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Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 05-08 March 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 05-08 March 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.

1.2. Agenda of the meeting on 05-08 March 2018

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

1.3. Minutes of the previous meeting on 05-08 February 2018

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 05-08 February 2018 were published on the EMA website on 06 April 2018 ([EMA/PRAC/218598/2018](#)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

3.1.1. Daclizumab - ZINBRYTA (CAP) - EMEA/H/A-20/1462

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia; PRAC Co-rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

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

Background

The European Commission (EC) sent a letter of [notification](#) dated 26 February 2018 triggering a procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Zinbryta (daclizumab), a centrally authorised medicine, indicated in adult patients for the treatment of 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 another DMT is contraindicated or otherwise unsuitable due to a risk of immune-mediated liver injury.

The review was initiated following cases of serious immune-mediated adverse reactions in the central nervous system (CNS), including encephalitis and encephalo-meningitis. Taking into account the seriousness of the newly available information and its biological plausibility, it was considered that further investigation of the risk of immune-mediated encephalitis was warranted to assess its impact on the benefit-risk balance of the medicinal product and the adequacy of the related risk minimisation measures (RMMs). As a consequence, the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the EMA to assess the above concerns and their impact on the benefit-risk balance for Zinbryta (daclizumab).

The EC also requested the EMA to give its opinion at the latest by 31 July 2018 on whether the marketing authorisation(s) for Zinbryta (daclizumab) should be maintained, varied, suspended or revoked. In addition, the EC requested the EMA to consider as soon as possible whether provisional measures were necessary to protect public health.

Discussion

The PRAC noted the notification letter from the EC.

The PRAC appointed Eva Segovia as Rapporteur and Marcia Sofia Sanches de Castro Lopes Silva as Co-Rapporteur for the procedure.

The PRAC reviewed the assessment report prepared by the Rapporteurs and discussed the need for provisional measures to protect public health while the review of the risk of immune-mediated encephalitis is ongoing as well as a list of questions to be addressed during the procedure together with a timetable for conducting the review.

The PRAC reviewed the totality of the available data, including data provided by the MAH in writing and in an oral explanation on the twelve cases of serious encephalitis and meningo-encephalitis (of which three were fatal) reported since the initial marketing authorisation, and the safety data from clinical trials, in relation to the overall risk of immune-mediated disorders with CNS involvement during treatment with Zinbryta (daclizumab). The PRAC concluded that these adverse reactions could be causally associated with Zinbryta (daclizumab). In addition, the PRAC considered the known serious immune-mediated liver toxicity associated with Zinbryta (daclizumab) as well as other potential immune-mediated disorders affecting other organs than the brain or the liver.

Overall, the PRAC considered that the benefit-risk balance of Zinbryta (daclizumab) is no longer favourable and that urgent measures are needed to protect patients.

The PRAC recommended, as provisional measures, to suspend the use and the marketing authorisation(s) for Zinbryta (daclizumab), and to recall all the batches of the medicinal product from the market up to the level of pharmacies and hospitals.

Furthermore, PRAC recommended that a healthcare professional communication should be disseminated to inform healthcare professionals (HCPs) about the risks related to Zinbryta (daclizumab) and provide instructions related to the cessation of the treatment and the follow-up of patients having received Zinbryta (daclizumab).

Summary of recommendation(s)/conclusions

- The Committee adopted a list of questions ([EMA/PRAC/135878/2018](#)) and a timetable for the ongoing procedure ([EMA/PRAC/135968/2018](#)).
- The PRAC recommended, as provisional measures, to suspend the use and the marketing authorisation(s) for Zinbryta (daclizumab), and to recall all the batches of the medicinal product from the market up to the level of pharmacies and hospitals, without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004. See EMA press release ([EMA/134289/2018](#)) entitled 'EMA recommends immediate suspension and recall of multiple sclerosis medicine Zinbryta - Evidence indicates risk of serious inflammatory brain disorders'.
- The PRAC agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure¹ ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

¹ Rules of procedure on the organisation and conduct of public hearings at the PRAC

Post-meeting note: On 8 March 2018, the EC issued a Commission Decision on the provisional measures. The PRAC assessment report on provisional measures ([EMA/159031/2018](#)) was published on the EMA website on 14 March 2018.

3.2. Ongoing procedures

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

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

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for quinolone- and fluoroquinolone-containing medicines for systemic and inhalational use, indicated for the treatment of bacterial infections, in particular those which are serious and life-threatening, in order to assess the persistence of side effects known to occur with quinolone and fluoroquinolone antibiotics, following reports of long-lasting side effects mainly affecting musculoskeletal and nervous systems. The ongoing review also assesses the need for adequate and consistent risk minimisation measures (RMMs) as well as the impact of this safety concern if confirmed on the overall benefit-risk balance of quinolones and fluoroquinolones for systemic and inhalational use, especially in authorised indications which are related to treatment of non-serious/non-severe infections. For further background, see [PRAC minutes February 2017](#), [PRAC minutes June 2017](#), [PRAC minutes October 2017](#), [PRAC minutes November 2017](#) and [PRAC minutes February 2018](#).

Summary of recommendation(s)/conclusions

- The PRAC reconsidered the option to conduct a public hearing in the context of the ongoing referral under Article 31 of Directive 2001/83/EC for quinolone- and fluoroquinolone-containing medicines for systemic and inhalational use, according to the pre-defined criteria set out in the rules of procedure² ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage in the assessment, a public hearing would be appropriate.
- The Committee adopted a revised timetable for the procedure accordingly ([EMA/PRAC/38618/2017](#)).

Post-meeting note: On 23 March 2018, the PRAC adopted by written procedure the summary of safety concerns ([EMA/166405/2018](#)) for the public hearing. The public hearing will be held at the EMA on 13 June 2018.

² Rules of procedure on the organisation and conduct of public hearings at the PRAC

Applicant: Bayer AG

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

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Xofigo (radium-223 dichloride) to review the results of a phase 3 study (ERA 223³) and assess their potential impact on the benefit-risk balance of Xofigo in the authorised indication of the treatment of chemotherapy-naïve adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. The review was started after analyses of uncleaned preliminary data from this clinical trial, evaluating Xofigo in combination with abiraterone acetate and prednisone/prednisolone in a patient population with asymptomatic or mildly symptomatic prostate cancer, found that the incidences of treatment emergent fractures and deaths were increased in the treatment arm (radium-223 dichloride plus abiraterone acetate and prednisone/prednisolone) compared to the control arm (placebo plus abiraterone acetate and prednisone/prednisolone). For further background, see [PRAC minutes December 2017](#).

