18) is updated accordingly, in line with the new RMP template and include proposals to remove the missing information 'long term safety in aHUS patients', to align the frequency of the submission of the reports on the healthcare professionals (HCP) survey as well as the controlled distribution and the aHUS registry to PSUR submission every 2 years

15.3.11. Enoxaparin sodium - INHIXA (CAP) - EMEA/H/C/004264/X/0026

Applicant: Techdow Europe AB

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to add two new strengths of 30,000 IU (300 mg)/3 mL and 50,000 IU (500 mg)/5 mL for enoxaparin sodium solution for injection in vial, for subcutaneous, extracorporeal and intravenous administration. The RMP (version 3) is updated accordingly

15.3.12. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0050

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC based on the final clinical study report (CSR) of study EXSCEL (EXenatide Study of Cardiovascular Event Lowering): 'a randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus' in fulfilment of PAM (LEG 009). The package leaflet and the RMP (version 31) are updated accordingly

15.3.13. 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 a PASS, the Salford lung study (SLS)-asthma (HZA115150) (listed as a category 1 study in the RMP): a 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate/vilanterol inhalation powder delivered once daily via a novel dry powder inhaler compared with usual maintenance therapy in subjects with asthma to further investigate the risk of pneumonia (ANX005). The RMP (version 9.2) is updated accordingly. In particular, the RMP is updated to amend the important identified risk of pneumonia in line with findings from the study, to provide a justification for the removal of the important potential risk of asthma related intubations and deaths as well as to provide a justification for the removal of missing information related to long term use in asthma (>1 year). Consequently, Annex II is updated

15.3.14. 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

15.3.15. 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

15.3.16. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0069, Orphan

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include treatment of cystic fibrosis in children age 12 to less than 24 months who have one of the currently approved gating mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene for Kalydeco (ivacaftor) 50 mg and 75 mg granules. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Relevant consequential changes are made to Kalydeco (ivacaftor) 150 mg film-coated tablet product information. The package leaflet and the RMP (version 7.2) are updated accordingly

15.3.17. Lapatinib - TYVERB (CAP) - EMEA/H/C/000795/II/0051

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.1 and 5.1 of the SmPC based on results from study EGF114299/LAP016A2307 (listed as a condition (ANX027.4) in Annex II): a phase 3 trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI versus lapatinib plus an AI as first- or second-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received prior trastuzumab and endocrine therapies. Annex II is updated accordingly. In addition, the RMP (version 34.0) is updated accordingly

15.3.18. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/X/0034/G

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Grouped variations consisting of: 1) extension application to introduce a new pharmaceutical form (granules) in 2 strengths (100/125 mg and 150/188 mg) for paediatric use from 2 to 5 years. The RMP (version 4.0) is updated accordingly; 2) update of sections 4.1, 4.2, 4.5, 4.8 and 5.3 of the SmPC of the tablet formulations to bring it in line with the

proposed paediatric 2-5 year old extension application

15.3.19. 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

15.3.20. 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 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-cytotoxic 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

15.3.21. 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

15.3.22. 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

15.3.23. Octocog alfa - ADVATE (CAP) - EMEA/H/C/000520/II/0092

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to add new data on immune tolerance induction (ITI) following the final results from study PASS-INT-004: a prospective, multicentre, uncontrolled, open-label, non-interventional post-authorisation safety surveillance study conducted to evaluate Advate (octocog alfa) in ITI therapy in subjects with moderate or severe haemophilia A (baseline factor VIII \leq 2%) and a high titre ($>$ 5 Bethesda units (BU)) inhibitor to FVIII. The RMP (version 16.0) is updated accordingly

15.3.24. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0021

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of SmPC sections 4.5, 4.6 and 5.2 to reflect the results of study D5160C00036 assessing the effect of single and multiple oral doses of osimertinib on the pharmacokinetics of a P-glycoprotein (P-gp) probe drug (fexofenadine) in patients with advanced epidermal growth factor receptor mutated (EGFRm) non-small-cell lung carcinoma (NSCLC) that have progressed on a prior epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) regimen. The package leaflet and the RMP (version 9) are updated accordingly. In addition, the MAH took the opportunity to make a minor correction in Annex II and to implement minor editorial and/or QRD template related changes in the SmPC and package leaflet

15.3.25. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0024

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2 and 5.2 of the SmPC based on the results from study D5160C00008 to determine the pharmacokinetics, safety and tolerability of osimertinib following a single oral dose to patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment. The RMP (version 9) is updated accordingly

