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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 08-11 January 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 08-11 January 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 welcomed the new Bulgarian presidency of the Council of the EU.

1.2. Agenda of the meeting on 08-11 January 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 27-30 November 2017

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 27-30 November 2017 were published on the EMA website on 31 January 2018 ([EMA/PRAC/64990/2018](#)).

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

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

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

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

Scope: Review of the benefit-risk balance following notification by Sweden of a referral under Article 107i of Directive 2001/83/EC, based on pharmacovigilance data

Background

Hydroxyethyl starch (HES) is a colloid indicated for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient.

A referral procedure under Article 107i of Directive 2001/83/EC, for the review of HES-containing solutions further to the results of drug utilisation studies (DUS) requested by PRAC as a condition to their marketing authorisations in line with the conclusions of two previous referral procedures under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1348](#)) and under Article 107i of Directive 2001/83/EC ([EMEA/H/A-107i/1376](#)) respectively conducted by the PRAC in 2013 for those medicinal products, is to be concluded. For further background see [PRAC minutes October 2013](#), [PRAC minutes July 2014](#), [PRAC minutes October 2014](#), [PRAC minutes February 2015](#), [PRAC minutes July 2015](#), [PRAC minutes October 2017](#), [PRAC minutes November 2017](#) and [PRAC minutes December 2017](#).

A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs. The PRAC reviewed all newly available data, including results from drug utilisation studies (DUS), clinical studies, meta-analyses of clinical studies, post-marketing experience, EudraVigilance data, literature review, responses submitted by the MAHs in writing and at oral explanations, stakeholders' submissions and views expressed by experts during an ad-hoc expert meeting held on 18 December 2017.

With regard to efficacy, the PRAC considered that there is no new significant information related to the approved indication. Overall, the evidence for this indication is based on studies for which the sample size and the duration of follow-up are limited. It is also noted that although the benefit has been demonstrated in terms of a volume-sparing effect, and there is some support for short-term hemodynamic effects, it remains uncertain to what extent this translates into more patient-relevant outcomes. Therefore, the benefits in the approved indication remain modest.

With regard to the two separate DUSs conducted to assess the effectiveness of the risk minimisation measures imposed as an outcome of the 2013 referrals, the PRAC concluded that these studies, despite limitations due to possible misclassification are representative of clinical usage in the European Union and that the key results are reliable. The results indicate that the implemented restrictions in use are not adhered to. Overall non-adherence to the

¹ Solution for infusion

revised product information was reported to be high, and PRAC was particularly concerned that approximately 9% of patients exposed to HES solutions for infusion were critically ill, approximately 5-8% of patients had renal impairment and approximately 3-4% of patients had sepsis.

The PRAC conclusions of previous reviews under Article 31 of Directive 2001/83/EC and Article 107i of Directive 2001/83/EC were that HES is associated with an increased risk of mortality and renal failure in patients with sepsis or critical illness. The PRAC confirmed that the available information, including more recent submitted clinical data, do not change the established risk of increased mortality and renal failure related to the use of HES solutions for infusion in these patients. The new data provided does not change the conclusions from the previous 2013 referral that the benefits of HES solutions for infusion do not outweigh the serious risks in patients with sepsis or critical illness.

The PRAC also noted the overall exposure to HES solutions for infusion in the EU, estimated to be about 1.5 to 2 million patients per year since 2014. In view of this exposure and the results from the two DUSs, the PRAC concluded that the estimated level of continued usage in populations where serious harm has been demonstrated raises important public health concerns, including a potentially increased mortality.

The PRAC further acknowledged that the current clinical experience suggests that it is difficult to clearly separate patient populations where randomised clinical trials have shown serious harm from populations targeted by the approved indication. Patients in the approved indication may become critically ill or septic shortly after receiving HES solutions for infusion and these patients cannot be identified prospectively. This complicates effective risk minimisation in these patients.

Furthermore, the PRAC considered other options for measures to further mitigate these risks, including changes to the product information, direct healthcare professional communications, educational materials, warning on the primary container of the products, a sign-in for medication form and prescription sheet/checklists. Nevertheless, the available evidence shows that non-adherence is not only due to a lack of awareness of the restrictions by prescribers, rendering further communication and education unlikely to be sufficiently effective. The medication form/checklists would also raise feasibility issues in an emergency setting. The PRAC concluded that no additional risk minimisation measures to ensure safe and effective use of HES solutions for infusion could be identified.

In view of the above, the PRAC concluded that the risks related to the use of HES outweigh their benefits and thus the benefit-risk balance of HES solutions for infusion is no longer favourable. Therefore, the PRAC recommended the suspension of the marketing authorisations for all medicinal products referred to in the procedure.

Summary of recommendation(s)/conclusions

- The PRAC adopted, by majority, the suspension of the marketing authorisations for HES-containing solutions and adopted a recommendation to be considered by CMDh for a position. Nineteen members voted in favour of the recommendation whilst fourteen members had divergent views².
- The PRAC agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

²The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded

- For lifting the suspension, the MAHs should provide reliable and convincing evidence on a favourable benefit-risk balance in a well-defined population, with feasible and effective measures to adequately minimise exposure of patients at an increased risk of serious harm.

See EMA press release ([EMA/4068/2018](#)) entitled 'PRAC recommends suspending hydroxyethyl-starch solutions for infusion from the market - Review finds measures to protect patients have not been sufficiently effective'.

Post-meeting note: the press release 'Hydroxyethyl-starch solutions for infusion to be suspended – CMDh endorses PRAC recommendation' representing the position provided by the CMDh ([EMA/35795/2018](#)) was published on the EMA website on 26 January 2018.

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures³

None

3.5. Others

None

4. Signals assessment and prioritisation⁴

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

³ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

⁴ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

4.2. New signals detected from other sources

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

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

PRAC Rapporteur: Ulla Wändel Liminga

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

EPITT 19121 – New signal

Background

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

The exposure for Humira, a centrally authorised medicine containing adalimumab, is estimated to have been more than 5.09 million patient-years worldwide, in the period from first authorisation in 2002 to 2016.

Following the publication in JAMA by *Lemaitre M, et al.*⁵, a signal of risk of lymphoma in patients with inflammatory bowel disease was identified by France, suggesting an increased risk of lymphoma associated with thiopurines. Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted that lymphoma is already addressed in the product information, both in a form of warnings and among undesirable effects for both adalimumab- and infliximab-, as well as for thiopurines-containing products.

Having considered the evidence arising from this recent publication, the PRAC concluded that this signal merited further investigation. The PRAC will perform an assessment of the study within 60 days, considering the need to engage with the study authors as well as the need to amend the product information.

The PRAC appointed Ulla Wändel Liminga as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed to perform an assessment of the study, considering the need to engage with the study authors as well as the need to amend the product information.

⁵ Lemaitre M, Kirchgessner J, Rudnichi A, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. *JAMA*. 2017;318(17):1679–1686. doi:10.1001/jama.2017.16071

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

4.2.2. Hormonal contraceptives:

Chlormadinone, estradiol (NAP); chlormadinone acetate, ethinylestradiol (NAP); conjugated estrogens, medrogestone (NAP); conjugated estrogens, medroxyprogesterone acetate (NAP); conjugated estrogens, norgestrel (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol⁶ (NAP); dienogest, ethinylestradiol (NAP); drospirenone, estradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, estriol, levonorgestrel (NAP); estradiol, gestodene (NAP); estradiol, levonorgestrel (NAP); estradiol, medroxyprogesterone acetate (NAP); estradiol, norgestimate acetate (NAP); estradiol, norethisterone (NAP); estradiol, norgestimate (NAP); estradiol (17-beta), progesterone (NAP); estradiol (17-beta), trimegestone (NAP); estradiol valerate, norgestrel (NAP); ethinylestradiol, etonogestrel (NAP); ethinylestradiol, etynodiol (NAP); ethinylestradiol, gestodene⁷ (NAP); ethinylestradiol, gestodene⁸ (NAP); ethinylestradiol, levonorgestrel (NAP); ethinylestradiol, lynestrenol (NAP); ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol⁹ (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); mestranol, norethisterone (NAP); norgestimate (NAP); norgestimate acetate, estradiol – ZOELY (CAP); norelgestromin, ethinyl estradiol – EVRA (CAP), NAP; norethisterone (NAP)

Applicant(s): Teva B.V (Zoely), Janssen-Cilag International NV (Evra), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of a known association between hormonal contraceptives and breast cancer following a recent publication

EPITT 19143 – New signal

Background

Hormonal contraceptives are composed of steroid hormones, with two main types of formulations: the combined hormonal contraceptives that contain both an oestrogen and progestin, and the progestogen-only contraceptives that contain only progesterone or progestin. Hormonal contraceptives are primarily used for the prevention of pregnancy, but can also be indicated for the treatment of polycystic ovary syndrome, or menstrual disorders.

Following the recent publication in the New England Journal of Medicine by *Morch L.S., et al.*¹⁰, a signal related to the known association between hormonal contraceptives and a small increase in the risk of breast cancer was identified by Denmark. Denmark confirmed that the signal needed initial analysis.

Discussion

Having considered the available evidence arising from this recent publication on a known association between hormonal contraceptives and breast cancer, the PRAC concluded that

⁶ Contraception indication

⁷ All route of administrations except transdermal

⁸ Transdermal application

⁹ Combination pack

¹⁰ Morch, L. S., Skovlund, C. W., Hannaford, P. C., Iversen, L., Fielding, S. and Lidegaard, O. 2017. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med*, 377, 2228-2239

this signal merits further investigation.

The PRAC agreed to perform an assessment of the study, considering the need to engage with the study authors in relation to the new findings and in the context of the known data.

The PRAC appointed Menno van der Elst as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed to perform an assessment of the study within 60 days considering the need to engage with the study authors in relation to the new findings and in the context of the known data.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3.

Hormonal contraceptives:

Chlormadinone, estradiol (NAP); chlormadinone acetate, ethinylestradiol (NAP); conjugated estrogens, medrogestone (NAP); conjugated estrogens, norgestrel (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol¹¹ (NAP); dienogest, ethinylestradiol (NAP); drospirenone, estradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, estriol, levonorgestrel (NAP); estradiol, gestodene (NAP); estradiol, levonorgestrel (NAP); estradiol, medroxyprogesterone acetate (NAP); estradiol, nomegestrol acetate (NAP); estradiol, norethisterone (NAP); estradiol, norgestimate (NAP); estradiol (17-beta), progesterone (NAP); estradiol (17-beta), trimegestone (NAP); estradiol valerate, norgestrel (NAP); ethinylestradiol¹² (NAP); ethinylestradiol, conjugated estrogens, medroxyprogesterone acetate (NAP); ethinylestradiol, etonogestrel (NAP); ethinylestradiol, etynodiol (NAP); ethinylestradiol, gestodene¹³ (NAP); ethinylestradiol, gestodene¹⁴ (NAP); ethinylestradiol, levonorgestrel (NAP); ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel (NAP); levonorgestrel, ethinylestradiol; lynestrenol (NAP); medroxyprogesterone (NAP); mestranol, norethisterone (NAP); nomegestrol (NAP); nomegestrol acetate, estradiol – ZOELY (CAP); norelgestromin, ethinyl estradiol – EVRA (CAP), NAP; norethisterone (NAP)

Applicant(s): Teva B.V (Zoely), Janssen-Cilag International NV (Evra), various

PRAC Rapporteur: Doris Stenver

Scope: Signal of suicidality with hormonal contraceptives following a recent publication

EPITT 19144 – New signal

Background

Hormonal contraceptives are composed of steroid hormones, with two main types of formulations: the combined hormonal contraceptives that contain both an oestrogen and progestin, and the progestogen-only contraceptives that contain only progesterone or progestin. Hormonal contraceptives are primarily used for the prevention of pregnancy, but can also be indicated for the treatment of polycystic ovary syndrome, or menstrual disorders.

¹¹ Contraception indication

¹² Combination pack

¹³ All route of administrations except transdermal

¹⁴ Transdermal application

Following the recent publication in the American Journal of Psychiatry by *Skovlund et al.*¹⁵, a signal of suicidality with hormonal contraceptives was identified by Denmark. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence arising from this recent publication on the signal of suicidality with hormonal contraceptives, the PRAC considered that despite some limitations of the data, this signal merits further investigation.

The PRAC concurred to request additional clarification from the authors on the study findings in order to better perform an in-depth analysis of the results and assess the need for further action on this issue.

The PRAC appointed Doris Stenver as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed to request additional clarification from the authors on the study findings in order to better perform an in-depth analysis of the results and assess the need for further actions on this issue.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.4.

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: To be appointed

Scope: Signal of skin cancer

EPITT 19138 – New signal

Background

Hydrochlorothiazide is a diuretic used alone or in combination for the treatment of hypertension, congestive heart failure, symptomatic oedema, diabetes insipidus, and renal tubular acidosis.

Following the publications in the Journal of Internal Medicine and in the Journal of the

¹⁵ Skovlund K. C. W., Mørch L. S., Kessing L. V., Lange T. & Lidegaard O. 2017. Association of hormonal contraception with suicide attempts and suicides. *Am J Psychiatry*, appiajp201717060616

American Academy of Dermatology by *Pottegård A et al.*¹⁶ and *Arnsfang S et al.*¹⁷ respectively, a signal of skin cancer was identified with hydrochlorothiazide by Denmark. Finland, Germany and Portugal confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence arising from two recent publications on the signal of skin cancer with hydrochlorothiazide-containing products, the PRAC concluded that this signal merits further investigation.

The PRAC agreed to request the publication authors to provide additional clarification on their study findings in order to better perform an in-depth analysis of the results and assess the need for further actions on this issue.