Discussion

The PRAC discussed the assessment reports prepared by the Rapporteurs. The PRAC reviewed the preliminary data analyses of study ERA 223 that suggested an increased risk of fracture and mortality when radium-223 dichloride-treatment, compared to placebo, is initiated concurrently with abiraterone acetate and prednisone/prednisolone treatment. The PRAC also considered other available data, including further data from the ALSYMPCA⁴ clinical trial submitted in support of the initial marketing authorisation, in relation to the potential impact of the results of study ERA 223 on the benefit-risk balance of radium-223 dichloride in its authorised indication. The PRAC noted that the use of radium-223 dichloride in study ERA 223 was at earlier stages of the disease, albeit partially overlapping with that included in the authorised indication. The PRAC also noted that data available show that radium-223 dichloride is used to some extent in clinical practice in combination with anti-androgens such as abiraterone and enzalutamide. Further to the review of the preliminary analyses available, the PRAC considered that the underlying mechanism for the increased risks of fracture and mortality observed in ERA 223, and the potential impact of these findings in the authorised indication, remain uncertain.

In view of the seriousness of the events observed, the PRAC therefore recommended provisional amendments to the product information to contraindicate the use of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone, and inform on the results of study ERA 223. In addition, in the absence of definitive evidence that the results observed were specific to the combination with abiraterone acetate and prednisone/prednisolone, the PRAC considered that healthcare professionals and patients

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

⁴ A double-blind, randomised, multiple dose, phase 3, multicentre study of radium-223 chloride in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases (ALSYMPCA)

should be warned that the safety and efficacy of radium-223 dichloride in combination with second generation androgen receptor antagonists including enzalutamide have not been established.

Summary of recommendation(s)/conclusions

- The PRAC adopted a list of outstanding issues (LoOI), to be addressed by the MAH in accordance with a revised timetable ([EMA/PRAC/791811/2017 Rev.1](#)).
- The PRAC also agreed on the need to convene a Scientific Advisory Group (SAG) meeting in the course of the procedure.
- Meanwhile, the Committee recommended the variation to the terms of the marketing authorisation(s) for Xofigo (radium-223) as a provisional measure, without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004. See EMA press release ([EMA/146483/2018](#)) entitled 'Prostate cancer medicine Xofigo must not be used with Zytiga and prednisone/prednisolone'.
- The PRAC also agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Post-meeting note: On 19 March 2018, the European Commission issued a Commission Decision on the provisional measures. The PRAC assessment report on provisional measures ([EMA/170170/2018](#)) was published on the EMA website on 21 March 2018.

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

Applicant: Gedeon Richter Plc.

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

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

Background

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

Summary of recommendation(s)/conclusions

- The PRAC discussed the assessment reports prepared by the Rapporteurs.
- The PRAC adopted a second list of outstanding issues (LoOI) to be addressed by the MAH of Esmya (ulipristal acetate) together with a revised timetable for conducting the review ([EMA/PRAC/791197/2017 Rev. 1](#)).
- The PRAC also adopted a list of questions (LoQ) to the ad-hoc experts group to be consulted on 3 May 2018.
- Moreover, the extension of the scope of the procedure to other ulipristal acetate-containing products was discussed by the PRAC. The Committee agreed that at this

stage of the assessment, in light of the currently available data (including EudraVigilance data) and the different indication and posology, there is no scientific reason justifying extending the scope of the referral procedure.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures⁵

3.4.1. Retinoids: acitretin (NAP); adapalene (NAP); alitretinoin - PANRETIN (CAP); bexarotene – TARGRETIN (CAP); isotretinoin (NAP); tazarotene (NAP); tretinoin (NAP) - EMEA/H/A-31/1446

Applicant(s): Eisai Ltd (Panretin, Targretin), various

PRAC Rapporteur: To be appointed; PRAC Co-rapporteur: To be appointed

Scope: Request for re-examination of the review of the benefit-risk balance following notification by United Kingdom of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background/summary of recommendation(s)/conclusions

- Following further clarification on the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC for retinoids-containing medicinal products, the PRAC noted the withdrawal on 05 March 2018 of the intention by one MAH to request a re-examination of the recommendation adopted by the PRAC at its February 2018 plenary meeting.

3.5. Others

None

4. Signals assessment and prioritisation⁶

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Norepinephrine (NAP)

Applicant(s): various

⁵ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

⁶ 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

PRAC Rapporteur: Almath Spooner

Scope: Signal of stress cardiomyopathy

EPITT 19172 – New signal

Lead Member State: IE

Background

Norepinephrine, as a concentrate for solution for infusion, is indicated for the emergency restoration of blood pressure in cases of acute hypotension.

During routine signal detection activities, a signal of stress cardiomyopathy was identified by Ireland. Following a review of the case reports available in EudraVigilance, Ireland confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the MAH(s) of norepinephrine-containing medicinal products should submit a variation for amending the product information to include stress cardiomyopathy as an undesirable effect.

The PRAC appointed Almath Spooner as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH(s) for norepinephrine-containing products should submit to the relevant national competent authorities of the MSs, within 60 days, a variation to amend the product information⁷.

For the full PRAC recommendation, see [EMA/PRAC/136563/2018](#) published on 03/04/2018 on the EMA website.

4.2. New signals detected from other sources

4.2.1. Amitriptyline (NAP)

Applicant(s): various

PRAC Rapporteur: Agni Kapou

Scope: Signal of dry eye

EPITT 19173 – New signal

Lead Member State: GR

Background

Amitriptyline is a tricyclic antidepressant with potent anticholinergic, antihistaminergic and sedative properties which potentiates the effects of catecholamines. It is indicated for the treatment of depression under certain conditions; nocturnal enuresis where organic pathology is excluded and when non-drug therapy and first line pharmacotherapy has failed;

⁷ Recommendation to update SmPC section 4.8. The package leaflet is to be updated accordingly

and chronic pain (central or peripheral neuropathic pain, fibromyalgia), as an adjunct under certain conditions.

Amitriptyline is estimated to have been used by more than 8,158,237 patients worldwide cumulatively in marketing experience, in the period from 1988 to 2014.

Following the publication in the WHO⁸ Pharmaceuticals Newsletter No. 5, 2017 by *Taavola H.*⁹, a signal of dry eye was identified by Greece. Greece confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence in EudraVigilance and in the literature with regard to the risk of dry eyes associated with amitriptyline, the PRAC agreed that there was sufficient evidence to warrant an amendment of the product information. Nevertheless, the PRAC considered important to obtain comments from the respective MAHs on the proposed wording.

The PRAC appointed Agni Kapou as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for amitriptyline-containing products should submit to EMA, within 15 days, comments on the proposed product information wording¹⁰.
- A 30-day timetable was recommended for the assessment of the MAHs' comments leading to a further PRAC recommendation.

For the full PRAC recommendation, see [EMA/PRAC/136563/2018](#) published on 03/04/2018 on the EMA website.

4.3. Signals follow-up and prioritisation

4.3.1. Cefalexin¹¹ (NAP)

Applicant(s): various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

EPITT 18911 – Follow-up to September 2017

Background

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

The MAH of the innovator of cefalexin-containing product replied to the request for information on the signal of acute generalised exanthematous pustulosis (AGEP) and the responses were assessed by the Rapporteur.