15.3.26. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0043

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include first line treatment of non-squamous non-small cell lung cancer (NSCLC) in combination with pemetrexed and platinum chemotherapy based on the efficacy and safety data from pivotal study KEYNOTE-189, supported by data from KEYNOTE-021 cohorts C and G. KEYNOTE-189 is a phase 3, randomized, placebo-controlled study undertaken to evaluate the efficacy and safety of pembrolizumab + pemetrexed + carboplatin or cisplatin (pembrolizumab combo) versus saline placebo + pemetrexed + carboplatin or cisplatin (control) in previously untreated subjects with advanced/metastatic non-squamous NSCLC with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations. KEYNOTE-021 is a phase 1/2 study of pembrolizumab in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 16.2) are updated accordingly

15.3.27. Regadenoson - RAPISCAN (CAP) - EMEA/H/C/001176/II/0027

Applicant: GE Healthcare AS

PRAC Rapporteur: Patrick Batty

Scope: Extension of indication to include use in the measurement of fractional flow reserve (FFR) during invasive coronary angiography (ICA) in patients presenting a coronary artery stenosis based on results from study 060912001: a comparison of Rapiscan (regadenoson) and central intravenous adenosine for measurement of fractional flow reserve and data from published literature. 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 10.0) are updated accordingly

15.3.28. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0149

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the maintenance of remission of granulomatosis with polyangiitis (GPA) (Wegener's) and microscopic polyangiitis (MPA). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 17.0) are updated accordingly. In addition, the MAH took the opportunity to implement a terminology change in Annex II

15.3.29. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0150

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the treatment of patients with moderate to severe pemphigus vulgaris (PV). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 17.0) are updated accordingly

15.3.30. 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 lymphangioliomyomatosis. 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 reflect minor formatting changes in the labelling

15.3.31. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0027

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 4.8 of the SmPC in order to add safety information based on the final results from study 16099 (listed as a post-authorisation efficacy study (PAES) in the RMP): a prospective, randomized, open-label, active-controlled, multicentre study to evaluate the efficacy and safety of tedizolid in Japanese patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections (skin and soft tissue infection (SSTI) and SSTI-related bacteraemia). The RMP (version 4.0) is updated accordingly in line with the RMP template, revision 2

15.3.32. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0076

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include as a paediatric indication 'treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids' to RoActemra (tocilizumab) 162 mg solution for injection in pre-filled syringe formulation, based on data from phase Ib pharmacokinetic/pharmacodynamic bridging study WA28118 (JIGSAW 118), designed to confirm the RoActemra subcutaneous dosing regimens in patients aged 1 to 17 years old with sJIA, as well as assess the safety of the RoActemra subcutaneous formulation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 24.0) are updated accordingly. In addition, sections 4.2, 4.8 and 5.2 of the SmPC of RoActemra (tocilizumab) 20 mg/mL concentrate for solution for infusion formulation are updated to reflect data from the pivotal intravenous study WA18221 (TENDER), a randomised, placebo-controlled study to evaluate the effect of tocilizumab on disease response in patients with active sJIA

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

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include slowing the progression of cyst development and

renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 4 at initiation of treatment with evidence of rapidly progressing disease 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 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

15.3.34. Vardenafil - LEVITRA (CAP) - EMEA/H/C/000475/WS1390/0062; VIVANZA (CAP) - EMEA/H/C/000488/WS1390/0058

Applicant: Bayer AG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.4 and 4.8 of the SmPC to reflect data from two post-marketing observational studies namely 1) study NCT00759174: a study to assess whether phosphodiesterase type 5 inhibitor (PDE5) inhibitors increase the chance of triggering the onset of acute non-arteritic anterior ischaemic optic neuropathy (NAION)', 2) study NCT01131104: 'a study to determine if there is a possible association between NAION and PDE5 inhibitors'; indicating an increased risk of NAION when using phosphodiesterase 5 (PDE5) inhibitors. The MAH also proposed to terminate the NAION study 12912: a prospective case crossover study to assess whether PDE5 inhibitor exposure in men with erectile dysfunction increases the risk for the development of NAION. The RMP (version 5.0) is updated accordingly. In addition, the product information is brought in line with the QRD template (version 10.0) and the contact details of the Bulgarian local representative are updated in the package leaflet. The package leaflets for the 5 mg, 10 mg and 20 mg film-coated tablet strengths are combined into a single package leaflet and the product information for the 10 mg orodispersible tablet is updated for aspartame and sorbitol, according to the annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, the MAH took the opportunity to introduce some editorial amendments to the product information