The PRAC appointed Kirsti Villikka as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed to request the publication authors to provide additional clarification on their study findings in order to better perform an in-depth analysis of the results and assess the need for further actions on this issue.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/SDA/009

Applicant(s): Eli Lilly Nederland B.V

PRAC Rapporteur: Carmela Macchiarulo

Scope: Signal of gastrointestinal stenosis and obstruction

EPITT 18931 – Follow-up to September 2017

Background

For background information, see [PRAC minutes September 2017](#).

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

Discussion

Having considered the available evidence in EudraVigilance, the literature as well as the data submitted by the MAH, including a cumulative review of cases of gastrointestinal stenosis and obstruction using the MedDRA HLG¹⁸ and related terms in association with dulaglutide, the PRAC agreed that the product information should be amended to reflect the

¹⁶ Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, Friis S (University of Southern Denmark; Odense University Hospital, Odense; Kaiser Permanente Northern California, Oakland, CA, USA; Danish Cancer Society, Copenhagen, Denmark). Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med* 2017; 282: 322–331.

¹⁷ Sidsel Arnsfang Pedersen, David Gaist, Sigrun Alba Johannesdottir Schmidt, Lisbet Rosenkrantz Hölmich, Søren Friis, Anton Pottegård. Hydrochlorothiazide use and risk of non-melanoma skin cancer: A nationwide case-control study from Denmark, *Journal of the American Academy of Dermatology*, 2017, ISSN 0190-9622, <https://doi.org/10.1016/j.jaad.2017.11.042>

¹⁸ Medical dictionary for regulatory activities – High Level Group Term

occurrence of the undesirable effects.

Summary of recommendation(s)

- The MAH for Trulicity (dulaglutide) should submit to EMA, within 60 days, a variation for amending the product information¹⁹ to add non-mechanical intestinal obstruction among the gastrointestinal disorders undesirable effects with an unknown frequency.

For the full PRAC recommendation, see [EMA/PRAC/8429/2018](#) published on 05/02/2018 on the EMA website.

4.3.2. [Megestrol \(NAP\); Vitamin K antagonists: acenocoumarol \(NAP\); fluindione \(NAP\); phenindione \(NAP\); phenprocoumon \(NAP\); warfarin \(NAP\)](#)

Applicant(s): various

PRAC Rapporteur: Almath Spooner

Scope: Signal of drug interaction leading to elevated international normalised ratio (INR)/haemorrhage with megestrol and vitamin K antagonists

EPITT 18910 – Follow up to September 2017

Background

For background information, see [PRAC minutes September 2017](#).

The MAH replied to the request for information on the signal of drug interaction leading to elevated international normalised ratio (INR)/haemorrhage with megestrol and vitamin K antagonists and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence including from EudraVigilance, literature as well as the cumulative reviews and detailed analysis of all cases suggestive of an interaction between megestrol and vitamin K antagonists submitted by the MAHs, the PRAC considered that there is insufficient evidence at this time to confirm a specific clinically-relevant drug-drug interaction between megestrol and vitamin K antagonists leading to elevated INR/haemorrhage. However, the PRAC acknowledged that as vitamin K antagonists have a narrow therapeutic index, care is required with all concomitant therapy and increased monitoring should be considering when commencing any new therapy in the absence of reassuring drug-drug interaction studies. The PRAC noted the absence of such drug-drug interaction studies for megestrol and vitamin K antagonists. In this context, the monitoring of the potential drug-drug interaction should be continued as part of routine safety surveillance.

Summary of recommendation(s)

- The MAHs for megestrol- and vitamin K antagonists- (warfarin, acenocoumarol, phenprocoumon, phenindione and fluindione) containing products should continue to monitor the potential for drug-drug interactions as part of routine safety surveillance. As part of the signal detection activities, special focus should be given in the upcoming PSURs and MAHs on closely monitoring this potential interaction and any relevant findings should be promptly submitted.

¹⁹ Update of SmPC section 4.8. The package leaflet should be updated accordingly

4.3.3. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP) - EMEA/H/C/003983/SDA/002.1; NAP

Applicant(s): Nordic Group B.V. (Nordimet); Therakind Limited (Jylamvo); various

PRAC Rapporteur: Martin Huber

Scope: Signal of pulmonary alveolar haemorrhage

EPITT 18850 – Follow-up to September 2017

Background

For background information, see [PRAC minutes September 2017](#).

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

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the product information of methotrexate (MTX)-containing medicinal products with non-oncologic indications, of methotrexate-containing medicinal products with oncologic indications and of methotrexate-containing medicinal products with both non-oncologic and oncologic indications should be amended to reflect the reports of pulmonary alveolar haemorrhage with MTX.

Summary of recommendation(s)

- The MAHs for MTX-containing medicinal products with non-oncologic indications should submit to EMA or to the national competent authorities of the MSs, as applicable, within 60 days, a variation in order to amend the product information²⁰ to include the occurrence of pulmonary alveolar haemorrhage with MTX.
- The MAHs for MTX-containing medicinal products with oncologic indications should submit to EMA and to the national competent authorities of the MSs, as applicable, within 60 days, a variation in order to amend the product information²¹ to include the occurrence of pulmonary alveolar haemorrhage with MTX.
- The MAHs for MTX-containing medicinal products with both non-oncologic and oncologic indications should submit to EMA and to the national competent authorities of the MSs, as applicable, within 60 days, a variation in order to amend the product information²² to include the occurrence of pulmonary alveolar haemorrhage with MTX.

For the full PRAC recommendation, see [EMA/PRAC/8429/2018](#) published on 05/02/2018 on the EMA website.

4.3.4. Pemetrexed - ALIMTA (CAP) - EMEA/H/C/000564/SDA/027

Applicant(s): Eli Lilly Nederland B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Signal of nephrogenic diabetes insipidus

²⁰ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

²¹ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

²² Update of SmPC sections 4.4 and 4.8. The package leaflet should be updated accordingly

EPITT 18930 – Follow-up to September 2017

Background

For background information, see [PRAC minutes September 2017](#).

The MAH for Alimta (pemetrexed) replied to the request for information on the signal of nephrogenic diabetes insipidus and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature as well as the data submitted by the MAH, the PRAC agreed that the product information should be amended to reflect the reporting of nephrogenic diabetes insipidus and renal tubular necrosis in the post-marketing setting.

Summary of recommendation(s)

- The MAHs for pemetrexed-containing products should submit to EMA or to the relevant national competent authorities of the MSs, within 60 days, a variation to amend the product information²³ to add the reports of nephrogenic diabetes insipidus and renal tubular necrosis in the post-marketing setting.

For the full PRAC recommendation, see [EMA/PRAC/8429/2018 Corr1](#) published on 05/02/2018 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Caplacizumab - EMEA/H/C/004426, Orphan

Applicant: Ablynx NV

Scope: Treatment of acquired thrombotic thrombocytopenic purpura (aTTP)

5.1.2. Dolutegravir, rilpivirine - EMEA/H/C/004427

Scope: Treatment of human immunodeficiency virus-1 (HIV-1) infection in virologically-suppressed (HIV-1 RNA²⁴<50 c/mL) adult subjects without known or suspected resistance

²³ Update of SmPC sections 4.4 and 4.8. The package leaflet should be updated accordingly

²⁴ Ribonucleic acid

to either component

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0034

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC in order to include the safety and efficacy information on cardiovascular events following the final results from the CANVAS programme consisting of study DIA3008 (CANVAS study): a phase 3 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM); and study DIA4004 (CANVAS-R study): a phase 4 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM. The package leaflet and the RMP (version 7.2) are updated accordingly

Background

Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated in adults aged 18 years and older with type 2 diabetes mellitus (TD2M) to improve glycaemic control as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications; and as add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

The CHMP is evaluating a type II variation for Invokana, a centrally authorised medicine containing canagliflozin, assessing the MAH's proposal to update the safety and efficacy information on cardiovascular events following the final results from the CANVAS (CANagliflozin cardioVascular Assessment Study) programme integrating results from two clinical trials exploring cardiovascular and renal events. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP for Invokana (canagliflozin) in the context of the type II variation under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 7.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- Following the alignment of the canagliflozin-containing medicines (Invokana, Vokanamet) RMP format with amended principles according to standards of revision 2 of GVP module V on 'Risk management systems', the PRAC agreed to remove from the RMP vulvovaginal candidiasis, balanitis or balanoposthitis, urinary tract infections (UTI),

hypoglycaemia in combination with insulin or glucose independent insulin secretagogues, and hypersensitivity as important identified risks; as well as hypoglycaemia in the absence of insulin or glucose independent insulin secretagogues, and off-label use for weight loss as important potential risks. In addition, the use in patients with congestive heart failure defined as NYHA²⁵ class IV, use in paediatric patients between 10 and 18 years of age, use in very elderly patients, use in patients with severe hepatic impairment and use in patients with severe renal impairment can be removed from the RMP as missing information. Nevertheless, with regard to use in pregnancy and use in nursing mothers, the PRAC supported that these are kept under missing information in the RMP and that the MAH should evaluate and report in the upcoming PSURs the number of pregnant and breastfeeding women treated with canagliflozin-containing product(s).

5.3.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0034

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC in order to include the safety and efficacy information on cardiovascular events following the final results from CANVAS programme consisting of study DIA3008 (CANVAS study): a phase 3 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM); and study DIA4004 (CANVAS-R study): a phase 4 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM. The package leaflet and the RMP (version 7.2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest QRD template (version 10)

Background

Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and metformin a biguanide. In combination canagliflozin/metformin is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in patients not adequately controlled on their maximally tolerated doses of metformin alone, in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products including insulin, when these do not provide adequate glycaemic control, as well as in patients already being treated with the combination of canagliflozin and metformin as separate tablets.

The CHMP is evaluating a type II variation for Vokanamet, a centrally authorised medicine containing canagliflozin/metformin, assessing the MAH's proposal to update the safety and efficacy information on cardiovascular events following the final results from the CANVAS (CANagliflozin cardioVascular Assessment Study) programme integrating results from two clinical trials exploring cardiovascular and renal events. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

²⁵ New York Heart Association

- The RMP for Vokanamet (canagliflozin/metformin) in the context of the type II variation under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 7.2 and satisfactory responses to the request for supplementary of information (RSI) are submitted.
- Following the alignment of the canagliflozin-containing medicines (Invokana, Vokanamet) RMP format with amended principles according to standards of revision 2 of GVP module V on 'Risk management systems', the PRAC agreed to remove, from the RMP, vulvovaginal candidiasis, balanitis or balanoposthitis, urinary tract infections (UTI), hypoglycaemia in combination with insulin or glucose independent insulin secretagogues and hypersensitivity as important identified risks; as well as hypoglycaemia in the absence of insulin or glucose independent insulin secretagogues and off-label use for weight loss as important potential risks. In addition, use in patients with congestive heart failure defined as NYHA²⁶ class IV, use in paediatric patients between 10 and 18 years of age, use in very elderly patients, use in patients with severe hepatic impairment and use in patients with severe renal impairment can be removed from the RMP as missing information. Nevertheless, with regard to use in pregnancy and use in nursing mothers, the PRAC supported that these are kept under missing information in the RMP and that the MAH should evaluate and report in the upcoming PSURs the number of pregnant and breastfeeding women treated with canagliflozin-containing product(s).

5.3.3. Insulin aspart - FIASP (CAP) - EMEA/H/C/004046/II/0003/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Julie Williams

Scope: Grouped variations to: 1) update the RMP (version 2.0) to reclassify the risk of mix-up between basal and bolus insulin from a potential to an important identified risk; 2) update the secondary packaging material (carton, label, instructions for use (IFU)) design and change the colour of selected plastic components from yellow to red. In addition, the MAH submitted as part of this variation a proposal for communication to healthcare professionals (HCPs) and patients (indirectly) regarding similarity between Fiasp and Tresiba (insulin degludec)

Background

Insulin aspart is a fast-acting insulin analogue indicated for the treatment of diabetes mellitus in adults.

The CHMP is evaluating a grouping of type II variations for Fiasp, a centrally authorised medicine containing insulin aspart, assessing the MAH's proposal to update the secondary packaging material design and change the colour of selected plastic components, to distribute some communication material on possible medication errors between Fiasp and Tresiba (insulin degludec) and to update the RMP regarding the risk of a mix-up between basal and bolus insulin. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this grouping of type II variations.

Summary of advice

²⁶ New York Heart Association

- The RMP for Fiasp (insulin aspart) in the context of the grouped variations under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 2.0 and satisfactory responses to the request for supplementary of information (RSI) are submitted.
- The PRAC supported the implementation, as an immediate first step, of colour changes in the packaging material design and pen components of Fiasp to minimise and prevent the risk of mix-ups between insulin pens. The MAH should provide clarity on the timelines for implementation and availability of the new colour-coded pens to the EU market as well as information on the removal of the current pens from the EU market. Clarity on the timelines for implementation of the new colour-coded pens and labels is essential for assessing the need for, and appropriateness of, the proposed communications. Depending on these timelines, if communication was considered necessary, it should be limited, and directed to pharmacies/dispensing clinics. In addition, any future launches of Fiasp to the EU market should be performed using the new proposed colour-coded pens and labels. Finally, PRAC advised some amendments to the follow-up medication error questionnaires to optimise the follow-up of reported medication errors.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Ambrisentan - VOLIBRIS (CAP) - PSUSA/00000129/201706

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Ambrisentan is an endothelin receptor antagonist indicated for the treatment of adult patients with pulmonary arterial hypertension classified as WHO²⁷ functional class II and III, to improve exercise capacity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Volibris, a centrally authorised medicine containing ambrisentan, 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 Volibris (ambrisentan) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

²⁷ World Health Organization

- The MAH should submit to EMA within 90 days, a variation in order to reassess the need for educational material and a controlled distribution system. In addition, the MAH should provide a proposal to modify the key elements and additional risk minimisation measures.
- In the next PSUR, the MAH should submit a cumulative review of cases of thrombocytopenia.