Discussion

⁸ World Health Organization

⁹ Taavola, H. 'Amitriptyline and dry eyes – an ADR overlooked in labelling', WHO Pharmaceuticals Newsletter No.5, 2017: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO

¹⁰ Recommendation to update SmPC section 4.8. The package leaflet is to be updated accordingly

¹¹ First-generation cephalosporin

Having considered the available evidence in EudraVigilance and in the literature with regard to the risk of cefalexin with AGEP, the PRAC agreed that the MAH(s) of cefalexin-containing medicinal products should submit a variation to amend the product information to add a warning on the reports of AGEP in association with cefalexin treatment as well as to include AGEP among the undesirable effects of unknown frequency.

Summary of recommendation(s)

- The MAHs for cefalexin-containing products should submit to the relevant national competent authorities of the MSs, within 60 days, a variation to amend the product information¹².

For the full PRAC recommendation, see [EMA/PRAC/136563/2018](#) published on 03/04/2018 on the EMA website.

4.3.2. Abacavir - ZIAGEN (CAP), NAP; abacavir, lamivudine - KIVEXA (CAP), NAP; abacavir, lamivudine, zidovudine - TRIZIVIR (CAP), NAP; abacavir sulfate, dolutegravir sodium, lamivudine - TRIUMEQ (CAP); atazanavir - REYATAZ (CAP), NAP; atazanavir, cobicistat - EVOTAZ (CAP); darunavir - PREZISTA (CAP), NAP; darunavir, cobicistat - REZOLSTA (CAP); darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP); didanosine (NAP); dolutegravir - TIVICAY (CAP); efavirenz - STOCRIN (CAP) - EMEA/H/C/000250/SDA/072, SUSTIVA (CAP), NAP - EMEA/H/C/000249/SDA/083; efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP), NAP - EMEA/H/C/000797/SDA/043; emtricitabine, tenofovir disoproxil (NAP); emtricitabine - EMTRIVA (CAP) - EMEA/H/C/000533/SDA/052; enfuvirtide - FUZEON (CAP); etravirine - INTELENCE (CAP); fosamprenavir - TELZIR (CAP); indinavir - CRIXIVAN (CAP); lamivudine - EPIVIR (CAP), NAP; lamivudine, zidovudine - COMBIVIR (CAP), NAP; tenofovir, lamivudine (NAP); lopinavir, ritonavir - KALETRA (CAP), NAP; maraviroc - CELSENTRI (CAP); nevirapine - VIRAMUNE (CAP), NAP; raltegravir - ISENTRESS (CAP); rilpivirine - EDURANT (CAP); ritonavir - NORVIR (CAP), NAP; saquinavir - INVIRASE (CAP); stavudine - ZERIT (CAP); tenofovir disoproxil - VIREAD (CAP), NAP - EMEA/H/C/000419/SDA/275; tipranavir - APTIVUS (CAP); zidovudine (NAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG (Atripla, Sustiva), Gilead Sciences International Limited (Emtriva, Viread), Merck Sharp & Dohme Limited (Stocrin)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of autoimmune hepatitis

EPITT 18956 – Follow-up to November 2017

Background

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

The MAHs for Sustiva/Stocrin (efavirenz), Viread (tenofovir disoproxil), Emtriva (emtricitabine) and Atripla (emtricitabine, tenofovir disoproxil) replied to the request for information on the signal of autoimmune hepatitis and the responses were assessed by the Rapporteur.

Discussion

¹² Recommendation to update SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

Having considered the evidence from EudraVigilance and the literature, the responses from the MAHs of efavirenz-, emtricitabine- and tenofovir-containing medicinal products, and the fact that immune reactivation syndrome is a class effect of combined antiretroviral therapy, the PRAC agreed that the review of autoimmune hepatitis should be extended to all medicinal products indicated in the treatment of human immunodeficiency virus (HIV) infection.

Therefore, the MAHs of all innovator antiretroviral medicinal products (AbbVie Ltd, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Gilead Sciences International Limited, Janssen-Cilag International N.V., Merck Sharp & Dohme Ltd, Roche Registration Limited, ViiV Healthcare) should submit a critical analysis of the available evidence on the occurrence of autoimmune hepatitis during HIV treatment, including data from spontaneous reports, clinical trials and the literature. When reviewing the cases, particular attention should be paid to the diagnostic criteria (e.g. type of autoantibody, liver biopsy results), treatment and outcome. The MAHs should also comment on the proposed update to the product information to add autoimmune hepatitis to the existing warning on the immune reactivation syndrome.

Summary of recommendation(s)

- The MAHs of all innovator antiretroviral medicinal products should submit to the EMA, within 60 days, a critical analysis of the available evidence on the occurrence of autoimmune hepatitis during HIV treatment, including data from spontaneous reports, clinical trials and the literature, and comment on the proposal for amending the product information¹³.
- A 60-day timetable was recommended for the assessment of the MAHs' responses leading to a further PRAC recommendation.

For the full PRAC recommendation, see [EMA/PRAC/136563/2018](#) published on 03/04/2018 on the EMA website.

4.3.3. Hormonal contraceptives:

Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol¹⁴ (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, norgestimate acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene¹⁵ (NAP); ethinylestradiol, gestodene¹⁶ (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol¹⁷ (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP)

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal related to a known association between hormonal contraceptives and a small increase in breast cancer following a recent publication

¹³ Recommendation to update SmPC sections 4.4 and 4.8

¹⁴ Contraception indication

¹⁵ All route of administrations except transdermal

¹⁶ Transdermal application

¹⁷ Combination pack

EPITT 19143 – Follow up to January 2018

Background

For background information, see [PRAC minutes January 2018](#). The Rapporteur further assessed the new information.

Discussion

Having considered the Rapporteur's assessment of the recent publication in the New England Journal of Medicine¹⁸, the PRAC agreed to request the authors of the study to provide additional clarifications on the findings in order to fully assess the need for further action on this issue.

The PRAC will assess the responses within a 60-day timetable.

Summary of recommendation(s)

- The authors of the publication (*Morch et al., 2017*) are asked to submit to EMA, within 60 days, additional clarifications on the study findings in accordance with a list of questions (LoQ) adopted by the PRAC.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Brexpiprazole - EMEA/H/C/003841

Scope: Treatment of schizophrenia

5.1.2. Tezacaftor, ivacaftor - EMEA/H/C/004682, Orphan

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

Scope: Treatment of cystic fibrosis

5.1.3. Tisagenlecleucel - EMEA/H/C/004090, Orphan

Applicant: Novartis Europharm Limited, ATMP¹⁹

Scope (accelerated assessment): Treatment of B cell acute lymphoblastic leukaemia (ALL) and diffuse large B cell lymphoma (DLBCL)

5.1.4. Vonicog alfa - EMEA/H/C/004454, Orphan

Applicant: Baxalta Innovations GmbH

Scope: Treatment of von Willebrand disease (VWD)

¹⁸ 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

¹⁹ Advanced therapy medicinal product

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. 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 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 mix-ups 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. For further background, see [PRAC minutes January 2018](#).