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

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

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

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

16.1.1. Tolvaptan⁵² - JINARC (CAP) - PSUSA/00010395/201711

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Aclidinium bromide, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP), DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201711K, WILL JUST HAVE A LOOK NOW IN THE AGENDA

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.3. Aflibercept⁵³ - EYLEA (CAP) - PSUSA/00010020/201711

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.4. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/201711

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.5. Autologous CD34⁺ enriched cell fraction that contains CD34⁺ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - PSUSA/00010505/201711

Applicant: GlaxoSmithKline Trading Services Limited, ATMP⁵⁴

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.6. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201712

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

⁵² Indicated for adults with autosomal dominant polycystic kidney disease (ADPKD)

⁵³ Ophthalmological indication(s) only

⁵⁴ Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.7. Daclizumab - ZINBRYTA⁵⁵ - PSUSA/00010518/201711 (with RMP)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.8. Dalbavancin - XYDALBA (CAP) - PSUSA/00010350/201711

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.9. Daratumumab - DARZALEX (CAP) - PSUSA/00010498/201711

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.10. Darbepoetin alfa - ARANESP (CAP) - PSUSA/00000932/201710

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.11. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin) (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) - INFANRIX HEXA (CAP) - PSUSA/00001122/201710

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.12. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/201712

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

⁵⁵ European Commission (EC) decision on the MA withdrawal of Zinbryta dated 27 March 2018

16.1.13. Elotuzumab - EMLICITI (CAP) - PSUSA/00010500/201711

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.14. Empagliflozin, linagliptin - GLYXAMBI (CAP) - PSUSA/00010539/201711

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.15. Eribulin - HALAVEN (CAP) - PSUSA/00001254/201711

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.16. Fentanyl⁵⁶ - IONSYS (CAP) - PSUSA/00010453/201711

Applicant: Incline Therapeutics Europe Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.17. Fluciclovine (¹⁸F) - AXUMIN (CAP) - PSUSA/00010594/201711

Applicant: Blue Earth Diagnostics Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.18. Follitropin delta - REKOVELLE (CAP) - PSUSA/00010554/201711

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.19. Fosamprenavir - TELZIR (CAP) - PSUSA/00001470/201710

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

⁵⁶ Transdermal system - centrally authorised product(s) only

[16.1.20. Glycerol phenylbutyrate - RAVICTI \(CAP\) - PSUSA/00010454/201711](#)

Applicant: Horizon Pharma Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

[16.1.21. Human papillomavirus vaccine \[types 16, 18\] \(recombinant, adjuvanted, adsorbed\) - CERVARIX \(CAP\) - PSUSA/00009175/201711](#)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

[16.1.22. Insulin detemir - LEVEMIR \(CAP\) - PSUSA/00001750/201710](#)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

[16.1.23. Ixazomib - NINLARO \(CAP\) - PSUSA/00010535/201711](#)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

[16.1.24. Ketoconazole⁵⁷ - KETOCONAZOLE HRA \(CAP\) - PSUSA/00010316/201711](#)

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

[16.1.25. Meningococcal group B vaccine \(recombinant, adsorbed\) - TRUMENBA \(CAP\) - PSUSA/00010607/201711](#)

Applicant: Pfizer Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

[16.1.26. Metformin, saxagliptin - KOMBOGLYZE \(CAP\) - PSUSA/00002686/201711](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

⁵⁷ Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.27. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/201711

Applicant: Amicus Therapeutics UK Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.28. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - PSUSA/00010296/201711

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.29. Necitumumab - PORTRAZZA (CAP) - PSUSA/00010471/201711

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.30. Nelarabine - ATRIANCE (CAP) - PSUSA/00002132/201710

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.31. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/201712

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.32. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/201711

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.33. Osimertinib - TAGRISSO (CAP) - PSUSA/00010472/201711

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.34. Pentosan polysulfate sodium⁵⁸ - ELMIRON (CAP) - PSUSA/00010614/201712

Applicant: bene-Arzneimittel GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.35. Rituximab - BLITZIMA (CAP), MABTHERA (CAP), RITEMVIA (CAP), RITUZENA (CAP), RIXATHON (CAP), RIXIMYO (CAP), TRUXIMA (CAP) - PSUSA/00002652/201711

Applicant(s): Roche Registration GmbH (MabThera), Sandoz GmbH (Rixathon, Riximyo), Celltrion Healthcare Hungary Kft. (Blitzima, Ritemvia, Rituzena, Truxima)

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.36. Rotavirus vaccine pentavalent (live, oral) - ROTATEQ (CAP) - PSUSA/00002666/201711