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

6.1.2. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201706

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Blinatumomab is an engager antibody construct indicated for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (R/R Ph negative ALL).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Blincyto, a centrally authorised medicine containing blinatumomab, 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 Blincyto (blinatumomab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'ataxia' as an undesirable effect with a common frequency. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.

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

6.1.3. Daclizumab - ZINBRYTA (CAP) - PSUSA/00010518/201705

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

²⁸ 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

Daclizumab is a humanised monoclonal antibody indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with any other DMT is contraindicated or otherwise unsuitable.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zinbryta, a centrally authorised medicine containing daclizumab, 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 Zinbryta (daclizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'sarcoidosis' and 'colitis' as undesirable effects with an uncommon and common frequency respectively. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.
- In the next PSUR, the MAH should discuss the findings regarding failure to control disease activity after switching from natalizumab to daclizumab, observed in the study conducted by *Uphaus et al*³⁰. In addition, the MAH should submit a cumulative review of cytopenia as well as of immune-mediated events, and should discuss the need for an update of the product information if considered necessary.

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

6.1.4. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201707

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults in monotherapy or in combination with ipilimumab, as well as for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. Nivolumab is also indicated for the treatment of advanced renal cell carcinoma, classical Hodgkin's lymphoma, squamous cell cancer of the head and neck, as well as for urothelial carcinoma in adults under certain conditions.

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

Summary of recommendation(s) and conclusions

²⁹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³⁰ Uphaus T., Oberwittler C., Groppa S. et al. Disease reactivation after switching from natalizumab to daclizumab. *J Neurol* (2017) 264: 2491. <https://doi.org/10.1007/s00415-017-8622-9>

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Opdivo (nivolumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'tumour lysis syndrome' as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.
- In the next PSUR, the MAH should submit a cumulative review of cases of aseptic meningitis or meningitis and of capillary leak syndrome, and discuss the need for an update of the product information as applicable.

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

6.1.5. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/201706

Applicant: Intercept Pharma Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Obeticholic acid is a farnesoid X receptor agonist indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ocaliva, a centrally authorised medicine containing obeticholic acid, 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 Ocaliva (obeticholic acid) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to clarify the recommended dosing regimen in PBC patients according to their hepatic impairment status. In addition, the product information should be updated to reflect that prior to initiation of treatment with obeticholic acid, patients' hepatic status must be known and patients should be monitored to determine whether dosage adjustment is needed. Therefore, the current terms of the marketing authorisation(s) should be varied³².
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan to remind prescribers of the differential dosing recommendations in patients with moderate and severe hepatic impairment.

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.

³¹ 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

³² Update of SmPC sections 4.2, 4.4 and 5.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

See also Annex I 16.2.

6.2.1. Lutetium (¹⁷⁷Lu) chloride - ENDOLUCINBETA (CAP); LUMARK (CAP); NAP - PSUSA/00010391/201706

Applicants: I.D.B. Holland B.V. (LuMark), ITG Isotope Technologies Garching GmbH (EndolucinBeta), various

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Lutetium (¹⁷⁷Lu) chloride is a radiopharmaceutical precursor indicated for the radiolabelling of carrier molecules.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lumark and EndolucinBeta, centrally authorised medicines containing lutetium (¹⁷⁷Lu) chloride, and nationally authorised medicines containing lutetium (¹⁷⁷Lu) chloride, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of lutetium (¹⁷⁷Lu) chloride-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'mild and temporary alopecia' as an undesirable effect with a very common frequency. Therefore, the current terms of the marketing authorisations should be varied³³.

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

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

See also Annex I 16.3.

6.3.1. Alteplase (NAP) - PSUSA/00000112/201705

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

Background

Alteplase is a recombinant tissue plasminogen activator indicated for the thrombolytic treatment in acute myocardial infarction (AMI), in acute massive pulmonary embolism (PE) with haemodynamic instability, as well as for the thrombolytic treatment of acute ischaemic stroke (AIS) under certain conditions. In addition, alteplase is also indicated for the thrombotic treatment of occluded central venous access devices including those used for haemodialysis.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of alteplase-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to better reflect the risk of 'angioedema' of the alteplase-containing products indicated for the thrombolytic treatment in acute myocardial infarction, in acute massive pulmonary embolism with haemodynamic instability and of acute ischaemic stroke. In addition, in all alteplase-containing products, the product information should be updated to better reflect the risk of hypersensitivity reactions. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAH should submit cumulative reviews on off-label use in patients with minor strokes, in patients with seizures at onset of stroke, as well as on major bleeding and mortality in elderly patients irrespective of the indication and with a special focus on patients with ischaemic stroke.

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. Azithromycin³⁵ (NAP) - PSUSA/00010491/201704

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Azithromycin is a macrolide antibiotic indicated for systemic use, for the treatment of some bacterial infections, including respiratory tract infections, acute otitis media, odontostomatological infections, in skin and soft tissue infections and of some genital infections.

³⁴ Update of SmPC section 4.4, 4.5 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³⁵ Formulations for systemic use only

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of azithromycin-containing medicinal products under review in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the interaction between azithromycin and colchicine due to the possible increased serum levels of P-glycoprotein substrates. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.
- In the next PSUR, the MAH should present a review on the possible harms associated with concomitant use of azithromycin and ivabradine.

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

6.3.3. Bismuth subcitrate potassium, metronidazole, tetracycline (NAP) - PSUSA/00010199/201705

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Bismuth subcitrate potassium is a salt of bismuth, potassium and citrate. Bismuth is a chemical element and a pentavalent post-transition metal, and chemically resembles arsenic and antimony. Metronidazole is an antibiotic and an antiprotozoal, and tetracycline is a broad-spectrum antibiotic of the polyketide class. Their combination is indicated for the eradication of helicobacter pylori and prevention of relapse of peptic ulcers in patients with active or a history of helicobacter pylori associated ulcers in combination with omeprazole (quadruple therapy).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of bismuth subcitrate potassium/metronidazole/tetracycline-containing medicinal products in the approved indications remains unchanged.

³⁶ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Nevertheless, the product information should be updated to include 'aseptic meningitis' as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied³⁷.
- In the next PSUR, the MAH should present follow-up information on the acute generalised exanthematous pustulosis (AGEP) case.

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. Candesartan (NAP); candesartan, hydrochlorothiazide (NAP) - PSUSA/00000527/201704

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Candesartan is an angiotensin II receptor blocker and hydrochlorothiazide is a diuretic. Candesartan is indicated as monotherapy for the treatment of hypertension and heart failure, as well as in combination with hydrochlorothiazide for the treatment of hypertension.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of candesartan- and candesartan/hydrochlorothiazide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'diarrhoea' as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisations should be varied³⁸.
- In the next PSUR, the MAHs should submit detailed reviews of cases of squamous cell carcinoma (SCC), taste disorders, thrombocytopenia, pancreatitis, and vasculitis. In addition, the MAH should provide a detailed review of cases of acute hepatocellular injury secondary to candesartan administration and discuss any possible mechanisms of action.

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.

³⁷ 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

³⁸ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.5. Folic acid (NAP) - PSUSA/00001459/201706

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Folic acid is vitamin B9, and is indicated for the prevention of folic acid deficiency, for the treatment of folic acid deficiency and for the prevention of neural tube defects in the developing foetus.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of folic acid-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'anaphylactic reaction' as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied³⁹.

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

6.3.6. Irinotecan⁴⁰ (NAP) - PSUSA/00001783/201705

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Irinotecan is a topoisomerase I inhibitor indicated for the treatment of patients with advanced/metastatic colorectal cancer either as a single agent or in combination.

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

Summary of recommendation(s) and conclusions

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

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 All except liposomal formulations

- Nevertheless, the product information should be updated to include ‘fungal infections (such as *pneumocystis jirovecii* pneumonia, bronchopulmonary aspergillosis and systemic candida)’ as well as ‘viral infections (herpes zoster, influenza, hepatitis B reactivation and cytomegalovirus colitis)’ as undesirable effects with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied⁴¹.
- In the next PSUR, the MAHs should submit detailed reviews of cases of convulsions, interaction with vitamin K antagonists, and haemolytic anaemia as well as of inappropriate antidiuretic hormone secretion.

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.

6.3.7. Methyl salicylate, levomenthol (NAP) - PSUSA/00010241/201704

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Methyl salicylate is an ester of salicylic acid and methanol, and levomenthol is an essential oil extract. Their combination is indicated for the symptomatic relief of pain in muscles and joints associated with strains and sprains.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of methyl salicylate/levomenthol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include ‘burns at application site’ as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied⁴².

The frequency of PSUR submission should be revised to five-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. In addition, the EURD list should be updated to cover in a single entry ‘menthol/methyl salicylate’, ‘menthol/methyl salicylate/camphor’ as well as all menthol and camphor stereoisomers and isomer mixtures in these combinations. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

Considering that data from PSURs for products referred to in Articles 10(1), 10a, 14, 16a of

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

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

Directive 2001/83/EC did not raise any safety concerns, the PRAC agreed that no further PSURs are required for those products. The EURD list is also updated accordingly.

6.3.8. Methyl salicylate, levomenthol, DL-camphor (NAP) - PSUSA/00010117/201704

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Methyl salicylate is an ester of salicylic acid and methanol, and levomenthol and DL-camphor are essential oil extracts. Their combination is indicated for the symptomatic relief in muscle-skeletal conditions, for the treatment of upper respiratory tract congestion and for the treatment of colds and hay fever.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of methyl salicylate/levomenthol/DL-camphor-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'burns at application site' as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied⁴³.

The frequency of PSUR submission should be revised to five-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. In addition, the EURD list should be updated to cover in a single entry 'menthol/methyl salicylate', 'menthol/methyl salicylate/camphor' as well as all menthol and camphor stereoisomers and isomer mixtures in these combinations. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

Considering that data from PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC did not raise any safety concerns, the PRAC agreed that no further PSURs are required for those products. The EURD list is also updated accordingly.

6.3.9. Mifepristone, misoprostol (NAP) - PSUSA/00010378/201705

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

⁴³ 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

Mifepristone is a synthetic steroid and misoprostol is a synthetic analogue of prostaglandin E1. Their combination is indicated for medical termination of intra-uterine pregnancy of up to 63 days of amenorrhoea.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of mifepristone/misoprostol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'uterine rupture' as an undesirable effect with a rare frequency. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁴.

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

6.3.10. Misoprostol⁴⁵ (NAP) - PSUSA/00010354/201705

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Misoprostol is a synthetic prostaglandin E1 analogue indicated for medical termination of early pregnancy and for cervical preparation before surgical abortion during the first trimester. In addition, misoprostol has other EU-approved indications outside the scope of this PSUSA procedure, i.e. a gastrointestinal indication, an indication for labour induction, and an indication for expansion of non-pregnant uterine cervix.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of misoprostol-containing medicinal products in the relevant approved indications remains unchanged.
- Nevertheless, the product information should be updated to reflect that failure of pregnancy termination is associated with an increased risk of birth defects/malformation for ongoing pregnancies and therefore to advise to schedule a follow-up visit to check the status of medical termination of early pregnancy. In addition, 'foetal malformations'

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

⁴⁵ Gynaecological indication - termination of pregnancy only

including the increased risk of central nervous system anomalies should be added as an undesirable effect with a common frequency. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁶.

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

6.3.11. Tramadol (NAP) - PSUSA/00003002/201705

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Tramadol is an opioid analgesic indicated for the treatment of moderate to severe pain.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of tramadol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include warnings on CYP2D6⁴⁷ metabolism of tramadol, as well as on tramadol use in children in post-operative settings and with compromised respiratory function. Updates should be also made to better reflect the information on tolerance and clinical interactions with tramadol. Moreover, since the risks of dependence and withdrawal symptoms have been better characterised through the evaluation of the available literature and post-marketing surveillance, the product information should be updated accordingly. Finally, the information regarding breastfeeding should be amended in order to avoid potential accumulation in newborns, indicating that breastfeeding mothers should not be administered repetitive doses, or alternatively, breastfeeding should be interrupted during prolonged treatment. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁸.
- In the next PSUR, the MAHs should provide cumulative reviews of adrenal insufficiency associated with exposure to tramadol, hepatic injuries and hepatitis, purpura and vascular purpura, as well as of insomnia. Additionally, the MAHs should submit cumulative reviews of decreased sex hormone levels and sexual dysfunction in relation to tramadol and discuss the potential mechanism. Finally, the MAHs for tramadol-containing oral drops should provide a cumulative review of cases of unintentional overdose involving confusion between dosing devices.

⁴⁶ Update of SmPC section 4.4, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁴⁷ Cytochrome P450 2D6

⁴⁸ Update of SmPC section 4.4, 4.6 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

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁴⁹

7.1.1. Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Daclatasvir – DAKLINZA (CAP); dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir – ZEPATIER (CAP); glecaprevir, pibrentasvir – MAVIRET (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatasvir – EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir – VOSEVI (CAP) - EMEA/H/N/PSP/J/0056.2

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

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to EMEA/H/N/PSP/J/0056.2 [Joint PASS protocol for a prospective, non-interventional study evaluating the risk of early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAAV) therapy compared to HCV-infected patients without previous DAA therapy during routine clinical care with previously successfully treated HCC, as per 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 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted at the December 2017 PRAC meeting

Background

A review of direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free) (daclatasvir (Daklinza), dasabuvir (Exviera), ombitasvir/paritaprevir/ritonavir (Viekirax), simeprevir (Olysio), sofosbuvir (Sovaldi), sofosbuvir/ledipasvir (Harvoni)) was carried out by the PRAC in a referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)) to assess the risk of hepatitis B virus (HBV) reactivation as well as the risk of unexpected early hepatocellular carcinoma (HCC) recurrence in patients treated with a DAAV and to establish whether any measures are necessary to minimise these risks. The benefit-risk balance of Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax was considered to remain favourable subject to amendments to the product information and to [conditions](#). As a condition, in order to

⁴⁹ In accordance with Article 107n of Directive 2001/83/EC

evaluate the risk of early recurrence of hepatocellular carcinoma associated with DAAV, the MAHs shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. For further background, see [PRAC minutes December 2016](#).