Summary of advice

- The RMP for Fiasp (insulin aspart) version 2.1 in the context of the grouped variations under evaluation by the CHMP is considered acceptable.
- The PRAC agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan to be addressed to pharmacies and dispensing clinics in order to minimise the risk of mix-ups between Fiasp (insulin aspart) and insulin degludec. This communication also highlights future measures to strengthen differentiation between the medicinal products and include advice to be given to patients while dispensing the existing products.

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. Cobicistat - TYBOST (CAP) - PSUSA/00010081/201708

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Tybost (cobicistat) is indicated as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tybost, a centrally authorised medicine containing cobicistat, 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 Tybost (cobicistat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a contraindication and a warning on co-administration with lurasidone. Therefore the current terms of the marketing authorisation(s) should be varied²⁰.
- In the next PSUR, the MAH should provide an update on the outcome of the procedure reviewing the signal of decreased exposure in pregnancy.

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

6.1.2. Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - PSUSA/00010082/201708

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

²⁰ Update of SmPC sections 4.3 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Cobicistat is a selective, mechanism-based inhibitor of cytochrome P450 of the CYP3A subfamily, elvitegravir is a human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor (INSTI), emtricitabine is a nucleoside analogue of cytidine and tenofovir is a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil) is indicated for the treatment of HIV-1 infection in adults aged 18 years and over who are antiretroviral treatment-naïve or are infected with HIV-1 without known mutations associated with resistance to any of the antiretroviral agents in Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil). Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil) is also indicated for the treatment of HIV-1 infection in adolescents aged 12 to < 18 years weighing \geq 35 kg who are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil) and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil fumarate.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Stribild, a centrally authorised medicine containing cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil, 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 Stribild (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a contraindication and a warning on co-administration with luradison. Therefore the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should provide an update on the outcome of the procedure reviewing the signal of decreased exposure in pregnancy.

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

6.1.3. Ibuprofen²² - PEDEA (CAP) - PSUSA/00001712/201707

Applicant: Orphan Europe SARL

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) and is indicated, as Pedeia, for the treatment of a haemodynamically significant patent *ductus arteriosus* in preterm newborn infants less than 34 weeks of gestational age.

²¹ Update of SmPC sections 4.3 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²² Indicated in ductus arteriosus only

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Pedea, a centrally authorised medicine containing ibuprofen, 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 Pedea (ibuprofen) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add gastric perforation as an undesirable effect with frequency: unknown. Therefore the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAH should provide further clarity on the revised exposure data and present a critical analysis of all new and cumulative cases of gastrointestinal necrosis as well as a critical analysis of all new and cumulative cases of intussusception and related terms, with a discussion on any appropriate amendments to the product information.

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

6.1.4. Natalizumab - TYSABRI (CAP) - PSUSA/00002127/201708

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Natalizumab is a selective immunosuppressive agent indicated as single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis for patients with highly active disease despite a full and adequate course of treatment with at least one DMT or for patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in one year, and with one or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tysabri, a centrally authorised medicine containing natalizumab, 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 Tysabri (natalizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 90 days, a detailed study report of the retrospective analysis of extended interval dosing (EID) versus standard interval dosing

²³ 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

(SID), a proposal for further investigation of efficacy and safety in terms of progressive multifocal leukoencephalopathy (PML) risk reduction with EID relative to SID, and updated pharmacokinetic/pharmacodynamic (PK/PD) modelling taking into account body weight and extended dosing intervals.

- In the next PSUR, the MAH should perform an analysis of hepatic injury including a cumulative review of cases of cholelithiasis, chronic lithiasis cholecystitis and biliary colic. In addition, the MAH should consider the deletion of 'hypersensitivity reactions' from the list of important identified risks with the next RMP update.

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

6.1.5. [Ospemifene - SENSHIO \(CAP\) - PSUSA/00010340/201708](#)

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Ospemifene is a selective oestrogen receptor modulator. Senshio (ospemifene) is indicated for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Senshio, a centrally authorised medicine containing ospemifene, 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 Senshio (ospemifene) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add headache as an undesirable effect with frequency: common. Therefore the current terms of the marketing authorisation(s) should be varied²⁴.

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

6.1.6. [Sitagliptin - JANUVIA \(CAP\), RISTABEN \(CAP\), TESAVEL \(CAP\), XELEVIA \(CAP\) - PSUSA/00002711/201708](#)

Applicant: Merck Sharp & Dohme Limited

²⁴ 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

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Sitagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated in monotherapy or in combination in adult patients with type 2 diabetes mellitus (T2DM) to improve glycaemic control under certain conditions as well as an add-on to insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Januvia, Ristaben, Tesavel and Xelevia, centrally authorised medicines containing sitagliptin, 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 Januvia, Ristaben, Tesavel and Xelevia (sitagliptin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include thrombocytopenia as an undesirable effect with frequency: rare. Therefore the current terms of the marketing authorisations should be varied²⁵.
- In the next PSUR, the MAH should provide a detailed review of adverse drug reactions reported in patients with chronic kidney disease (CKD) stratified by glomerular filtration rate (GFR) (i.e. <29 mL/min, 30-44 mL/min, 45-59 mL/min, >60 mL/min).

The PRAC considered that sitagliptin- and sitagliptin/metformin-containing products should be assessed in the future within the same PSUSA procedure. Therefore, the list of Union reference dates (EURD list) should be updated accordingly. The next PSUR should be submitted in accordance with the requirements set out in the EURD list provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.7. Sitagliptin, metformin hydrochloride - EFFICIB (CAP), JANUMET (CAP), RISTFOR (CAP), VELMETIA (CAP) - PSUSA/00002003/201708

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Sitagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor and metformin a biguanide. In combination, sitagliptin/metformin is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin. Sitagliptin/metformin is also indicated in combination with a sulphonylurea as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated

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

dose of metformin and a sulphonylurea, as well as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPAR γ) agonist as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPAR γ agonist. Sitagliptin/metformin is also indicated as add-on to insulin as an adjunct to diet and exercise to improve glycaemic control in patients when a stable dose of insulin and metformin alone do not provide adequate glycaemic control.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Efficib, Janumet, Ristfor and Velmetia, centrally authorised medicines containing (sitagliptin/metformin), and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Efficib, Janumet, Ristfor and Velmetia, centrally authorised medicines containing (sitagliptin/metformin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include thrombocytopenia as an undesirable effect with frequency: rare. Therefore the current terms of the marketing authorisations should be varied²⁶.
- In the next PSUR, the MAH should provide a detailed review of adverse drug reactions reported in patients with chronic kidney disease (CKD) stratified by glomerular filtration rate (GFR) (i.e. <29 mL/min, 30-44 mL/min, 45-59 mL/min, >60 mL/min). In addition, the MAH should include a further detailed review of cases of lactic acidosis associated with sitagliptin/metformin fixed dose combination collected through a follow-up questionnaire.