Applicant: MSD Vaccins

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.37. Sapropterin - KUVAN (CAP) - PSUSA/00002683/201712

Applicant: BioMarin International Limited

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.38. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/201712

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.39. Simeprevir - OLYSIO⁵⁹ - PSUSA/00010255/201711

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.40. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/201711

Applicant: Baxalta Innovations GmbH

⁵⁸ Centrally authorised product(s) only

⁵⁹ European Commission (EC) decision on the MA withdrawal of Olysio dated 5 March 2018

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.41. [Tenofovir alafenamide - VEMLIDY \(CAP\) - PSUSA/00010575/201711](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.42. [Tilmanocept - LYMPHOSEEK \(CAP\) - PSUSA/00010313/201711](#)

Applicant: Norgine B.V.

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.43. [Turoctocog alfa - NOVOEIGHT \(CAP\) - PSUSA/00010138/201710](#)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

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. [Bosentan - STAYVEER \(CAP\), TRACLEER \(CAP\); NAP - PSUSA/00000425/201711](#)

Applicants: Marklas Nederlands BV (Stayveer), Actelion Registration Limited (Tracleer), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.2.2. [Erlotinib - TARCEVA \(CAP\); NAP - PSUSA/00001255/201711](#)

Applicants: Roche Registration GmbH (Tarceva), various

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.2.3. [Insulin human - ACTRAPID \(CAP\), INSUMAN \(CAP\); insulin human, insulin isophane⁶⁰ - ACTRAPHANE \(CAP\), INSULATARD \(CAP\), MIXTARD \(CAP\), PROTAPHANE \(CAP\); NAP - PSUSA/00001753/201710](#)

Applicants: Novo Nordisk A/S (Actraphane, Actrapid, Insulatard, Mixtard, Protaphane),

⁶⁰ Subcutaneous and intravenous routes of administration only

Sanofi-Aventis Deutschland GmbH (Insuman), various

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.2.4. [Sevelamer - RENAGEL \(CAP\), RENVELA \(CAP\), SEVELAMER CARBONATE ZENTIVA \(CAP\), TASERMITY \(CAP\); NAP - PSUSA/00002697/201710](#)

Applicants: Genzyme Europe BV (Renagel, Renvela, Sevelamer carbonate Zentiva, Tasermy), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3. [PSUR single assessment \(PSUSA\) procedures including nationally authorised products \(NAPs\) only](#)

16.3.1. [Acitretin \(NAP\) - PSUSA/00000051/201710](#)

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.2. [Atovaquone, proguanil \(NAP\) - PSUSA/00000266/201710](#)

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.3. [Carvedilol, ivabradine \(NAP\) - PSUSA/00010586/201711](#)

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.4. [Diphtheria, tetanus, pertussis \(acellular, component\), haemophilus type b conjugate vaccine \(adsorbed\) \(NAP\) - PSUSA/00001121/201710](#)

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.5. [Etifoxine \(NAP\) - PSUSA/00001321/201710](#)

Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

16.3.6. Ezetimibe (NAP) - PSUSA/00001346/201710

Applicant(s): various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.3.7. Flupirtine (NAP) - PSUSA/00010225/201710

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.8. Hydroxyzine (NAP); hydroxyzine chloride, hydroxyzine pamoate⁶¹ (NAP) - PSUSA/00001696/201711

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.9. Ketotifen⁶² (NAP) - PSUSA/00001813/201710

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.10. Methoxyflurane (NAP) - PSUSA/00010484/201711

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.11. Methylphenidate (NAP) - PSUSA/00002024/201710

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

⁶¹ Including all fixed combinations

⁶² Oral formulations only

16.3.12. Minoxidil⁶³ (NAP) - PSUSA/00002067/201710

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/LEG 028.2

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to LEG 028.1 [review on the feasibility of conducting a PASS in order to evaluate the risk of adverse cardiovascular events associated with long-term use of anakinra in patients with rheumatoid arthritis (RA) as requested in the conclusions of EMEA/H/C/PSUSA/00000209/201605 adopted by PRAC in December 2016] as per the request for supplementary information (RSI) adopted at the December 2017 meeting

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)⁶⁴

17.1.1. Chlormadinone acetate, ethinyl estradiol (NAP) - EMEA/H/N/PSA/J/0030

Applicant: Gedeon Richter Plc (multiple product names)

PRAC Rapporteur: Valerie Strassmann

Scope: Amendment to a protocol previously agreed by PRAC in January 2016 for a case control study comparing levonorgestrel and chlormadinone acetate in order to evaluate the role of oral contraceptives and the Risk of VEnous Thromboembolism (VTE) (RIVET CC study), to include additional countries, update the study milestones and the statistical analysis plan (SAP) as per the advice by PRAC adopted in January 2018 on the assessment of the first PASS progress report