A revised joint PASS protocol for a prospective, non-interventional study evaluating the risk of early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after DAAV therapy compared to HCV-infected patients without previous DAAV therapy during routine clinical care with previous successfully treated HCC, was presented for further review by the PRAC. For further background, see [PRAC minutes September 2017](#) and [PRAC minutes December 2017](#).

Endorsement/Refusal of the protocol

- The PRAC, having considered the joint final draft protocol version 2.2 in accordance with Article 107n of Directive 2001/83/EC, endorsed the draft protocol for the above listed medicinal product(s) for its primary objective and secondary objective A. Therefore, the recruitment of patients may commence as of the date of receipt of this letter.
- The PRAC considered, however, that the definition of secondary objectives and endpoints related to the historical comparator cohort (secondary objectives/endpoints B and C) require further clarification.
- The MAH should submit a revised PASS protocol addressing the remaining outstanding issues on secondary objectives and endpoints within 30 days to EMA. A 60 days-assessment timetable will be applied.

Post-meeting note: a further discussion was organised via TC on 29 January 2018 to gain clarity on the above-mentioned aspects of the study design.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁵⁰

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)⁵¹

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁵²

See Annex I 17.4.

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

See Annex I 17.5.

⁵⁰ 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

⁵¹ In accordance with Article 107p-q of Directive 2001/83/EC

⁵² 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

7.6. Others

See also Annex I 17.6.

7.6.1. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/MEA 005

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: PASS protocol for study RGH-188-303: a randomized, open-label, ophthalmologist-masked study in approximately 1,000 patients to compare lens opacity changes during long-term treatment for schizophrenia with Cariprazine versus risperidone (from initial opinion/MA)

Background

Cariprazine is an atypical antipsychotic indicated for the treatment of schizophrenia in adult patients.

As part of the RMP for Regalia (Cariprazine), the MAH was required to conduct, as a category 3 study, a long-term safety study to detect cataractogenic changes to further characterize the safety concern of 'ocular adverse events (lenticular changes and cataract)' in clinical practice (PASS RGH-188-303). The MAH Gedeon Richter Plc submitted on 27 October 2017 a PASS protocol original version to the EMA.

Summary of advice

- Based on the preliminary review of the PASS protocol, the PRAC discussed its limitations and agreed to further consider and consolidate its advice at the February 2018 PRAC meeting.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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 Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

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. General anaesthetics and sedative medicines: Desflurane (NAP); enflurane (NAP); etomidate (NAP); esketamine (NAP); halothane (NAP); isoflurane (NAP); ketamine (NAP); midazolam (NAP); propofol (NAP); sevoflurane (NAP); thiopental (NAP)

Applicants: various

PRAC Lead: Ghania Chamouni

Scope: PRAC advice on the scientific relevance to update the product information for general anaesthetics and sedative medicines regarding the risk of developmental disorders when used in children and pregnant women, in light of available safety data from preclinical and clinical studies, FDA action taken in April 2017, and national variations submitted for isoflurane-, sevoflurane- and propofol-containing medicines, on request of France

Background

General anaesthetics are a structurally diverse group of compounds whose mechanisms encompass multiple biological targets involved in the control of neuronal pathways. General anaesthetics, however, typically elicit several key reversible effects: analgesia, amnesia, unconsciousness, immobility, and reduced autonomic responsiveness to noxious stimuli. Sedatives are central nervous depressants and interact with brain activity causing its deceleration. They induce sedation by reducing irritability or excitement.

In the context of the evaluation of type II variation procedures in view of amending the product information of isoflurane-, sevoflurane- and propofol-containing products, France requested PRAC advice on its assessment of the scientific relevance to update the product information for general anaesthetics and sedative medicines regarding the risk of developmental disorders when used in children and pregnant women, given the available safety data from preclinical and clinical studies, the FDA action taken in April 2017, and national variations submitted for isoflurane, sevoflurane and propofol.

Summary of advice

- On the basis of the assessment, the PRAC did not support the addition of the proposed warning in the product information⁵³. As the clinical significance of the non-clinical data remains unclear and no firm recommendations can be given, the usefulness of this information for prescribers would be limited. The inclusion of relevant information in the preclinical safety data⁵⁴ section was considered to be in principle sufficient. Nevertheless, the PRAC advised that the exact wording for this section of the product information should be further considered after consultation with the CHMP Safety Working Party (SWP). The PRAC noted that France will liaise with the SWP in order to further review the robustness of the data before any decision on possible regulatory action is proposed.

⁵³ As a SmPC sections 4.4 and 4.6 update

⁵⁴ As a SmPC section 5.3 update

11.2. Other requests

11.2.1. Chlormadinone acetate, ethinylestradiol (NAP)

Applicants: Gedeon Richter Plc.

PRAC Lead: Valerie Strassmann

Scope: PRAC consultation on the progress report assessment of the RIVET-case control (RIVET-CC) study: a non-interventional PASS (EMA/H/N/PSP/J/0012) imposed following the completion in 2013 of a referral procedure under Article 31 of Directive 2001/83/EC (EMA/607314/2013) for the review of combined hormonal contraceptives (CHCs). The study aims at assessing the risk of venous thromboembolism, (VTE) associated with chlormadinone acetate (CMA) containing combined oral contraceptives (COCs) compared to levonorgestrel (LNG) containing COCs in a large case-control study, on request of Germany

Background

Chlormadinone acetate (CMA) is a steroidal synthetic progestin that can be used as the progestogen component in combined oral contraceptives (COCs). Ethinylestradiol is an oestrogen that can also be used in COCs. In January 2016, the PRAC endorsed in accordance with Article 107n of Directive 2001/83/EC, a revised protocol (version 1.6) for a post-authorisation safety study, to study the risk of venous thromboembolism (VTE) associated with chlormadinone/ethinylestradiol (CMA/EE)-containing products, submitted by a consortium of MAHs in accordance with the conditions to the marketing authorization included in the EC decision [Annex IV](#) for the referral under Article 31 of Directive 2001/83/EC ([EMA/607314/2013](#)) for combined hormonal contraceptives. For further background, see [PRAC minutes May 2014](#), [PRAC Minutes April 2015](#) and [PRAC minutes September 2015](#) and [PRAC minutes January 2016](#). PRAC advice was sought by Germany in September and December 2016 with regards to the corresponding statistical analysis plan. See [PRAC minutes September 2016](#) and [PRAC minutes December 2016](#).

The MAH Gedeon Richter Plc. submitted on 31 August 2017 a PASS progress study report to the German National Agency ([BfArM](#)) addressing the current status and the challenges of the study conduct. The recruitment has been low and several activities have been implemented to improve enrolment. The evaluation of this progress study report is handled at national level by BfArM. PRAC advice is sought by Germany on its assessment.

Summary of advice

- The PRAC agreed with Germany that the MAH should contact additional organisations, engage with physician associations and include additional EU countries in order to increase recruitment into the study. The impact of these new measures should be further monitored as part of new interim reports to be submitted in January 2019 and January 2020.
- In addition, the PRAC considered that the study milestones of the protocol should be amended to reflect the need for amended milestones and to include the new proposed date for submission of the final study report in July 2021. A substantial amendment to the agreed imposed PASS protocol would need to be submitted under Article 107o of Directive 2001/83/EC to reflect inclusion of additional countries and the updated study milestones. This amendment will be assessed by PRAC, and the CMDh will be informed of the change to the imposed condition for any subsequent regulatory action needed for

the nationally authorised marketing authorisation. Finally, the PRAC advised that the substantial amendment to the agreed imposed PASS protocol should be submitted within 60 days of this PRAC advice.

11.2.2. Levothyroxine (NAP) – DE/H/XXXX/WS/356

Applicant: Merck Serono GmbH (Euthyrox)

PRAC Lead: Valerie Strassmann

Scope: PRAC consultation on the handling of the transition period and related communication strategy in the context of a worksharing quality variation for Euthyrox (levothyroxine) on a change in the composition of excipients on request of Germany

Background

Levothyroxine (or L-thyroxine), is a synthetic isomeric form of the thyroid hormone, thyroxine (T4). It is used to treat thyroid hormone deficiency including the severe form known as myxedema coma.

A worksharing variation (DE/H/XXXX/WS/356) on quality aspects is currently being assessed by Germany. The proposed change in the composition is identical to the one approved by the French National Agency ([ANSM](#)) and introduced on the market in France in March 2017.

The German National Agency ([BfArM](#)) took notice of increased number of patient complaints following the introduction of levothyroxine sodium tablets containing mannitol and citric acid in France, which is the first EU Member State where the medicinal product with this composition has been placed on the market.

In the context of the evaluation of this worksharing variation procedure, Germany requested PRAC advice on BfArM's conclusions following the assessment of information provided by ANSM regarding the introduction of the new formulation and on the proposed communication strategy.

Summary of advice

- The PRAC noted the Member State's request for PRAC advice regarding the worksharing variation procedure (DE/H/XXXX/WS/356) for Euthyrox (levothyroxine) with regard to handling of the transition period and a communication strategy to support a secure transition.
- The PRAC supported the BfArM assessment suggesting that the currently available information does not indicate any difference in the pattern of adverse events/reactions reported before and after the transition to levothyroxine new formulation tablets. The PRAC also acknowledged that the particularly high media attention and strengthened surveillance may have played a role in the increased reporting of side effects.
- The PRAC supported to undertake close monitoring and supervision during the transition period for all patients to ensure that the patient's individual dose remains appropriate.
- The PRAC agreed on the need for effective communication during the transition period for both healthcare professionals and patients. Additional communication tools, such as a patient information sheet, may be considered. However, the PRAC acknowledged the role of each individual National Competent Authority in adapting the content of the risk communication/minimisation tools.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

12.3.1. Scientific advice working party (SAWP) – re-nomination of PRAC representative(s)

As a follow-up to the November 2017 PRAC discussion on the CHMP Scientific Advice Working Party ([SAWP](#)) revised mandate and the call to PRAC delegates to express interest in fulfilling the role of joint PRAC-SAWP members (see [PRAC minutes November 2017](#)), the EMA secretariat announced that Brigitte Keller-Stanislawski had been appointed as joint PRAC-SAWP member and Hervé Le Louet as joint PRAC-SAWP alternate.

12.4. Cooperation within the EU regulatory network

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

The EMA Secretariat provided PRAC with a status update on the Brexit preparedness business continuity plan, including Committees' operational preparedness activities in view of the withdrawal of the UK from the European Union and taking into account the future relocation of EMA in Amsterdam, Netherlands.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2018

PRAC lead: June Raine, Almath Spooner

At the organisational matters teleconference held on 25 January 2018, following previous discussions on the PRAC work plan 2018 (see [PRAC minutes November 2017](#)), the PRAC further consolidated the draft final document and supported making the final adjustments and adopting the final work plan 2018 by written procedure.

Post-meeting note: On 31 January 2018, the PRAC adopted its work plan 2018 (EMA/PRAC/139104/2018) by written procedure.

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) expected for 2018 – Q4 2017 update

The EMA Secretariat presented, at the organisational matters teleconference held on 25 January 2018, for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline'). For previous update, see [PRAC minutes October 2017](#).

12.8.2. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q4 2017 and predictions

The EMA secretariat presented, at the organisational matters teleconference held on 25 January 2018, quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators, as well as some predictions in terms of workload by procedure type, where available, and per EU National Competent Authority (NCA) for the upcoming months. For previous update, see [PRAC minutes November 2017](#).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections – Union procedure on follow-up of pharmacovigilance inspections

Further to previous discussion on the draft 'Union procedure on the follow-up of pharmacovigilance inspections' (see [PRAC minutes November 2017](#)), the EMA Secretariat together with a representative from the 'Pharmacovigilance Inspectors Working Group' ([PhV IWG](#)) presented to PRAC an updated draft of the document. Discussions mainly focussed on aspects relating to routine interaction within and between MSs and the EMA as well as actions to be taken following the identification of inspection findings which may impact on the robustness of the benefit-risk profile of medicinal product(s), and re-inspection planning. Specifically, the PRAC discussed aspects of what is considered appropriate local assessment before PRAC escalation as well as aspects regarding referrals and definition of risk levels. The PRAC agreed in principle to a 6 to 12 month pilot where inspection outcomes that may impact the robustness of the benefit risk profile of products will be used as examples and discussed by the PhV IWG-PRAC subgroup and at PRAC level to better

understand how to best to assess corrective and preventive actions (CAPA), additional information and impact assessment received from MAHs and to further define the criteria and process for escalation of inspection outcomes to PRAC. As next steps, the draft document will be updated in light of the PRAC comments and will be discussed at CMDh and PhV IWG before final endorsement at PRAC.

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

At the organisational matters teleconference held on 25 January 2018, the PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the progress made. The PRAC endorsed the GPAG work plan 2018.

12.10.3. PSURs repository

None

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

At the organisational matters teleconference held on 25 January 2018, the PRAC endorsed the draft revised EURD list version December 2017 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 January 2018, the updated EURD list was adopted by the CHMP and CMDh at their January 2018 meetings and published on the EMA website on 31/01/2018, 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

At the organisational matters teleconference held on 25 January 2018, the PRAC was updated on the outcome of the SMART Working Group (SMART WG) meeting held on 8 January 2018. The WG discussed and agreed the work plan 2018 for 'SMART Processes and Methods' covering the mandate, objectives and some operational aspects relating to the two working groups ('SMART WG on processes' previously known as 'PRAC WG work stream (WS)1' and 'SMART WG on methods' previously known as 'PRAC WG WS 2-3'). A particular emphasis was placed on the role of the SMART WG in supporting the overall signal management process and provide guidance in the area. The PRAC endorsed the SMART WG work plan 2018. In addition, the SMART WG discussed the frequency of production of electronic reaction monitoring reports (eRMR) following a survey across the pharmacovigilance EU network. Finally, the SMART WG consolidated the [stand-alone signal notification form](#) in line with GVP module IX on 'Signal management', revision 1. This is to be used by MAHs as part of the pilot to notify signals detected in EudraVigilance for which further analysis is required by the EU regulatory network. Products that are part of the pilot are for a pre-determined list of active substances and combinations (see '[list of active substances and combinations involved in the pilot on signal detection in EudraVigilance by marketing authorisation holders](#)').