The PRAC considered that sitagliptin- and sitagliptin/metformin-containing products should be assessed in the future within the same PSUSA procedure. Therefore, the list of Union reference dates (EURD list) should be updated accordingly. The next PSUR should be submitted in accordance with the requirements set out in the EURD list provided for under Article 107c(7) of Directive 2001/83/EC.

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

See also Annex I 16.2.

6.2.1. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP); NAP - PSUSA/00002014/201706

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

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jylamvo and Nordimet, centrally authorised medicines containing methotrexate, together with nationally authorised medicines containing methotrexate, 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 methotrexate-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to revise the wording on overdose associated with daily rather than weekly administration, revise the warning on pregnancy, contraception and fertility, and include information on increased toxicity through concomitant use of methotrexate and nitrous oxide. Additionally, the product information for methotrexate-containing medicinal products indicated in rheumatoid arthritis should be updated to include osteonecrosis of the jaw (secondary to lymphoproliferative disorder) as an undesirable effect. Therefore the current terms of the marketing authorisations should be varied²⁷.
- The MAH(s) for nationally authorised oral methotrexate-containing products used only in indications requiring dosing once a week (e.g. oral formulations only used for rheumatologic/dermatological diseases or Crohn's disease), and oral methotrexate-containing products with at least one indication requiring treatment once a week and at least one indication requiring a different treatment schedule (e.g. oral formulations used for rheumatologic/dermatological diseases/Crohn's disease and oncology) should complete, as a condition to the marketing authorisations of nationally authorised medicines, within 30 days of the EC decision, the implementation of a visual reminder on the outer and immediate packaging with the key element to warn patients to take the product once a week for those indications requiring dosing once a week. The details of the visual reminder should be agreed at national level. These should be submitted to the National Competent Authorities (NCAs) and NCAs shall ensure that the condition is fulfilled.
- In the next PSUR, all MAHs should provide a detailed review on all interval and cumulative cases of toxicities related to inadvertent daily rather than weekly administration of oral and parenteral methotrexate-containing medicinal products with a particular attention to be given to fatal toxicities and including a detailed root cause analysis as well as a further discussion on the effectiveness of the existing risk minimisation measures (RMMs).
- In addition, based on this review, MAHs should discuss the need for additional RMMs, in particular the modification of the presentation from bottles of tablets into blister packaging with a decrease of the number of tablets per package. The MAHs should also

²⁷ Update of SmPC sections 4.2, 4.4, 4.5, 4.6 and 4.9. The SmPC section 4.8 is updated in addition for methotrexate-containing products indicated in rheumatoid arthritis. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

make proposals to measure the effectiveness of the proposed RMMs. Moreover, the MAHs should further discuss the concomitant use of methotrexate and nitrous oxide leading to increased toxicity, present and discuss all available evidence on the potential association of methotrexate with 'osteonecrosis of the jaw', and perform a cumulative review on encephalopathy and systematic use of levofolinic acid after high dose methotrexate treatment, and the use of vitamin B12 as corrective treatment and the need for product information (PI) updates. The MAHs for methotrexate-containing products indicated in at least one indication with medium-dose (single dose 100-1000 mg/m²) or high-dose methotrexate therapy (single dose >1000 mg/m²) should provide a proposal to update the PI with a recommendation for dose adjustment in patients with renal impairment. The MAHs with methotrexate-containing products in oncologic indications are requested to perform a cumulative review on tumour lysis syndrome and to discuss the need for consequent PI updates. The MAHs of the product Metoject should perform a cumulative review on injection site necrosis to evaluate if a PI update is warranted accordingly.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of PSUR submission should be revised to sixteen-monthly and the list of Union reference dates (EURD list) will be updated accordingly. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC is required and the EURD list should be updated accordingly.

Post-meeting note: In view of the above, the seriousness of the risk of overdose toxicity as a consequence of inadvertent daily intake instead of weekly intake, Spain initiated in April 2018 a referral procedure under Article 31 of Directive 2001/83/EC ([EMA/H/A-31/1463](#)) and requested the EMA to assess the above concerns and their impact on the benefit-risk balance for oral formulations of methotrexate-containing products.

6.2.2. Oxybutynin - KENTERA (CAP); NAP - PSUSA/00002253/201707

Applicants: Nicobrand Limited (Kentera), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Oxybutynin is a urinary antispasmodic indicated for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in adult patients with unstable bladder.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Kentera, a centrally authorised medicine containing oxybutynin, and nationally authorised medicines containing oxybutynin, 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 oxybutynin-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.

- In the next PSUR, the MAHs should provide a follow-up on the risk of dementia further to the recent publications, the signal of cardiac disorders, and report on any new cases of asthenic conditions. In addition, the MAH Mylan should provide a follow-up on the risk of allergic reactions and report on any new information regarding the safety concern 'depression' as well as the safety concern 'intestinal obstruction'.

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. Carbetocin (NAP) - PSUSA/00000546/201706

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Carbetocin is an oxytocic used immediately following an elective caesarean section when a local or spinal anaesthesia has been administered.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing carbetocin, 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 carbetocin-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

Nevertheless, the PRAC considered that the risk of myocardial ischaemia, arrhythmia and angina pectoris and the risk of anaphylaxis in patients with latex allergy needed to be further assessed. Further consideration is to be given at the level of the CMDh.

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

6.3.2. Cefadroxil (NAP) - PSUSA/00000584/201707

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Cefadroxil is a first-generation cephalosporin, a beta-lactam anti-bacterial, indicated for the treatment of the following infections caused by susceptible microorganisms: upper and lower respiratory tract infections, skin and soft tissue infections, genito-urinary tract infections, and other infections including osteomyelitis and septic arthritis in adults and paediatric patients.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing cefadroxil, 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 cefadroxil-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a drug-drug interaction with probenecid. Therefore the current terms of the marketing authorisation(s) should be varied²⁸.
- In the next PSUR, the MAHs should provide a review of all available data of the safety issues of drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis, leukocytoclastic vasculitis, as well as related to the risk of tongue discolouration and risk of encephalopathy.

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. Delapril, manidipine (NAP); delapril, indapamide (NAP) - PSUSA/00010496/201706

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Delapril is an angiotensin converting enzyme (ACE) inhibitor, manidipine, a dihydropyridine calcium antagonist and indapamide, a non-thiazide chlorosulphonamide indole derivative. Delapril/indapamide and delapril/manidipine are indicated in essential hypertension.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing delapril/indapamide or delapril/manidipine, 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 delapril/indapamide- and delapril/manidipine-containing medicinal products in the approved indications remains unchanged.

²⁸ 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 of medicinal products containing the combination delapril/indapamide should be updated to add dysgeusia/ageusia and loss of consciousness/syncope as undesirable effects with frequency: unknown, as well as to remove the statement concerning the association with significant variations in serum potassium levels. Therefore the current terms of the marketing authorisation(s) should be varied²⁹.