⁶³ Topical formulations only

⁶⁴ In accordance with Article 107n of Directive 2001/83/EC

17.1.2. 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, paritaprevir, ritonavir – VIEKIRAX (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatasvir – EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir - VOSEVI - EMEA/H/C/PSA/J/0028.1

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

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to PSA/J/0028 [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 Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in April 2018

17.1.3. Velmanase alfa – LAMZEDE (CAP) - EMEA/H/C/PSP/S/0060

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Protocol for the alfa-mannosidosis registry: a multicentre, multi-country, non-interventional, prospective cohort, in alfa-mannosidosis patients to evaluate the long-term effectiveness and safety profile of treatment with Lamzede (velmanase alfa) under conditions of routine clinical care and to characterize the entire alfa-mannosidosis population, including variability of clinical manifestation, progression and natural history

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁵

17.2.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 005.3

Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA005.2 [PASS protocol in order to collect long-term data using the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR) psoriatic arthritis (PsA) registry 'BSRBR PsA registry': a disease registry in the EU for PsA and psoriasis] as per the request for supplementary information (RSI) adopted in January 2018

⁶⁵ 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

17.2.2. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 003

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: PASS protocol for study D3250R00026 'the benralizumab pregnancy exposure study': a post-marketing surveillance study on vaccines and medications in pregnancy surveillance system (VAMPSS) (from initial opinion/MA)

17.2.3. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.1

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002 [Protocol (version 1.0) for study NIS-KYNTHEUM-1345: an observational PASS of suicidal behaviour, serious infections, major adverse cardiovascular events (MACE) and malignancy in psoriasis patients treated with brodalumab. The brodalumab assessment of hazards: a multinational safety (BRAHMS) study in electronic healthcare databases [final report expected in Q3 2030] (from initial opinion/MA)] as per the request for supplementary information (RSI) adopted in January 2018

17.2.4. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/MEA 004

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a non-interventional prospective cohort study in the treatment of children with X-linked hypophosphataemia (XLH) to assess the long term safety of Crysvida (burosumab) during routine clinical care using data collected in a European disease registry for XLH [final report expected in December 2028] (from initial opinion/MA)

17.2.5. Conestat alfa - RUCONEST (CAP) - EMEA/H/C/001223/MEA 019.2

Applicant: Pharming Group N.V

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 019.1 [revised protocol for a survey to measure the effectiveness of risk minimisation materials distributed to treatment centres/prescribing physicians] as per the request for supplementary information (RSI) adopted in January 2018

17.2.6. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/MEA 020.2

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 020.1 [protocol for a survey to evaluate the physician education component of the simplified Ozurdex (dexamethasone) educational materials in order to assess the effectiveness of the educational material provided to physicians treating

patients with Ozurdex by evaluating the physicians' knowledge and understanding of the key information in the Ozurdex injector's guide] as per the request for supplementary information (RSI) adopted in January 2018

17.2.7. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 047

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: Protocol for study No GS EU 276 4487: a prospective, longitudinal, observational registry of emtricitabine/tenofovir disoproxil fumarate for human immunodeficiency virus 1 (HIV-1) pre-exposure prophylaxis (PrEP) in the European Union (as requested in the conclusions of variation II/135)

17.2.8. Florbetaben (¹⁸F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.6

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Patrick Batty

Scope: Amended protocol to previously agreed protocol in September 2016 for PASS study FBB-01_03_13 (PASS 2): a non-interventional, prospective observational multicentre, multi-country registry to observe usage pattern, safety and tolerability of the diagnostic agent NeuraCeq (florbetaben (¹⁸F)) in clinical practice [final clinical study report (CSR) expected in Q2/2020]

17.2.9. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/MEA 002

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for PsoBEST registry: a registry on the treatment of psoriasis with biologics and systemic therapeutics exploring the long-term safety and effectiveness of conventional systemic and biological treatment of psoriasis and psoriatic arthritis in clinical routine in Germany

17.2.10. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/MEA 003

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study PSOLAR: a multicentre, open long-term safety registry study of guselkumab in adult patients with psoriasis, specifically in serious infections, major adverse cardiovascular events (MACE), serious hypersensitivity reactions and malignancies

17.2.11. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Draft protocol synopsis for the extension of the Dutch melanoma treatment registry

(DMTR) to include paediatric subjects and collect safety data to obtain additional safety information in paediatric patients [final clinical study report (CSR) expected in December 2028] (from variation II/44)