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on 31/01/2018 on the EMA website (see: [Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#)).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.13.2. Article 57⁵⁵ database⁵⁶ – Publication of a subset of data on medicinal products

At the organisational matters teleconference held on 25 January 2018, the EMA Secretariat presented to PRAC its plan to publish a subset of Article 57 data on medicinal products authorised in the EU, as per the legal requirement to publish contact details for pharmacovigilance enquiries and the locations in the EU where pharmacovigilance system master files are kept. The publication, planned in Q1/Q2 2018, will also include several additional fields to give more context to the data. 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. 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

⁵⁵ Article 57(2) of Regulation (EU) 726/2004

⁵⁶ Also known as the eXtended EudraVigilance medicinal product dictionary (XEVMPPD)

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) – revision planned for 2018 - update on GVP status overview

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. Strategy on measuring the impact of pharmacovigilance – final pilot report and work planning 2018

PRAC lead: Valerie Strassmann

Further to the December 2017 PRAC discussion and adoption of revision 1 of the 'PRAC strategy on measuring the impact of pharmacovigilance activities' (see [PRAC minutes December 2017](#)), the PRAC was presented at the organisational matters teleconference on 25 January 2018 with the final report of the PRAC interest group (IG) impact pilot, including recommendations. The PRAC welcomed the progress made and endorsed the report.

12.20.3. Codeine - Best evidence pilot study

PRAC lead: Julie Williams, Dolores Montero Corominas

The EMA Secretariat, on behalf of the collaborative initiative carried out by Spain, the UK and EMA, presented the preliminary results of the completed drug utilisation study (DUS)

for codeine in the treatment of pain in children using BIFAP⁵⁷ (Spain), CPRD⁵⁸ (UK) and IMS⁵⁹ disease analyser (France and Germany) databases. The study methodology, results and conclusions were introduced to PRAC, as well as the lessons learnt. The main study goal was achieved, all databases delivered on all study objectives and the feasibility of regulators' collaborative studies based on a common study protocol has been demonstrated. It was noted that there were slight differences in approaches taken to some analyses, but overall good communication between the research groups was key for the success of the approach. In addition, it was noted that the results from a DUS may not necessarily be extrapolated to countries not included in the study due to local or regional prescribing patterns that vary widely between countries. Furthermore, it was pointed out that the value of a study to measure drug utilisation and evaluate risk minimisation impact is dependent on the number of National Competent Authorities (NCAs) with access to databases who are able to participate in the study. Overall, PRAC expressed its satisfaction in the concept of collaborative studies with a common protocol using different datasets. The PRAC encouraged the conduct of further collaborative studies in view of the valuable outcome.

13. Any other business

Next meeting: 05-08 February 2018

⁵⁷ Base de datos para la investigacion Farmacoepidemiologica en Atencion Primaria

⁵⁸ Clinical Practice Research Datalink

⁵⁹ Intercontinental Marketing Services disease analyser

14. Annex I – Signals assessment and prioritisation⁶⁰

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 timetables⁶¹.

14.1.1. Adalimumab – AMGEVITA (CAP), CYLTEZO (CAP), HUMIRA (CAP), IMRALDI (CAP), SOLYMBIC (CAP)

Applicant(s): AbbVie Limited (Humira), Amgen Europe B.V. (Amgevita, Solymbic), Boehringer Ingelheim International GmbH (Cyltezo), Samsung Bioepis UK Limited (Imraldi)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of lichenoid keratosis

EPITT 19128 – New signal

Lead Member State(s): SE

14.1.2. Apixaban – ELIQUIS (CAP)

Applicant(s): Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Signal of tubulointerstitial nephritis

EPITT 19127 – New signal

Lead Member State(s): NL

14.1.3. Apixaban – ELIQUIS (CAP); edoxaban – LIXIANA (CAP), ROTEAS (CAP); Serotonin and noradrenaline reuptake inhibitors (SNRI): desvenlafaxine (NAP); duloxetine - ARICLAIM (CAP), CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP); milnacipran (NAP); venlafaxine (NAP) Selective serotonin reuptake inhibitors (SSRI): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP)

Applicant(s): Bristol-Myers Squibb / Pfizer EEIG (Eliquis), Daiichi Sankyo Europe GmbH (Lixiana, Roteas), Eli Lilly Nederland B.V. (Ariclaim, Cymbalta, Duloxetine Lilly, Xeristar, Yentreve), Generics UK Limited (Duloxetine Mylan); Zentiva k.s. (Duloxetine Zentiva);

⁶⁰ ⁶⁰ 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

⁶¹ 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

various

PRAC Rapporteur: Julie Williams

Scope: Signal of drug interaction between apixaban or edoxaban and SSRI and/or SNRI leading to increased risk of bleeding

EPITT 19139 – New signal

Lead Member State(s): ES, NL, UK

14.1.4. Concentrate of proteolytic enzymes enriched in bromelain – NEXOBRID (CAP)

Applicant(s): MediWound Germany GmbH

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of haemorrhage

EPITT 19133 – New signal

Lead Member State(s): DE

14.1.5. Lenalidomide – REVLIMID (CAP)

Applicant(s): Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19130 – New signal

Lead Member State(s): FR

14.1.6. Pembrolizumab – KEYTRUDA (CAP)

Applicant(s): Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of aseptic meningitis

EPITT 19115 – New signal

Lead Member State(s): NL

14.2. New signals detected from other sources

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. Pemetrexed - EMEA/H/C/003958

Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer (NSCLC)

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. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0018, Orphan

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Updated RMP (version 8.0) to address the requests made in the conclusion of procedure IB/14, including updates from pre-approval information to post-marketing information, an update of the number of patients treated in clinical trials, special access schemes and commercial distribution, change in the development of the custom-made device, postponement of pharmacokinetic (PK) study CUV052 (study on the PK profile in erythropoietic protoporphyria (EPP) patients after administration of implant 1 on day 1 and implant 2 on day 60), update on timelines for safety extension study CUV037 from Q12013 to Q12018, update on timelines for on-going and planned pharmacovigilance studies, key elements of educational and training programme, replacement of 'pigmentary lesions' by 'pigmentary expressions' and general update of safety information

15.2.2. Cetrotirelix - CETROTIDE (CAP) - EMEA/H/C/000233/II/0064

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Updated RMP (version 5.0) in order to update the list of important identified risks by adding 'ovarian hyperstimulation syndrome' (OHSS) and removing injection site reactions (ISR). In addition, further minor RMP updates were introduced

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

Applicant: AbbVie Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Updated RMP (version 4) to incorporate changes requested by PRAC (in procedures PSUSA/00010363/201701 and PSUSA/00010367/201701): addition of a new

potential risk of depression and suicide as newly identified safety concerns; removal of off-label use and medication error as potential risks; renaming of the potential risk of development of resistance to lack of efficacy/risk of development of resistance. In addition, the commitment dates for 4 ongoing studies (on-going and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan) have been revised

15.2.4. [Rivastigmine - EXELON \(CAP\) - EMEA/H/C/000169/WS1293/0115, PROMETAX \(CAP\) - EMEA/H/C/000255/WS1293/0115](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Updated RMP (version 9.0) to: 1) reflect milestone changes for study ENA713D2409: a drug utilisation study (DUS) on the appropriate use and estimate amount/type of inappropriate drug use of all doses of Exelon/Prometax patch, based on the PRAC outcome of procedures MEA 034.2 and MEA 035.1 protocol amendment version 2; 2)- remove the important identified risk 'pancreatitis' based on the PRAC outcome of procedure PSUSA/00002654/201501 finalised in September 2015; 3) discontinue the use of the targeted checklist to document cases of medication error/misuse based on the PRAC outcome of procedure PSUSA/00002654/201601 finalised in September 2016; 4) change the frequency of 'the effectiveness of risk minimisation measures for multiple patch use' from 6 monthly to annually based on the PRAC outcome of the fourth 6 monthly report. The RMP is also updated to include information on the submission of an interim analysis report for drug utilisation study (DUS) ENA713D2409 regarding the distribution of a healthcare professional (HCPs) letter in Japan, information on the request from the Brazilian health authority to include a statement in local Exelon patch leaflet to minimize the potential risk of skin irritation, information that the core data sheet (CDS) was amended to include 'nightmares' as an adverse drug reaction (ADR)

15.2.5. [Telbivudine - SEBIVO \(CAP\) - EMEA/H/C/000713/II/0048](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Caroline Laborde

Scope: Updated RMP (version 11.0) in order to reclassify the risk of lactic acidosis from an important potential risk to an important identified risk and to include a targeted questionnaire for fatal cases as additional risk minimisation measure as requested by the PRAC as part of the assessment of PSUSA/00002880/201608 adopted in April 2017

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. [Apixaban - ELIQUIS \(CAP\) - EMEA/H/C/002148/II/0050](#)

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to update the posology, method of administration and efficacy and safety information based on final results from study B0661025/CV185267: a phase IV trial to assess the effectiveness of apixaban compared with usual care anticoagulation in subjects with non-valvular atrial fibrillation (NVAf) undergoing cardioversion (EMANATE) listed as a post-authorisation efficacy study (PAES) in the RMP. The Package Leaflet and the RMP (version 19) are updated accordingly. In addition, the MAH took the opportunity to update the list of addresses in the product information

15.3.2. Bortezomib - BORTEZOMIB ACCORD (CAP) - EMEA/H/C/003984/X/0008

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Line extension application to add a new strength of powder for solution for injection (1 mg) to the currently approved strength (3.5 mg) of Bortezomib Accord. The RMP (version 6.0) is updated accordingly

15.3.3. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0049, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with data from study C25002: a phase 1/2, non-randomised single arm study of brentuximab vedotin (SGN-35) in paediatric patients with relapsed or refractory systemic anaplastic large cell lymphoma or Hodgkin lymphoma (listed in the agreed paediatric investigation plan (PIP) covering the conditions of Hodgkin lymphoma and anaplastic large cell lymphoma for Adcetris (EMEA-000980-PIP01-10-M04)). The RMP (version 11.0) is updated accordingly

15.3.4. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/II/0002/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Grouped variations to 1) submit the results of study GS-US-311-1089: a phase 3, randomized, double-blind, switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in human immunodeficiency virus 1 (HIV-1) positive subjects who are virologically suppressed on regimens containing emtricitabine/tenofovir disoproxil fumarate (FTC/TDF). The RMP (version 5.0) is updated accordingly; 2) update of the RMP to remove pancreatitis, convulsion, and cardiac conduction abnormalities as risks in the RMP in alignment with the RMP for Prezista (darunavir) and Rezolsta (darunavir/cobicistat)

15.3.5. [Diphtheria, tetanus, pertussis \(acellular, component\), hepatitis B \(rDNA\), poliomyelitis \(inactivated\) and haemophilus type B conjugate vaccine \(adsorbed\) - VAXELIS \(CAP\) - EMEA/H/C/003982/II/0021](#)

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to update the efficacy section on immune persistence based on the final results from study PRI03C: a study on long-term persistence of hepatitis B and pertussis antibody responses in healthy 4 to 5 year old children previously vaccinated with a 2 dose or 3 dose infants series and toddler dose of Vaxelis or Infanrix Hexa (diphtheria, tetanus, pertussis (acellular, component) (Pa), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type-b conjugate vaccine (adsorbed)) listed as a P46 study in the paediatric investigation plan (PIP). The RMP (version 2.2) is updated accordingly. In addition, the MAH took the opportunity to introduce editorial changes in Annex IIIa

15.3.6. [Exenatide - BYDUREON \(CAP\) - EMEA/H/C/002020/X/0048/G](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

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

15.3.7. [Febuxostat - ADENURIC \(CAP\) - EMEA/H/C/000777/II/0047](#)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to reflect the results of preclinical study MRPO-2015-PKM-005: 'a pharmacokinetic study of azathioprine in the rat after one-week daily oral treatment at three different dosages and with the concomitant oral administration of febuxostat or allopurinol' and clinical study REP-POPPK-MRP-2015-PKM-005: 'a population pharmacokinetic analysis from study titled pharmacokinetics of azathioprine in the rat after one-week daily oral treatment at three different dosages and with the concomitant oral administration of febuxostat or allopurinol', investigating the drug-drug interaction with azathioprine when co-administered with febuxostat. The RMP (version 6.0) is updated accordingly. In addition, the MAH took the opportunity to correct typing errors and to bring the product information in line with the latest QRD template (version 10)

15.3.8. Fosaprepitant - IVMEND (CAP) - EMEA/H/C/000743/II/0037

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include adolescents, infants, toddlers and children aged 6 months and older for prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 5.0) are updated accordingly

15.3.9. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/II/0004

Applicant: AbbVie Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to update information on the use of Maviret in liver or kidney transplant patients, based on new clinical data from study M13-596 (MAGELLAN-2): a post-authorisation phase 3 study listed as a category 3 study in the RMP, which evaluated the efficacy and safety of the glecaprevir/pibrentasvir regimen in adult subjects with chronic hepatitis C virus genotypes 1-6 infection, who have received a liver or renal transplant. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.10. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0008, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of section 4.5 of the SmPC to include that CYP3A4⁶² substrates known to have a narrow therapeutic index should be administered with caution in patients receiving idebenone, based on the final study report for study SNT-I-017: an open-label study to assess the potential for pre-systemic inhibition of cytochrome P450 3A4 (CYP3A) by idebenone in healthy male subjects using midazolam as a substrate'. The package leaflet and the RMP (version 1.5) are updated accordingly. The provision of the study report fulfils MEA 005.1