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. Diclofenac, misoprostol (NAP) - PSUSA/00001040/201707

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) and misoprostol a synthetic prostaglandin E₁ analogue. In combination, diclofenac/misoprostol is indicated for the symptomatic treatment of rheumatoid arthritis, osteoarthritis in patients with a special need for the prophylaxis of NSAID-induced gastric and duodenal ulceration. In some countries the diclofenac-misoprostol medicines are also indicated for the symptomatic treatment of ankylosing spondylitis and acute musculoskeletal disorders for patients with a special need for the prophylaxis of NSAID-induced gastric and duodenal ulceration.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing diclofenac/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 diclofenac/misoprostol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to contraindicate use in women of child bearing potential not using effective contraception, strengthen warnings related to teratogenicity with misoprostol use and to update information on the possible risks associated with exposure to diclofenac during pregnancy to ensure it appropriately and fully reflects the known risks of NSAID use during pregnancy. Therefore the current terms of the marketing authorisation(s) should be varied³⁰.

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.

²⁹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³⁰ Update of SmPC sections 4.3, 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

6.3.5. Ezetimibe, rosuvastatin (NAP) - PSUSA/00010271/201707

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Ezetimibe is a lipid modifying agent and rosuvastatin is a β -Hydroxy β -methylglutaryl-CoA (HMG-CoA) reductase inhibitor. In combination, ezetimibe/rosuvastatin is indicated as a substitution for adjunctive therapy to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) for use in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or homozygous familial hypercholesterolaemia, which are already treated and adequately controlled on the combination of ezetimibe and rosuvastatin.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing the combination of ezetimibe/rosuvastatin, 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 ezetimibe/rosuvastatin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the interaction with regorafenib and simeprevir. Therefore the current terms of the marketing authorisation(s) should be varied³¹.

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

6.3.6. Flecainide (NAP) - PSUSA/00001396/201706

Applicant(s): various

PRAC Lead: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

Background

Flecainide is a class 1 anti-arrhythmic (local anaesthetic) agent indicated in the treatment of supraventricular arrhythmia and ventricular arrhythmia.

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

Summary of recommendation(s) and conclusions

³¹ 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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of flecainide-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- Nevertheless, the PRAC considered that the antiarrhythmic efficacy of flecainide in combination with beta blockade in patients carrying the Gly389 variant in the beta-1 adrenoceptor gene needed to be further assessed. The PRAC also considered of value to consult the Pharmacogenomics Working Party ([PgWP](#)) and request the MAH(s) to answer a list of questions (LoQ).

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. Levocetirizine (NAP) - PSUSA/00001850/201707

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Levocetirizine is an oral anti-histaminic indicated for the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria in adults and children aged 6 years and above as film-coated tablets, and for the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria in adults and children aged 2 years and above as oral drops, solution/oral solution.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levocetirizine, 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 levocetirizine-containing medicinal product(s) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add oculogyration as an undesirable effect with frequency: unknown. Therefore the current terms of the marketing authorisation(s) should be varied³².
- In the next PSUR, the MAH should provide cumulative reviews of acute generalised exanthematous pustulosis, arrhythmia, dystonia and dyskinesia and thrombocytopenia.

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.

³² 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

6.3.8. Methylaminolevulinate (NAP) - PSUSA/00002019/201706

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Methylaminolevulinate is an antineoplastic agent, a sensitizer used in photodynamic/radiation therapy. Metvix (methylaminolevulinate) is indicated in adults for the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other therapies are considered less appropriate, for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for other available therapies due to possible treatment related morbidity and poor cosmetic outcome and for the treatment of squamous cell carcinoma in situ (Bowen's disease) when surgical excision is considered less appropriate. Luxera (methylaminolevulinate) is indicated in adults for the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses (AKs) on the face and scalp when other therapies are considered less appropriate.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing methylaminolevulinate, 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 methylaminolevulinate-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include information about treatment in immunosuppressed patients as a warning/precaution for use. Therefore the current terms of the marketing authorisation(s) should be varied³³.
- In the next PSUR, the MAH(s) should provide a detailed review of the use of methylaminolevulinate in pregnancy, in immunosuppressed patients and in children or adolescents. In addition the MAH(s) should monitor and report herpes virus infections, drug reaction with eosinophilia and systemic symptoms (DRESS), eye disorders and occupational exposure.

The PRAC considered that the risk of transient global amnesia (including confusional state and confusion) needed to be further assessed. Further consideration is to be given at the level of the CMDh.

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

6.3.9. Oxytocin (NAP) - PSUSA/00002263/201706

Applicant(s): various

³³ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC Lead: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

Background

Oxytocin, identical to the natural oxytocin hormone released by the posterior lobe of the pituitary, is indicated for the induction of labour for medical reasons, the enhancement of labour in selected cases of uterine inertia, as well as in early stages of pregnancy as adjunctive therapy for management of incomplete, inevitable or missed abortion. Oxytocin is also indicated during caesarean section but after the delivery of the child and for the prevention and treatment of post-partum uterine atony and haemorrhage. In addition, as a nasal spray, oxytocin is indicated for the promotion of milk ejection in women who experience difficulties in breast-feeding or use of a breast pump and for the prevention and treatment of breast engorgement, and prevention of mastitis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing oxytocin, 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 oxytocin-containing medicinal product(s) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add a warning on anaphylaxis in women with latex allergy. Therefore the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAHs should monitor the MedDRA PT³⁵ 'post-partum depression' and related terms and discuss potential mechanisms relating to oxytocin. In addition, the MAH Novartis is asked to provide an overview of serious cases (including whether they were fatal or not) of medication error and discuss every adverse drug reaction (ADRs) associated with these reports that are not listed in the product information (PI).

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. Theophylline (NAP) - PSUSA/00002921/201706

Applicant(s): various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

Background

Theophylline is a systemic xanthine derivative for obstructive airway diseases indicated for the treatment and prevention of bronchospasm in patients with asthma, chronic obstructive pulmonary disease (COPD) and emphysema in oral form with prolonged release formulations

³⁴ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³⁵ Medical dictionary for regulatory activities – Preferred Term

intended for maintenance treatment only. A parenteral formulation, a concentrate solution for infusion, is indicated for emergency treatment of dyspnea caused by narrowing of the airways (bronchoconstriction) in bronchial asthma and other obstructive airways disease. Other approved indications for theophylline-containing products include the adjuvant treatment of manifestations of heart failure, the treatment of cardiac asthma and left ventricular or congestive cardiac failure, cardiogenic pulmonary edema as well as neonatal apnea and bradycardia.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing theophylline, 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 theophylline-containing medicinal product(s) in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should monitor and provide an evaluation of suicidal ideation following theophylline toxicity and Takotsubo syndrome following theophylline toxicity.

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)³⁶

See Annex I 17.1.

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

See Annex I 17.2.

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

See also Annex I 17.3.