17.2.12. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/MEA 014.4

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to a previously agreed protocol by PRAC in November 2015 for study NN8022-4241: a drug utilisation study (DUS) in Europe including retrospective chart review to evaluate whether Saxenda (liraglutide) is used according to the approved indication and posology, as requested in the conclusions of MEA 014.3 on the pilot study adopted in February 2018

17.2.13. Mercaptamine - CYSTADROPS (CAP) - EMEA/H/C/003769/MEA 001.1

Applicant: Orphan Europe SARL

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 001 [protocol for study CYT-DS-001 (listed as a category 3 study in the RMP): an open-label longitudinal PASS to assess the safety of Cystadrops (mercaptamine) in paediatric and adult cystinosis patients in long term use [final clinical study report (CSR) due date: by 2021] as per the request for supplementary information (RSI) adopted in February 2018

17.2.14. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 045 [protocol for study RRA-20745: a PASS to investigate the long-term safety in adult patients with moderately to severely active Crohn's disease] as per the request for supplementary information adopted in January 2018

17.3. Results of PASS imposed in the marketing authorisation(s)⁶⁶

17.3.1. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0012

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: PASS results for an observational post-authorisation modified prescription-event monitoring safety study to monitor the safety and utilization of Xarelto (rivaroxaban) for the prevention of stroke in patients with acute fibrillation (AF), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England, extended to include acute coronary syndrome patients

⁶⁶ In accordance with Article 107p-q of Directive 2001/83/EC

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁶⁷

17.4.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/II/0038

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Karen Pernille Harg

Scope: Submission of the final report from study CLE-20098-096 (listed as a category 3 study in the RMP): a non-interventional PASS, drug utilisation study (DUS) to assess the effectiveness of risk-minimisation measures of Thymanax/Valdoxan (agomelatine)

17.4.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/II/0039

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Karen Pernille Harg

Scope: Submission of the final report from study CLE-20098-096 (listed as a category 3 study in the RMP): a non-interventional PASS, drug utilisation study (DUS) to assess effectiveness of risk-minimisation measures of Thymanax/Valdoxan (agomelatine)

17.4.3. 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

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

Applicant: Gilead Sciences Ireland UC

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

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

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

⁶⁷ 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

Scope: Submission of the final report for the online survey for EU PAS register number EUPAS13634 measuring the effectiveness of the Mycamine (micafungin) prescriber checklist in the EU. The RMP (version 18.0) is updated accordingly

17.4.6. 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

17.4.7. 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

17.4.8. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0186

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Caroline Laborde

Scope: Submission of the final report from study GS-EU-174-1846 (listed as a category 3 study in the RMP, in fulfilment of MEA 273): a multicentre, non-interventional, retrospective, matched cohort study of patients mono-infected with chronic hepatitis B and with moderate or severe renal impairment treated with Viread (tenofovir disoproxil) or entecavir

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation⁶⁸

17.5.1. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.12

Applicant: Pfizer Limited

⁶⁸ In line with the revised variations regulation for any submission before 4 August 2013

PRAC Rapporteur: Martin Huber

Scope: Fifth annual report for PASS B1781044: a cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe [final clinical study report (CSR) expected in April 2020]

17.5.2. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/MEA 005.6

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 005.5 [annual reports from rheumatoid arthritis registries from the US National Databank of Rheumatic Diseases (RA0005), German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (RA0020), Register for Antirheumatic Therapies in Sweden (ARTIS) (RA0021), British Society for Rheumatology Biologicals Register (BSRBR) (RA0022)] as per the request for supplementary information (RSI) adopted in January 2018

17.5.3. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 002.3

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Third progress report and an interim report for study H9X-MC-B009, the dulaglutide European modified prescription-event monitoring and network database study: a multi-database collaborative research programme of observational studies to monitor the utilisation and safety of dulaglutide in the EU

17.5.4. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/MEA 005.5

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 005.3 [Interim study report for study DSE-EDO-01-14-EU (EUPAS17062): a drug utilisation study (DUS), multinational, multicentre involving a retrospective chart review of edoxaban users' medical records. Nested in the study, a cross-sectional survey of all participating prescribing physicians is performed, starting from the date of the first data abstraction and repeated over the course of the study to evaluate the effectiveness of the physician educational programme] as per the request for supplementary information (RSI) adopted in January 2018

17.5.5. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 010.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Second monitoring interim report for PASS study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]

[17.5.6. Empagliflozin, linagliptin - GLYXAMBI \(CAP\) - EMEA/H/C/003833/MEA 002.1](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Second monitoring interim report for PASS study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]