15.3.11. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0038

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to reflect information from a recent cumulative safety review of cases of organising pneumonia. The Package Leaflet and Labelling are updated accordingly. The RMP (version 2.6) is also updated to extend the deadlines for submission of final clinical study report (CSR) for three studies linked to Annex II conditions

⁶² Cytochrome P450 3A4

15.3.12. [Infliximab - REMICADE \(CAP\) - EMEA/H/C/000240/II/0209](#)

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC to amend the current warning on colon cancer and dysplasia based on the final report of the OPUS registry (P04808): a prospective, observational, non-interventional, post-marketing safety surveillance program in subjects with ulcerative colitis (UC). The provision of the study report fulfils MEA 121. In addition, the MAH took the opportunity to add a warning on screening tests for tuberculosis to align it with current medical practice, to add a reminder on the patient alert card in the package leaflet. Furthermore, the MAH introduced some editorial changes in line with the latest QRD template. The RMP (version 14.1) is updated accordingly

15.3.13. [Ivabradine - CORLENTOR \(CAP\) - EMEA/H/C/000598/WS1180, IVABRADINE ANPHARM \(CAP\) – EMEA/H/C/004187/WS1180, PROCORALAN \(CAP\) – EMEA/H/C/000597/WS1180](#)

Applicant(s): Les Laboratoires Servier (Corlentor, Procoralan), Anpharm Przedsiębiorstwo (Ivabradine Anpharm)

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC to add new adverse drug reactions (ADRs): ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. The Package Leaflet and the RMP (version 6) are updated accordingly. In addition the MAH took the opportunity to align the product information with the latest QRD template (version 10)

15.3.14. [Lapatinib - TYVERB \(CAP\) - EMEA/H/C/000795/II/0050/G](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report for non-clinical study 09DMR047 (listed as a category 3 study in the RMP): a non-clinical mechanistic study related to lapatinib metabolite identification in dog plasma, bile and liver. The RMP (version 33) is updated accordingly; 2) change to the final due date of study EGF117165: an open-label, phase 2 study to evaluate biomarkers associated with response to subsequent therapies in subjects with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer receiving treatment with trastuzumab in combination with lapatinib or chemotherapy (category 1 study, ANX034.2) from June 2018 to June 2019 in the RMP and Annex II. In addition, the MAH took the opportunity to update the RMP to include the removal of two identified risks (rash, diarrhoea) and update missing information (hepatic impairment and renal impairment) in line with the recent PSUSA PRAC recommendation

15.3.15. [Levetiracetam - KEPBRA \(CAP\) - EMEA/H/C/000277/II/0169/G](#)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

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

15.3.16. Moroctocog alfa - REFACTO AF (CAP) - EMEA/H/C/000232/II/0143

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update the existing safety, efficacy and pharmacokinetic information based on the final results from 1) study B1831005 (listed as a category 3 study in the RMP (MEA 111)): a non-randomized, open label study to evaluate the safety, efficacy, and pharmacokinetics (PK) of ReFacto AF in previously treated children less than 12 years of age with severe haemophilia A (factor VIII (FVIII):C<1%), already submitted in P46-143; 2) study B1831006 (listed as a category 3 study in the RMP (MEA 113)): an open-label study on the safety and efficacy of ReFacto AF in previously untreated patients (PUPs) in usual care settings, already submitted in P46-145). The RMP (version 12.0) is updated accordingly and include an update relating to study B1831083 (listed as a category 3 study in the RMP): an open-label, single-arm, post-authorisation pragmatic clinical trial on the safety and efficacy of moroctocog alfa in subjects with haemophilia A in usual care settings in China, already submitted as P46-144. Furthermore, the product information is brought in line with the latest QRD template (version 10) and amended to introduce an editorial change to the Czech local representative address in the package leaflet

15.3.17. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0018/G, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped variations consisting of: 1) update of section 4.4 in order to remove the current warning on co-administration with pirfenidone and update of section 5.1 to include the results of study 1199.222: a phase IV, 12 week, open label, randomised, parallel group study to evaluate the safety, tolerability and pharmacokinetic (PK) of oral nintedanib in combination with oral pirfenidone in comparison with nintedanib alone in patients with idiopathic pulmonary fibrosis (IPF); 2) update of section 5.2 of the SmPC in order to include the results of study 1199.229 (listed as a category 3 study in the RMP): a phase 4, open label, multidose, 2 groups study to investigate the drug-drug interaction (DDI) between nintedanib and pirfenidone in patients with IPF. The RMP (version 5.0) is updated accordingly. In addition, the MAH took the opportunity to implement some corrections to the French and Swedish translations

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

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include adjuvant treatment of adults and adolescents of 12 years of age and older with completely resected stage III and IV melanoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from pivotal study CA209238: a phase 3, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab after complete resection of stage IIIb/c or stage IV melanoma in subjects who are at high risk for recurrence. The package leaflet and the RMP (version 12.0) are updated 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-CTLA4 monoclonal antibody; and study CA209171: an open-label, multicentre clinical trial with nivolumab monotherapy in subjects with advanced or metastatic squamous cell (Sq) non-small cell lung cancer (NSCLC) who have received at least one prior systemic regimen for the treatment of stage IIIb/IV SqNSCLC. In addition, the MAH took the opportunity to make minor editorial changes to the product information

15.3.19. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0027, Orphan

Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.2, 4.4, and 4.8 of the SmPC in order to add new adverse drug reactions (ADR): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) following a review of reports on severe skin reactions. The package leaflet and the RMP (version 12.0) are updated accordingly

15.3.20. 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 make very minor formatting changes in the Labelling

15.3.21. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0016

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of Annex II to delete the condition 'post-authorisation efficacy study (PAES): submission of the final clinical study report (CSR) for study CLDE225A2201: a phase 2, randomized double-blind study of efficacy and safety of two dose levels of LDE225 (sonidegib) in patients with locally advanced or metastatic basal cell carcinoma, including an updated analysis of outcomes by aggressive vs. non-aggressive histological subtypes.' The RMP (version 7.0) is updated accordingly

15.3.22. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0074/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped quality variations

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. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201706

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.2. Alectinib - ALECENSA (CAP) - PSUSA/00010581/201707

Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.3. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201707

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.4. [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/00010505/201705](#)

Applicant: GlaxoSmithKline Trading Services Limited, ATMP⁶³

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.5. [Avanafil - SPEDRA \(CAP\) - PSUSA/00010066/201706](#)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.6. [Brinzolamide, brimonidine tartrate - SIMBRINZA \(CAP\) - PSUSA/00010273/201706](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.7. [Bromfenac - YELLOX \(CAP\) - PSUSA/00000436/201705](#)

Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.8. [Canakinumab - ILARIS \(CAP\) - PSUSA/00000526/201706](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

⁶³ Advanced therapy medicinal product

16.1.9. Chlorhexidine - UMBIPRO (Art 58⁶⁴) - EMEA/H/W/003799/PSUV/0003

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUR procedure

16.1.10. Daclatasvir - DAKLINZA (CAP) - PSUSA/00010295/201707

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.11. Dasatinib - SPRYCEL (CAP) - PSUSA/00000935/201706

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.12. Edotreotide - SOMAKIT TOC (CAP) - PSUSA/00010552/201706

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.13. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/201706 (with RMP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.14. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/201705

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.15. Emedastine - EMADINE (CAP) - PSUSA/00001207/201705

Applicant: Novartis Europharm Limited

⁶⁴ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

PRAC Rapporteur: Ghania Chamouni
Scope: Evaluation of a PSUSA procedure

16.1.16. Fidaxomicin - DIFICLIR (CAP) - PSUSA/00001390/201705

Applicant: Astellas Pharma Europe B.V.
PRAC Rapporteur: Qun-Ying Yue
Scope: Evaluation of a PSUSA procedure

16.1.17. Follitropin delta - REKOVELLE (CAP) - PSUSA/00010554/201705

Applicant: Ferring Pharmaceuticals A/S
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

16.1.18. Galsulfase - NAGLAZYME (CAP) - PSUSA/00001515/201705

Applicant: BioMarin Europe Ltd
PRAC Rapporteur: Patrick Batty
Scope: Evaluation of a PSUSA procedure

16.1.19. Glycerol phenylbutyrate - RAVICTI (CAP) - PSUSA/00010454/201705

Applicant: Horizon Pharma Ireland Limited
PRAC Rapporteur: Carmela Macchiarulo
Scope: Evaluation of a PSUSA procedure

16.1.20. Human fibrinogen, human thrombin - EVARREST (CAP), EVICEL (CAP), RAPLIXA (CAP), TACHOSIL (CAP) - PSUSA/00010297/201706

Applicants: Mallinckrodt Pharmaceuticals Ireland Limited (Raplixia), Omrix Biopharmaceuticals N. V. (Evarrest, Evicel), Takeda Austria GmbH (TachoSil)
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

16.1.21. Human papillomavirus [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201706

Applicant: MSD Vaccins
PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.22. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP), SILGARD (CAP) - PSUSA/00001634/201705

Applicants: MSD Vaccins (Gardasil), Merck Sharp & Dohme Limited (Silgard)

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.23. Human plasma protease C1 inhibitor - CINRYZE (CAP) - PSUSA/00010104/201706

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.24. Hydroxycarbamide⁶⁵ - SIKLOS (CAP) - PSUSA/00001692/201706 (with RMP)

Applicant: Addmedica

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.25. Influenza vaccine⁶⁶ (live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/201706

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.26. Lesinurad - ZURAMPIC (CAP) - PSUSA/00010470/201706

Applicant: Grunenthal GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.27. Levofloxacin⁶⁷ - QUINSAIR (CAP) - PSUSA/00010429/201705

Applicant: Chiesi Orphan B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

⁶⁵ For centrally authorised product only

⁶⁶ Intranasal use

⁶⁷ Centrally authorised product only

16.1.28. Lonococog alfa - AFSTYLA (CAP) - PSUSA/00010559/201707

Applicant: CSL Behring GmbH

PRAC Rapporteur: Daniela Philadelphy

Scope: Evaluation of a PSUSA procedure

16.1.29. Matrix-applied characterised autologous cultured chondrocytes - MACI (CAP) - PSUSA/00010116/201706

Applicant: Vericel Denmark ApS, ATMP⁶⁸

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.30. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/201705

Applicant: Amicus Therapeutics UK Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.31. Mirabegron - BETMIGA (CAP) - PSUSA/00010031/201706

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.32. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - PSUSA/00010296/201705

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.33. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201706

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.34. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201706

Applicant: AstraZeneca AB

⁶⁸ Advanced therapy medicinal product

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.35. Opicapone - ONGENTYS (CAP) - PSUSA/00010516/201706

Applicant: Bial - Portela & C^a, S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.36. Pertuzumab - PERJETA (CAP) - PSUSA/00010125/201706

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.37. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201706

Applicant: Actelion Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.38. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201706

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.39. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/201706

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.40. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201706

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.41. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201707

Applicant: Vanda Pharmaceuticals Ltd.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.42. [Tedizolid phosphate - SIVEXTRO \(CAP\) - PSUSA/00010369/201706](#)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.43. [Tigecycline - TYGACIL \(CAP\) - PSUSA/00002954/201706](#)

Applicant: Pfizer Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.44. [Trametinib - MEKINIST \(CAP\) - PSUSA/00010262/201705](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.45. [Varenicline - CHAMPIX \(CAP\) - PSUSA/00003099/201705](#)

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.46. [Venetoclax - VENCLYXTO \(CAP\) – PSUSA/00010556/201706](#)

Applicant: AbbVie Limited

PRAC Rapporteur: Patrick Batty

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. [Human normal immunoglobulin \(IgG\) - FLEBOGAMMA DIF \(CAP\); HIZENTRA \(CAP\); HYQVIA \(CAP\); KIOVIG \(CAP\); PRIVIGEN \(CAP\); NAP - PSUSA/00001633/201705](#)

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Amlodipine, candesartan (NAP) - PSUSA/00010191/201704

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.2. Amlodipine, olmesartan (NAP) - PSUSA/00002208/201704

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.3. Amlodipine besilate, hydrochlorothiazide, olmesartan medoxomil (NAP) - PSUSA/00002210/201704

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.4. Azithromycin⁶⁹ (NAP) - PSUSA/00010492/201704

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.5. Betaxolol (NAP) - PSUSA/00000401/201705

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.6. Buspirone (NAP) - PSUSA/00000463/201704

Applicant(s): various

⁶⁹ Formulations for ocular use only

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.7. Chlorpromazine (NAP) - PSUSA/00000715/201705

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.8. Cidofovir (NAP) - PSUSA/00010558/201706

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.9. Clevidipine (NAP) - PSUSA/00010288/201705

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.10. Cyproterone, ethinylestradiol (NAP) - PSUSA/00000906/201705

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.11. Diltiazem (NAP) - PSUSA/00001084/201705

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.12. Eprosartan (NAP) - PSUSA/00001243/201704

Applicant(s): various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.3.13. Eprosartan, hydrochlorothiazide (NAP) - PSUSA/00001244/201704

Applicant(s): various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.3.14. Esomeprazole, naproxen (NAP) - PSUSA/00001270/201704

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.15. Estradiol (NAP); estradiol, prednisolone⁷⁰ (NAP) - PSUSA/00010441/201704

Applicant(s): various

PRAC Lead: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.3.16. Fluorescein⁷¹ (NAP) - PSUSA/00009153/201704

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.17. Formoterol (NAP) - PSUSA/00001469/201705

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.18. Glimepiride (NAP) - PSUSA/00001534/201706

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.19. Halofantrine (NAP) - PSUSA/00001586/201705