³⁶ In accordance with Article 107n of Directive 2001/83/EC

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

³⁸ In accordance with Article 107p-q of Directive 2001/83/EC

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

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Results of an observational study to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis (CF), the frequency and outcomes of pregnancy in ivacaftor-treated patients, drug utilisation of ivacaftor and CF disease progression in ivacaftor-treated patients

Background

Kalydeco (ivacaftor) is a respiratory system product, potentiator of the CFTR³⁹ protein, indicated for the treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. The MAH was required as a condition to the marketing authorisation ([Annex IID](#)) to set up a post-authorisation safety study⁴⁰ (PASS) in the form of a 5-year long-term observational study with ivacaftor in patients with cystic fibrosis, including microbiological and clinical endpoints (e.g., exacerbations), according to a protocol agreed with the CHMP.

The final study report was submitted to EMA by MAH Vertex on 11 December 2017 with an update of the RMP and the product information (PI) resulting from the data presented in this PASS final study report. The PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'an observational study to evaluate the long-term safety of ivacaftor in patients with cystic fibrosis', the PRAC considered that supplementary information was required before a recommendation could be made on the benefit-risk balance of medicinal products containing ivacaftor concerned by the PASS final report. The MAH should provide within 30 days cumulative analyses of all the outcomes as well as further clarifications on the analyses including those performed on the US registry data. A 60 days-assessment timetable will be applied.
- The PRAC considered that the current RMP version is acceptable provided the additional risk minimisation measures are removed. The PRAC considered in addition that the MAH proposal to update the PI was not endorsed and therefore the information about the long-term safety study should be removed.
- Moreover, the PRAC recommended that the terms of the marketing authorisation(s) for Kalydeco (ivacaftor) should be varied to remove the condition from Annex II.

7.3.2. Strontium ranelate - OSSEOR (CAP), PROTELOS (CAP) - EMEA/H/C/PSR/S/0013

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Results for a European programme of PASS for Protelos/Osseor through EU-ADR

³⁹ Cystic fibrosis transmembrane conductance regulator

⁴⁰ EUPAS4270. An Observational Study to Evaluate the Long-term Safety of Ivacaftor in Patients With Cystic Fibrosis

Alliance⁴¹ exploring the effectiveness of the established risk minimisation measures (RMM) by characterising utilisation patterns of strontium ranelate, as imposed in the conclusions of a referral procedure (EMA/H/A20/1371) under Article 20 of Regulation (EC) No 726/2004 finalised in 2014

Background

Strontium ranelate is a drug affecting bone structure and mineralisation for the treatment of bone diseases. Protelos and Osseor (strontium ranelate) are indicated for the treatment of severe osteoporosis in postmenopausal women and in adult men at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. In postmenopausal women, strontium ranelate reduces the risk of vertebral and hip fractures. In line with the conclusions of the referral procedure under Article 20 of Regulation (EC) 726/2004 ([EMA/112925/2014](#)), the CHMP requested the MAH as a condition to the marketing authorisations ([Annex IV](#), [Annex II D for Osseor](#), [Annex II D for Protelos](#)) to conduct a PASS to assess whether, within the limited patient population which is expected to be exposed to strontium ranelate, there was compliance with the restrictions introduced, and to collect further information on the risks of the medicinal products and on the effectiveness of the risk minimisation measures. The European Commission (EC) decision was issued on 15 April 2014. In January 2015, the PRAC endorsed the PASS protocol. For further background, see [PRAC minutes January 2014](#), [PRAC minutes September 2014](#), and [PRAC minutes January 2015](#).

In order to fulfil the obligation to submit the results of an imposed non-interventional PASS in accordance with Article 107p of Directive 2001/83/EC, MAH Les Laboratoires Servier submitted to EMA on 12 December 2017 a PASS final study report for Protelos/Osseor (strontium ranelate). The PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'European programme of post-authorisation safety studies for Protelos/Osseor through EU-ADR Alliance', the PRAC considered that the benefit-risk balance of medicinal products containing the active substance strontium ranelate remains unchanged and recommended that the terms of the marketing authorisation(s) for Protelos/Osseor (strontium ranelate) should be varied to remove the condition from Annex II as it is considered fulfilled.
- In addition, the PRAC considered that an updated RMP should be submitted at the next regulatory opportunity.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴²

See Annex I 17.4.

⁴¹ Federated collaborative framework for drug safety studies

⁴² 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

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

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

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

None

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

None

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

10.1.1. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0085

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: PRAC consultation on a variation consisting of the evaluation of the results of study EPI-HPV-069: a meta-analysis assessing the risk of three autoimmune diseases following vaccination with Cervarix: autoimmune thyroiditis (AIT), Guillain-Barre syndrome (GBS) and inflammatory bowel disease (IBD). The RMP (version 18) is updated accordingly and includes minor updates related to other studies

Background

Human papillomavirus (HPV) vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) is an adjuvanted non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18, indicated for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic HPV types.

The CHMP is evaluating a type II variation for Cervarix, a centrally authorised HPV vaccine, evaluating a meta-analysis assessing the risk of several autoimmune diseases following vaccination with Cervarix, in particular, autoimmune thyroiditis (AIT). The PRAC is responsible for providing advice to the CHMP on specific questions falling under its remit on this type II variation. For further background, see [PRAC minutes December 2016](#), [PRAC minutes May 2017](#) and [PRAC minutes September 2017](#).

Summary of advice

- The PRAC noted the updated meta-analysis report and the assessment report.
- Based on the review of the available information, the PRAC agreed with the CHMP conclusion that the available evidence did not support a link between Cervarix (HPV

vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) and autoimmune thyroiditis and therefore no additional measures need to be taken.

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Thiocolchicoside (NAP) - EMEA/H/N/PSA/J/0010

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: PRAC consultation on the evaluation of a progress report for a non-interventional imposed PASS: a drug utilisation study assessing the effectiveness of risk minimisation measures (routine and additional) and further characterising the prescribing patterns for thiocolchicoside-containing medicinal products for systemic use, following the conclusions of a referral procedure under Article 31 of Directive 2001/83/EC finalised in 2014, at the request of Italy

Background

Thiocolchicoside is a semi-synthetic sulfurated colchicoside derivative with muscle relaxant pharmacological activity indicated as an adjuvant for the treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16-years onwards.

In line with the conclusions of a referral procedure under Article 31 of Directive 2001/83/EC conducted in 2014 for thiocolchicoside-containing medicines ([EMEA/H/A-1361](#)), MAHs were required as a condition to the marketing authorisations ([Annex IV](#)) to provide within the risk management plan submission a protocol to evaluate the effectiveness of the risk

minimisation activities. The final study report had to be submitted by November 2017 (within 18 months after the EC decision). The Consortium of the MAHs submitted on 21 December 2017 the first PASS interim report for thiocolchicoside to the Italian Medicines Agency ([AIFA](#)). For background information, see [PRAC minutes February 2013](#), [PRAC minutes January 2017](#), and [PRAC minutes June 2017](#).