[17.5.7. Empagliflozin, metformin - SYNJARDY \(CAP\) - EMEA/H/C/003770/MEA 006.1](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Second monitoring interim report for PASS study 1245.97: a non-interventional PASS assessing the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes mellitus (T2DM): a multi-database European study [final clinical study report (CSR) expected in June 2021]

[17.5.8. Estrogens conjugated, bazedoxifene - DUAVIVE \(CAP\) - EMEA/H/C/002314/MEA 002.8](#)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Third interim study report for a US (listed as category 3 study in the RMP) non-interventional PASS (B2311060 study): an active surveillance of conjugated oestrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data

[17.5.9. Estrogens conjugated, bazedoxifene - DUAVIVE \(CAP\) - EMEA/H/C/002314/MEA 003.4](#)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: First interim report for a drug utilisation study (DUS) on conjugated oestrogens/ bazedoxifene (CE/BZA) in the European Union (EU) to describe baseline characteristics and utilisation patterns of EU patients initiating Duavive (oestrogens conjugated/bazedoxifene) or oestrogen + progestin (E+P) combination hormone replacement therapy (HRT)

[17.5.10. Lipegfilgrastim - LONQUEX \(CAP\) - EMEA/H/C/002556/MEA 004.5](#)

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 004.4 [interim results for study XM22-ONC-50002: a multi-country, multicentre, retrospective observational drug utilisation study (DUS) to describe the pattern of lipegfilgrastim use and specifically to quantify the extent of lipegfilgrastim off-label use in routine clinical practice in several countries in the European Union (EU)] as per the request for supplementary information adopted in January 2018

17.5.11. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 023.1

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Second progress report for study V72_82OB 'Bexsero pregnancy registry': an observational study of the safety of Bexsero (meningococcal group B vaccine (recombinant, component, adsorbed)) exposure in pregnant women and their offspring

17.5.12. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/MEA 036.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Annual report (covering the period from 01 February 2017 to 31 January 2018) on the effectiveness of risk minimisation measures (RMM) for multiple patch use with copies of Council for International Organizations of Medical Sciences (CIOMS) reports of medication errors and misuse

17.5.13. Rivastigmine - PROMETAX (CAP) - EMEA/H/C/000255/MEA 037.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Annual report (covering the period from 01 February 2017 to 31 January 2018) on the effectiveness of risk minimisation measures (RMM) for multiple patch use with copies of Council for International Organizations of Medical Sciences (CIOMS) reports of medication errors and misuse

17.5.14. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.3

Applicant: Actelion Registration Limited

PRAC Rapporteur: Julie Williams

Scope: First annual interim report for PASS AC-065A401 (EXPOSURE): an observational cohort study of pulmonary arterial hypertension (PAH) patients newly treated with either Upravi (selexipag) or any other PAH-specific therapy in routine clinical practice

17.5.15. Somatropin - OMNITROPE (CAP) - EMEA/H/C/000607/MEA 010.2

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Third interim report for a phase 4 study in 200 small children born small for gestational age (SGA) to measure diabetogenic potential of recombinant human growth hormone (rhGH) therapy in short children born SGA and the occurrence and clinical implications of anti-rhGH antibodies

17.5.16. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/MEA 045.4

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final study report for SUMMACTA study (WA22479 and ML22928), UK British Society of Rheumatology Biologics Register (BSRBR) registry collecting further safety data, including data on hypersensitivity, in patients who switch route of tocilizumab administration from intravenous to subcutaneous pharmaceutical forms (from extension application X/30)

17.5.17. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/MEA 019

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Interim results for study BO39807: an observational study of cardiac events in patients with metastatic breast cancer who have low left ventricular ejection fraction (LVEF) prior to initiating treatment with Kadcyla (trastuzumab emtansine)

17.5.18. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second yearly progress report (28 January 2017-27 January 2018) for study PGL14-001: a prospective, multinational, multicentre, non-interventional study to evaluate the long-term safety of Esmya (ulipristal acetate) in particular the endometrial safety and the current prescription and management patterns of Esmya (ulipristal acetate) in a long-term treatment setting [final clinical study report (CSR) expected in 2023]