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

⁷⁰ Cream/balm/emulsion for application in the female genital area, only

⁷¹ For systemic use only

16.3.20. Human hemin (NAP) - PSUSA/00001629/201705

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.21. Human rabies immunoglobulin (NAP) - PSUSA/00001639/201704

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.22. Indobufen (NAP) - PSUSA/00001736/201705

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.23. Lanreotide (NAP) - PSUSA/00001826/201705

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.24. Methoxyflurane (NAP) - PSUSA/00010484/201705

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.25. Mifepristone (NAP) - PSUSA/00002060/201705

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.26. Misoprostol⁷² (NAP) - PSUSA/00010353/201705

Applicant(s): various

PRAC Lead: Doris Stenver

⁷² Gynaecological indication - labour induction only

Scope: Evaluation of a PSUSA procedure

16.3.27. Mometasone (NAP) - PSUSA/00002085/201705

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.28. Olodaterol, tiotropium (NAP) - PSUSA/00010489/201705

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.29. Olsalazine (NAP) - PSUSA/00002213/201705

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.30. Piracetam (NAP) - PSUSA/00002429/201704

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.31. Risperidone (NAP) - PSUSA/00002649/201705

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.32. Sodium tetradecyl sulfate (NAP) - PSUSA/00002767/201704

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.3.33. Strontium (⁸⁹Sr) chloride (NAP) - PSUSA/00002795/201705

Applicant(s): various

PRAC Lead: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

16.3.34. Technetium (^{99m}Tc) hynic-octetotide (NAP) - PSUSA/00010521/201706

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.35. Technetium (^{99m}Tc) tetrofosmin (NAP); tetrofosmin (NAP) - PSUSA/00002870/201705

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.36. Valsartan (NAP); valsartan, hydrochlorothiazide (NAP) - PSUSA/00010396/201704

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.37. Venlafaxine (NAP) - PSUSA/00003104/201705

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/LEG 041

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a comprehensive annual report for the ongoing study 20090522: a PASS on denosumab global safety assessment among women with postmenopausal osteoporosis (PMO) and men with osteoporosis in multiple observational databases [final report expected in 2023] as requested in the conclusions of PSUSA/00000954/201609 adopted in April 2017

16.4.2. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/LEG 008.2

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the annual case study report (CSR) of the ongoing osteonecrosis of the jaw (ONJ) registry case study 20101102 as requested in the conclusions of PSUSA/00009119/201609 adopted in April 2017

16.4.3. Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/LEG 014

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a cumulative review including a causality assessment of all cases of 'biliary disorders' identified in clinical trials and post-marketing setting, as requested in the conclusions of PSUSA/00010017/201701 adopted in September 2017

16.4.4. Plerixafor - MOZOBIL (CAP) - EMEA/H/C/001030/LEG 025

Applicant: Genzyme Europe BV

PRAC Rapporteur: Sabine Straus

Scope: Submission of a cumulative review of cases of arrhythmia and discussion on possible mechanism in view of available preclinical data and reports in healthy volunteers, as requested in the conclusions of PSUSA/00002451/201612 adopted in July 2017

16.4.5. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/LEG 039.3

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to LEG 039.2 [cumulative review on cases of liver-related events (hepatotoxicity) as requested in the recommendation of PSUSA/00002653/201509 adopted by PRAC in April 2016], as per the request for supplementary information (RSI) adopted in October 2017

16.4.6. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/LEG 007

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the clinical trial report for study NN7008-3809: safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in paediatric previously untreated patients with haemophilia A, as requested in the recommendation of PSUSA/00010138/201610 adopted by PRAC in June 2017

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

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC

adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

17.1. [Protocols of PASS imposed in the marketing authorisation\(s\)](#)⁷³

None

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

[17.2.1. Alirocumab - PRALUENT \(CAP\) - EMEA/H/C/003882/MEA 019.3](#)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 019.2 including revised protocol (version 3) [protocol for a drug utilisation study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low low-density lipoprotein (LDL)-C levels (study OBS14697)], as per the request for supplementary information (RSI) adopted in April 2017

[17.2.2. Apremilast - OTEZLA \(CAP\) - EMEA/H/C/003746/MEA 005.2](#)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 005.1 [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 July 2017

[17.2.3. Avelumab - BAVENCIO \(CAP\) - EMEA/H/C/004338/MEA 002](#)

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Doris Stenver

Scope: Protocol for a non-interventional cohort study to assess the characteristics and management of patients with Merkel cell carcinoma in Germany (listed as a category 3 study in the RMP) [final report expected in Q1 2024] (from initial opinion/MA)

[17.2.4. Baricitinib - OLUMIANT \(CAP\) - EMEA/H/C/004085/MEA 002.1](#)

Applicant: Eli Lilly Nederland B.V.

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

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

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 002 [PASS protocol for study I4V-MC-B003: a prospective observational US post-marketing registry study to assess the long-term safety of baricitinib compared with other therapies used in the treatment of adults with moderate-to-severe rheumatoid arthritis in the course of routine clinical care [final report due date: March 2031] (from initial opinion/MA)] as per the request for supplementary information (RSI) adopted at the September 2017 PRAC meeting

17.2.5. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002

Applicant: Leo Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: 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)

17.2.6. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 002

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Protocol for a long-term PASS: a prospective, observational cohort study evaluating the safety profile, in terms of incidence of adverse events of special interest, in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine [final report expected in Q2 2034] (from initial opinion/MA)

17.2.7. Conestat alfa - RUCONEST (CAP) - EMEA/H/C/001223/MEA 019.1

Applicant: Pharming Group N.V

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 019 including a revised protocol (version 1.0) [survey to measure the effectiveness of risk minimisation materials distributed to treatment centres/prescribing physicians] as adopted in July 2017

17.2.8. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/MEA 020.1

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 020 [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 at the October 2017 meeting

17.2.9. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 009.1

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 009 [PASS protocol for study 109MS303: a dose-blind, multicentre, extension study to determine the long-term safety and efficacy of two doses of BG00012 monotherapy in subjects with relapsing-remitting multiple sclerosis (ENDORSE) [final clinical study report expected in Q1 2024] as per the request for supplementary information (RSI) adopted at the September 2017 meeting

17.2.10. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/MEA 005.2

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA-005.1 including a revised protocol (version 1.2) [PASS protocol for study EVM-19596-00-001: a drug utilisation study (DUS) (RMP category 3) using relevant healthcare databases at two different time periods in order to define the compliance to contraindications over time and the number of subjects diagnosed with pancreatitis after eluxadoline treatment] as per the request for supplementary information (RSI) adopted at the September 2017 meeting

17.2.11. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 003.3

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Amendment to the previously agreed protocol for a drug utilisation study (DUS) to describe baseline characteristics and utilisation patterns of EU patients initiating Duavive or oestrogen + progestin combination hormone replacement therapy (HRT), DUS B2311061, adopted in May 2016

17.2.12. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/MEA 015.2

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 015.1 including a revised protocol (version 1.2) [PASS protocol for study GS-EU-313-4172: a non-interventional study to assess the safety profile of idelalisib in patients with refractory follicular lymphoma (FL)] as per the request for supplementary information (RSI) adopted at the September 2017 meeting

17.2.13. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 047.4

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Amendment to the protocol of the HUBIN registry PASS: a European observational cohort of patients with type 1 diabetes mellitus (T1DM) treated via intraperitoneal route with Insuman Implantable 400 IU/mL in MedtronicMiniMed implantable pump, and an amended statistical analysis plan (SAP) following phase out process of the pump manufacturer for Insuman, previously agreed in May 2017

17.2.14. [Mirabegron - BETMIGA \(CAP\) - EMEA/H/C/002388/MEA 009.1](#)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 009 [Protocol for PASS study 178-PV-002: a drug utilisation study (DUS) of Betmiga (mirabegron) using real-world healthcare databases from the Netherlands, Spain, United Kingdom and Finland] as per the request for supplementary information (RSI) adopted in July 2017

17.2.15. [Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA \(CAP\) - EMEA/H/C/003687/MEA 004.4](#)

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 004.3 including a revised protocol [PASS protocol for study NB-452: a cross-sectional survey to evaluate the effectiveness of the physician prescribing checklist (PPC) among physicians in the EU] as per the request for supplementary information (RSI) adopted in October 2017

17.2.16. [Plasmodium falciparum and hepatitis B vaccine \(recombinant, adjuvanted\) - MOSQUIRIX \(Art 58⁷⁵\) - EMEA/H/W/002300/MEA 002](#)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: PASS protocol for study EPI-MAL-002 to estimate the incidence of adverse events of special interest (AESI) of meningitis and of other adverse events (AE) leading to hospitalisation or death, in children, prior to implementation of Mosquirix (RTS, S/AS01E) (from initial opinion/MA)

17.2.17. [Plasmodium falciparum and hepatitis B vaccine \(recombinant, adjuvanted\) - MOSQUIRIX \(Art 58⁷⁶\) - EMEA/H/W/002300/MEA 003](#)

Applicant: GlaxoSmithkline Biologicals SA

⁷⁵ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

⁷⁶ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

PRAC Rapporteur: Jean-Michel Dogné

Scope: PASS protocol for study EPI-MAL-003 to estimate the incidence of protocol-defined potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with Mosquirix (RTS, S/AS01E) (from initial opinion/MA)

17.2.18. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁷⁷) - EMEA/H/W/002300/MEA 015

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: PASS protocol for study EPI-MAL-010: a phase 4, longitudinal, cross-sectional, retrospective, ancillary epidemiology study of the EPI-MAL-005 study to evaluate the genetic diversity in the Plasmodium falciparum parasite circumsporozoite sequences before and after the implementation of the Mosquirix (RTS, S/AS01E) vaccine in malaria-positive subjects ranging from 6 months to less than 5 years of age (from variation II/20)

17.2.19. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Protocol for study RRA-20745: a PASS to investigate the long-term safety in adult patients with moderately to severely active Crohn's disease

17.2.20. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.2

Applicant: AbbVie Limited

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 002.1 including a revised protocol [registry protocol for a prospective observational study P16-562 to assess the long term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients] as per the request for supplementary information (RSI) adopted at the October 2017 meeting

17.3. Results of PASS imposed in the marketing authorisation(s)⁷⁸

None

⁷⁷ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

⁷⁸ In accordance with Article 107p-q of Directive 2001/83/EC

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁷⁹

17.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0116/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of: 1) submission of the final report for study IM101537 (listed as a category 3 study in the RMP): a non-interventional healthcare professionals (HCP)/patient cross-sectional survey and retrospective chart review PASS to evaluate the effectiveness of the patient alert card for both intravenous (IV) and subcutaneous (SC) abatacept in a sample of EU countries; 2) submission of an updated RMP (version 24) in order to reflect the early closure of study IM101212 (listed as a category 3 study in the RMP): a post-marketing observational study assessing the long-term safety of abatacept using the DREAM database in the Netherlands. The MAH took the opportunity to introduce further administrative changes in the RMP

17.4.2. Afatinib - GIOTRIF (CAP) - EMEA/H/C/002280/II/0025

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study 1200.217 (listed as a category 3 study in the RMP): a phase 4 study to assess the efficacy and safety of afatinib as second-line therapy for patients with locally advanced or metastatic non-small cell lung cancer harbouring an epidermal growth factor receptor (EGFR) mutation who have failed first-line treatment with platinum-based chemotherapy. The RMP (version 6.0) is updated accordingly

17.4.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0052

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report for study HGS1006-C1074 (BEL112234) (listed as a category 3 study in the RMP, in fulfilment of a MEA 012): 'a multicentre, continuation trial of belimumab in subjects with systemic lupus erythematosus (SLE) who completed the phase 3 protocol HGS1006-C1056 or HGS1006-C1057'. The RMP (version 26.0) is updated accordingly. In addition, the MAH took the opportunity to update the RMP regarding study BEL116027: an open-label, non-randomized, 52-week study to evaluate treatment holidays and rebound phenomenon after treatment with belimumab 10 mg/kg in SLE subjects for the due date of the final study report and introduction of protocol changes (reduced study sample size), already agreed in the conclusions of recent procedures MEA 006.4 and MEA 006.5

⁷⁹ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

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

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

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

17.4.5. [Entecavir - BARACLUDE \(CAP\) - EMEA/H/C/000623/II/0053](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final study report for study AI463080: a long-term outcome study (10 years) to assess the rates of malignant neoplasms (all, hepatocellular carcinoma (HCC) and non-HCC), liver-related events of hepatitis B virus (HBV) disease progression and mortality. The RMP (version 14) is updated accordingly

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

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final report for study 205052 (PRJ2214): a drug utilisation study (DUS) to identify the extent of any off-label prescribing fluticasone furoate/vilanterol (FF/VI) in any dose in children less than 12 years of age; and prescribing of FF/VI 200/25 mcg in patients with a diagnosis of chronic obstructive pulmonary disease (COPD) considering the presence of a concurrent diagnosis of asthma. The RMP (version 9.1) is updated accordingly

17.4.7. [Interferon beta-1b - BETAFERON \(CAP\) - EMEA/H/C/000081/II/0118](#)

Applicant: Bayer AG

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for study BETAPAEDIC (listed as a category 3 study in the RMP): a non-interventional study evaluating safety and tolerability of Betaferon (interferon beta-1b) in paediatric patients with multiple sclerosis. The RMP (version 3.2) is updated accordingly

17.4.8. [Micafungin - MYCAMINE \(CAP\) - EMEA/H/C/000734/II/0035](#)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

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

17.4.9. Moroctocog alfa - REFACTO AF (CAP) - EMEA/H/C/000232/II/0142

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final study report for study B1831016 (listed as a category 3 in the RMP, in fulfilment of MEA 108.3: a non-interventional open-label study conducted at haemophilia treatment centres in Germany and Austria to generate information regarding the safety and effectiveness of treatment with ReFacto AF under routine clinical conditions