17.6. Others

17.6.1. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/MEA 013.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual report (integrated safety analysis report) for clinical studies: 1) study BRF113683 (BREAK-3): a two-arm, open-label, randomized phase 3 pivotal study comparing oral dabrafenib with intravenous dacarbazine (DTIC), 2) study MEK115306 (COMBI-d): a two-arm, double-blinded, randomized, phase 3 study comparing dabrafenib and trametinib combination therapy with dabrafenib administered with a trametinib placebo (dabrafenib monotherapy); 3) study MEK116513 (COMBI-v): a 2-arm, randomized, open-label, phase 3 study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma on secondary malignancies in patients treated with dabrafenib in randomised controlled trials to comply with the additional pharmacovigilance activity as requested in the RMP

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. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0053 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/R/0003 (without RMP)

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/R/0087 (without RMP)

Applicant: Noden Pharma DAC

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.2. [Aripiprazole - ABILIFY MAINTENA \(CAP\) - EMEA/H/C/002755/R/0025 \(with RMP\)](#)

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

18.3.3. [Etravirine - INTELENCE \(CAP\) - EMEA/H/C/000900/R/0052 \(with RMP\)](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Caroline Laborde

Scope: 5-year renewal of the marketing authorisation

18.3.4. [Macitentan - OPSUMIT \(CAP\) - EMEA/H/C/002697/R/0027 \(with RMP\)](#)

Applicant: Actelion Registration Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.5. [Memantine - MEMANTINE ACCORD \(CAP\) - EMEA/H/C/002766/R/0010 \(without RMP\)](#)

Applicant: Accord Healthcare Limited

PRAC Rapporteur: Dolores Montero Corominas

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 11-14 June 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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Anette 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
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 participation	4.3.1. Hydrochlorothia

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			in discussion, final deliberations and voting on:	zide (NAP); Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP),

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				PRITORPLUS (CAP), TOLUCOMBI (CAP)
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	7.5.12. Micafungin - MYCAMINE (CAP) - EMEA/H/C/0007 34/MEA 013.5
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Anne-Cécile Vuillemin	Alternate	Luxembourg	No restrictions applicable to this meeting	Full involvement
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting	3.2.2. Radium (223Ra) dichloride - XOFIGO (CAP) - EMEA/H/A-20/1459 4.3.1.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			on:	Hydrochlorothiazide (NAP); Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP) 4.3.2. Biotin (NAP) 5.1.1. Damoctocog alfa pegol - JIVI (CAP MAA) - EMEA/H/C/004054 , Orphan 11.1.1. Dienogest, ethinylestradiol (NAP) - DE/H/xxxx/WS/534
Adam Przybylkowski	Member - via telephone*	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
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	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
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
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Pernille Lyng Gammelgaard	Expert - in person*	Denmark	No interests declared	Full involvement
Marian Hjortlund Allon	Expert - in person*	Denmark	No interests declared	Full involvement
Helle Wallach Kildemoes	Expert - in person*	Denmark	No interests declared	Full involvement
Hanna Leskinen	Expert - via telephone*	Finland	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Tuire Prami	Expert - via telephone*	Finland	No restrictions applicable to this meeting	Full involvement
Radhakrishnan Rajaratnam	Expert - via telephone*	Finland	No interests declared	Full involvement
Päivi Ruokoniemi	Expert - via telephone*	Finland	No interests declared	Full involvement
Pierre Demolis	Expert - in person*	France	No interests declared	Full involvement
Thomas Grüger	Expert - in person*	Germany	No interests declared	Full involvement
Jelena Katic	Expert - via telephone*	Germany	No interests declared	Full involvement
Tobias Lamkemeyer	Expert - via telephone*	Germany	No interests declared	Full involvement
Nils Lilienthal	Expert - in person*	Germany	No interests declared	Full involvement
Walburga Luetkehermoelle	Expert - via telephone*	Germany	No interests declared	Full involvement
Christoph Unkrig	Expert - in person*	Germany	No interests declared	Full involvement
Grainne Kirwan	Expert - in person*	Ireland	No interests declared	Full involvement
Emma Lawless	Expert - via telephone*	Ireland	No interests declared	Full involvement
Frederika Adriana van Nimwegen	Expert - in person*	Netherlands	No interests declared	Full involvement
Vibeke Åbyholm	Expert - in person*	Norway	No interests declared	Full involvement
Yngvil Knudsen	Expert - in person*	Norway	No interests declared	Full involvement
Pilar Rayon Iglesias	Expert - in person*	Spain	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Marie Gårdmark	Expert - in person*	Sweden	No interests declared	Full involvement
Marta Busana	Expert - in person*	United Kingdom	No interests declared	Full involvement
Mattia Calissano	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - in person*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:

[Home>Committees>PRAC>Agendas, minutes and highlights](#)

21. Explanatory notes

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

[EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures](#)

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, 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=W0b01ac05800240d0

[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/>