17.4.10. Octocog alfa - ADVATE (CAP) - EMEA/H/C/000520/II/0089

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report for study 061501: a retrospective chart review aimed to evaluate safety and tolerability of Advate among previously untreated patients with moderate to severe haemophilia A

17.4.11. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - SYNFLORIX (CAP) - EMEA/H/C/000973/II/0124/G

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations consisting of the submission of the final study reports from two 5-year invasive pneumococcal disease (IPD) post-marketing surveillance (PMS) studies: 1) 'monitoring the population effectiveness of pneumococcal conjugate vaccination in the Finnish national vaccination programme' (MEA 019); 2) 'epidemiology of invasive pneumococcal disease in the Netherlands' (MEA 020), addressing the potential risks of 'possible serotype replacement of disease isolates' and 'possible breakthrough infections/vaccine failure'. The MAH also provided data from IPD surveillance from 5 other European countries (Austria, Bulgaria, Cyprus, Iceland and Sweden) and 6-year update results from a 5-year PMS in Kenya (pneumococcal conjugate vaccine impact study (PCVIS), MEA 021). The RMP (version 17) is updated accordingly

17.4.12. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/II/0069

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final 5-year report for study ZOL446H2422 (listed as a category 3 study in the RMP): a non-interventional post-authorisation safety study using health registries to compare safety of Aclasta against oral bisphosphonates and untreated

population controls

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation⁸⁰

17.5.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/MEA 010.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Third interim results (semi-annual report) for study TMC207TBC4002: a multi-country prospective multidrug-resistant tuberculosis (MDRTB) disease registry to monitor bedaquiline safety, utilisation, and emergence of resistance (listed as a category 3 study in RMP) [final study report expected in Q2 2020]

17.5.2. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/MEA 001.2

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 001.1 [Second interim annual report for EuroSIDA PASS study 201177: a prospective observational cohort study in patients receiving dolutegravir (category 3) to investigate the risk of hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (DAIDS) grading scale category 3 or 4)] as per the request for supplementary information (RSI) adopted in May 2017

17.5.3. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/MEA 007.2

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 007.1 [Second interim annual report for EuroSIDA PASS study 201177: a prospective observational cohort study in patients receiving dolutegravir (category 3) to investigate the risk of hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (DAIDS) grading scale category 3 or 4)] as per the request for supplementary information (RSI) adopted in May 2017

17.5.4. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/MEA 005.4

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Interim study report for study DSE-EDO-01-14-EU (EUPAS17062): a drug

⁸⁰ In line with the revised variations regulation for any submission before 4 August 2013

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

17.5.5. Etravirine - INTELENCE (CAP) - EMEA/H/C/000900/MEA 049.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Caroline Laborde

Scope: Fourth annual report for study TMC125-EPPICC: 'a study to define the long-term safety profile of etravirine in human immunodeficiency virus 1 (HIV-1) infected children and adolescents in Europe'

17.5.6. Florbetapir (¹⁸F) - AMYVID (CAP) - EMEA/H/C/002422/MEA 001.4

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: First interim report for study I6E-MC-AVBE: a non-interventional PASS evaluating the effectiveness of Amyvid reader training programme

17.5.7. Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) - GARDASIL 9 (CAP) - EMEA/H/C/003852/MEA 003

Applicant: MSD Vaccins

PRAC Rapporteur: Julie Williams

Scope: Second annual interim report for an US pregnancy registry: surveillance programme procedures for the pregnancy registry for Gardasil 9

17.5.8. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 089.13

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim study reports for the ENCORE patient registry in Europe in Crohn's disease, using data from the Swedish biologics register (anti-rheumatic therapy in Sweden: ARTIS) and the German rheumatoid arthritis observation of biologic therapy (RABBIT) cohort 2

17.5.9. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.8

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 004.7 [annual interim report for the passive enhanced

safety surveillance study (ESS) D2560C00008: a postmarketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age early 2016/2017 influenza season in England] as per the request for supplementary information (RSI) adopted at the September 2017 meeting

17.5.10. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/MEA 004.4

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: 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)

17.5.11. Nalmefene - SELINCRO (CAP) - EMEA/H/C/002583/MEA 003.2

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Interim (baseline) report for PASS 15649A: a cohort study on the use of Selincro (nalmefene) using longitudinal electronic medical records or claims databases in Europe (reports from the German, UK and Swedish databases)

17.5.12. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/ANX 001.4

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Second annual interim report for a PASS (ENCEPP/SDPP/8585) (listed as a category 1 in the RMP): an observational retrospective cohort study of ospemifene utilising existing databases in Germany, Italy, Spain, and the United States to evaluate the incidence of venous thromboembolism and other adverse events in vulvar and vaginal atrophy (VVA) patients treated with ospemifene as compared to: 1) patients newly prescribed selective oestrogen receptor modulators (SERM) for oestrogen-deficiency conditions or breast cancer prevention and; 2) the incidence in untreated VVA patients [final report expected in February 2021]

17.5.13. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/MEA 004.6

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Annual interim analysis for PASS study E2007-G000-402: a post-marketing observational safety study to evaluate the long-term safety and tolerability of Fycompa (perampanel) as add-on therapy in epilepsy patients

[17.5.14. Roflumilast - DALIRESP \(CAP\) - EMEA/H/C/002398/ANX 002.3](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: First interim results for PASS D7120R00003 (previously RO-2455-403-RD): a long-term post-marketing observational study exploring the safety of roflumilast in the treatment of chronic obstructive pulmonary disease (COPD), combined data results from Sweden, Germany and the US [final clinical study report (CSR) expected in March 2031]

[17.5.15. Roflumilast - DAXAS \(CAP\) - EMEA/H/C/001179/ANX 002.4](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: First interim results for PASS D7120R00003 (previously RO-2455-403-RD): a long-term post-marketing observational study exploring the safety of roflumilast in the treatment of chronic obstructive pulmonary disease (COPD), combined data results from Sweden, Germany and the US [final clinical study report (CSR) expected in March 2031]

[17.5.16. Roflumilast - LIBERTEK \(CAP\) - EMEA/H/C/002399/ANX 002.3](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: First interim results for PASS D7120R00003 (previously RO-2455-403-RD): a long-term post-marketing observational study exploring the safety of roflumilast in the treatment of chronic obstructive pulmonary disease (COPD), combined data results from Sweden, Germany and the US [final clinical study report (CSR) expected in March 2031]

[17.5.17. Romiplostim - NPLATE \(CAP\) - EMEA/H/C/000942/MEA 003.5](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Interim result for a post-marketing surveillance study 20070797: a population based prospective study evaluating the short and long term safety of romiplostim treatment in adult patients with chronic idiopathic (immune) thrombocytopenic purpura (ITP) based on national health registry systems in Denmark, Sweden, and Norway on a period 11 years

[17.5.18. Valproate – EMEA/H/N/PSI/J/0002](#)

Applicant: Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to PSI/J/0002 [second interim results report for a joint drug utilisation study (DUS) of valproate and related substances conducted in Europe aiming at describing the prescribing practices before and after the dissemination of risk

minimisation measures (RMM) (i.e. educational materials and direct healthcare professional communication (DHPC)) and assessing the effectiveness of these measures using databases, as requested in the outcome of the referral procedure on valproate and related substances (EMA/H/A-31/1387) concluded in 2014] as per the request for supplementary information (RSI) adopted at the October 2017 meeting

17.6. Others

17.6.1. Adalimumab - HUMIRA (CAP) - EMA/H/C/000481/LEG 101

Applicant: AbbVie Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a further review on exposure and sensitivity analysis, on missing data and on Cox regression analysis related to the final study report for the biologics registry: Anti-Rheumatic Treatment in Sweden (ARTIS), as requested in the conclusions of variation II/061/G adopted by CHMP/PRAC in May 2017

17.6.2. Canagliflozin - INVOKANA (CAP) - EMA/H/C/002649/MEA 006.8

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Bi-annual status reports for study DNE3001/CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (sixth IDMC report dated October 2017)

17.6.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMA/H/C/002656/MEA 005.8

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Bi-annual status reports for study DNE3001/CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (sixth IDMC report dated October 2017)

17.6.4. Daclatasvir - DAKLINZA (CAP) - EMA/H/C/003768/MEA 019.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 019 [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals

(DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 PRAC meeting

17.6.5. Dasabuvir - EXVIERA (CAP) - EMA/H/C/003837/MEA 007.1

Applicant: AbbVie Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 007 [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 meeting

17.6.6. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMA/H/C/004126/MEA 004.1

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 004 [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 meeting

17.6.7. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMA/H/C/004430/MEA 006

Applicant: AbbVie Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 meeting

17.6.8. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 017.1

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 017 [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 meeting

17.6.9. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/LEG 121

Applicant: AbbVie Limited

PRAC Rapporteur: Caroline Laborde

Scope: Submission of an assessment of the safety in children aged from 14 days to 2 years as regards to the chronic exposure to propylene glycol and ethanol, medication errors and lack of efficacy/resistance in relation to potentially suboptimal pharmacokinetic (PK) parameters, together with a discussion on the benefit/risk balance in this population and a discussion on the feasibility to search and identify for any case report of medication error, overdose and lack of efficacy reported in children aged between 14 days and 2 years receiving Kaletra oral solution based on existing paediatric cohorts, as requested in the conclusions of variation II/061/G adopted by CHMP/PRAC in June 2017

17.6.10. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 007.1

Applicant: AbbVie Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 007 [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 meeting

17.6.11. Simeprevir - OLYSIO (CAP) - EMEA/H/C/002777/MEA 013.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 013 [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 meeting

17.6.12. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/MEA 024.1

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 024 [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 meeting

17.6.13. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/MEA 008.1

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 008 [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 meeting

17.6.14. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/MEA 002

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response [Feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) (listed as category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (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 at the September 2017 meeting

17.6.15. Telavancin - VIBATIV (CAP) - EMEA/H/C/001240/ANX 007.6

Applicant: Theravance Biopharma Ireland Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's response to ANX 007.5 [Submission of a pregnancy exposure follow-up questionnaire in the context of the pregnancy exposure registry (9809-CL-1409)] as per the request for supplementary information (RSI) adopted in July 2017

17.6.16. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/MEA 014

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of primary analysis for study MO28231 (KAMILLA): a two-cohort, open label, multicentre, study of trastuzumab emtansine in human epidermal growth factor (HER2) positive locally advanced or metastatic breast cancer patients who have received prior anti-HER2 and chemotherapy-based treatment [final clinical study report expected in Q4 2021]

17.6.17. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/LEG 032

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a detailed analysis of a case of hypotension (KW-C14004-17-00092) including the CIOMS⁸¹ form, causality assessment report

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.

⁸¹ Council for International Organisations of Medical Sciences

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. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0009 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Annual reassessment of the marketing authorisation

18.1.2. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0026 (without RMP)

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0024 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Conditional renewal of the marketing authorisation

18.2.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0027 (with RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

18.2.3. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0007 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Almath Spooner

Scope: Conditional renewal of the marketing authorisation

18.2.4. Pixantrone - PIXUVRI (CAP) - EMEA/H/C/002055/R/0042 (without RMP)

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Patrick Batty

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Matrix applied characterised autologous cultured chondrocytes - MACI (CAP) - EMEA/H/C/002522/R/0017 (with RMP)

Applicant: Vericel Denmark ApS, ATMP⁸²

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.2. Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/R/0017 (without RMP)

Applicant: Lucane Pharma

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.3. Imatinib – IMATINIB ACCORD (CAP) - EMEA/H/C/002681/R/0020

Applicant: Accord Healthcare Limited

PRAC Rapporteur: Eva Segovia

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 08-11 January 2018 meeting.

⁸² Advanced therapy medicinal product

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
Daniela Philadelphly	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence De Fays	Alternate	Belgium	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No restrictions applicable to this meeting	Full involvement
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Melinda Palfi	Alternate	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Rhea Fitzgerald	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Alternate	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate - via telephone*	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No participation in final deliberations and voting on:	4.2.4. Hydrochlorothiazide 6.3.46. Tramadol
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Pauline Dayani	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Nathalie Dumarcet	Expert - in person*	France	No interests declared	Full involvement
Vincent Gazin	Expert - via telephone*	France	No interests declared	Full involvement
Maxim Frizler	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Tania Meier	Expert - via telephone*	Germany	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
Julian Paesler	Expert - via telephone*	Germany	No interests declared	Full involvement
Niamh Buckley	Expert - via telephone*	Ireland	No interests declared	Full involvement
Giuseppe Pimpinella	Expert - via telephone*	Italy	No interests declared	Full involvement
Reynold Francisca	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Thomas Scheeren	Expert - via telephone*	Netherlands	No restrictions applicable to this meeting	Full involvement
Magda Pedro	Expert - via telephone*	Portugal	No interests declared	Full involvement
Pilar Rayón Iglesias	Expert - in person*	Spain	No restrictions applicable to this meeting	Full involvement
Miguel-Angel Macia	Expert - via telephone*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - in person*	Sweden	No interests declared	Full involvement
Mari Thorn	Expert - in person*	Sweden	No restrictions applicable to this meeting	Full involvement
Ebru Agca	Expert - in person*	United Kingdom	No interests declared	Full involvement
Katherine Donegan	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Pauline Edwards	Expert - in person*	United Kingdom	No interests declared	Full involvement
Karen Grant	Expert - in person*	United Kingdom	No interests declared	Full involvement
Dee Mthimkhulu	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Nathalja Nolen	Expert - in person*	United Kingdom	No interests declared	Full involvement
Nicola Parkinson	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Kiernan Trevett	Expert - in	United Kingdom	No interests	Full

Name	Role	Member state or affiliation	Outcome following evaluation of e-DoI	Topics on agenda for which restrictions apply
	person*		declared	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=WC0b01ac05800240d0

[Signals assessment and prioritisation](#)

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

[Risk Management Plans \(RMPs\)](#)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website:

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