In the context of the national evaluation of the study progress report, Italy requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions presented by Italy and considered that the implementation of routine and additional risk minimisations measures (RMMs) and the distribution of a direct healthcare professional communication (DHPC) following the above-mentioned referral procedure have been only partially effective, and resulted only in moderate changes in the prescribing behaviour of the surveyed physicians. In addition, the PRAC considered that the high degree of non-compliance with the safety restrictions introduced within the 2014 referral, especially the contraindication in woman of child-bearing potential (WCBP) not using contraception, and during pregnancy and lactation, is a matter of concern and that the key messages for the additional RMMs (introduced within the 2014 referral procedure), at present, remain valid and do not require any revision. The PRAC also supported the Italian request for supplementary information for the Consortium of MAHs to provide AIFA within 60 days with the requested clarifications on the PASS interim data. Finally, the PRAC agreed with the conclusion from Italy that, at present, no further regulatory action is needed.

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. Healthcare Professionals' Working Party (HCPWP) – Consultation feedback on how best to cascade the information on the product information updates as well as to consider additional communication and risk minimisation tools to be used

PRAC lead: Doris Stenver

The PRAC received some feedback following the consultation agreed by the Committee in September 2017 with the Healthcare Professionals' Working Party ([HCPWP](#)) regarding intravenous (IV) fluids containing electrolytes and/or carbohydrates (NAP) and the risk of

hyponatraemia (EPITT 18631) with the view of determining how best to cascade the information on the product information updates as well as to consider additional communication and risk minimisation tools. Among the responses received, the PRAC highlighted the feedback regarding the point-of-care electronic systems being a good additional communication and risk minimisation tool to be used with certain limitations, mostly related to a certain degree of alert fatigue as well as the availability of these systems. The healthcare professional associations' feedback was considered extremely helpful, leading towards the improvement of our collaboration paths with regard to risk communication, the best paths as well as the most adequate tools. For further background, see [PRAC minutes July 2017](#).

12.3.2. Scientific Advice Working Party (SAWP) – Survey on scientific advice procedures with PRAC consultation

PRAC lead: Martin Huber, Brigitte Keller-Stanislawski

In line with the PRAC work plan 2018 ([EMA/PRAC/139104/2018](#)), the SAWP secretariat presented to the PRAC the results of a survey conducted to identify hurdles in participation of PRAC members acting as peer reviewers in scientific advice (SA) procedures with PRAC consultation. Overall, there is a low number of SA procedures with PRAC consultation (less than 10 per year) with an overall positive feedback from the PRAC members involved. As a next step, the joint SAWP/PRAC members will review the process for further improvements. Further update will be given in due course.

12.4. Cooperation within the EU regulatory network

12.4.1. European Network Training Centre (EU NTC) - Operation of Pharmacovigilance in the EU (EU PVOP) - Training curriculum (TC) – Implementation plan for 2018

PRAC lead: Dolores Montero Corominas

At the organisational matters teleconference on 22 March 2018, in line with the PRAC work plan 2018 ([EMA/PRAC/139104/2018](#)), the EMA Secretariat presented to the PRAC, on behalf of the Pharmacovigilance Training Curriculum Steering Group (EU PVOP-SG⁴³) composed of EMA and NCA representatives, the 2018 pharmacovigilance training delivery plan for priority areas and additional topics of interest, including the identification of training teams and leads.

Post-meeting note: On 23 March 2018, the PRAC adopted the implementation plan for 2018 via written procedure.

12.4.2. PRAC strategic review and learning meeting, Prague, Czech Republic, 19-20 April 2018

PRAC lead: Eva Jirsová

The PRAC was presented with a consolidated agenda for the 'PRAC strategic review and learning meeting (SRLM)', to be held on 19-20 April 2018, under the Bulgarian presidency of the Council of the EU. The meeting will be hosted by Czech Republic in Prague.

⁴³ Steering group of the 'operation of pharmacovigilance in the EU'

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. PRAC workload statistics – Q4 2017 and overview

The EMA secretariat presented, at the organisational matters teleconference held on 22 March 2018, quarterly and cumulative figures to estimate the evolution of the workload of the PRAC, by reflecting the number of procedures and agenda items covered at each PRAC plenary meeting. See previous update, [PRAC minutes July 2017](#).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections – template for sharing assessor’s information

The EMA Secretariat presented to the PRAC the finalised template for sharing of information between Assessors and Inspectors on pharmacovigilance matters which had been developed by the Pharmacovigilance Inspectors Working Group ([PhV IWG](#))-PRAC subgroup and consolidated further to PRAC comments. For further background, see [PRAC minutes October 2017](#). As a next step, a pilot phase will be initiated after the PRAC meeting in April 2018.

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the progress made including the update on the EURD tool. In addition, the PRAC was further presented the GPAG work plan 2018 in detail.

12.10.3. PSURs repository

None

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

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

Post-meeting note: following the PRAC meeting of March 2018, the updated EURD list was adopted by the CHMP and CMDh at their March 2018 meetings and published on the EMA website on 27/03/2018, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the SMART Working Group (SMART WG) meeting held on 5 March 2018. The WG discussed the practices to establish the periodicity of monitoring of medicinal products. It was noted that GPAG is developing guidance and criteria to set the periodicity of single assessment procedures, which would result in a tool to support decision-making on changing PSUR frequencies. PSUR frequencies were assigned with the knowledge that electronic reaction monitoring report (eRMR) monitoring continues with an appropriate frequency. In summary, it was considered helpful to collect the practices/standard operating procedures (SOPs)/decision trees/criteria used to decide on the frequency of monitoring at national level from MSs to inform the guidance on periodicity criteria via a non-urgent information (NUI). The WG received also an update on the paracetamol pilot (run between August 2017 and January 2018). The usefulness of collating and sharing information on safety issues originating from published studies that were reviewed but not validated as new signals was acknowledged. However, the WG recommended that ways to improve the visibility of such information should be further explored. In addition, the SMART WG discussed redistribution of products for which UK is the

lead Member State (LMS) for signal detection planned for end 2018. Finally, the SMART WG was updated on the pilot of signals from EudraVigilance (EV) in view of the access of MAHs to EV and their legal obligations. The pilot started on 22 February 2018, i.e. MAHs were required to start monitoring EV data for over 290 substances included in the pilot. Products that are part of the pilot are listed in the [‘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 – experience analysis

Further to the [implementation of the Pharmacovigilance legislation](#) in 2012, [additional monitoring](#) has been introduced for medicines that are being monitored particularly closely by regulatory authorities and that have an inverted black triangle printed on the product information. In February 2017, the EMA Secretariat updated the PRAC on an ongoing project to analyse the experience with additional monitoring in preparation for a report to the European Commission (EC) mandated by the legislation. In May 2017, the PRAC adopted the outline of the study aiming at describing the experience with the use of the additional monitoring list from its creation in 2013 until December 2016, as well as to investigate whether the inclusion of a product on the additional monitoring list has an effect on reporting of adverse drug reactions (ADRs). For further background, see [PRAC minutes February 2017](#), [PRAC minutes April 2017](#) and [PRAC minutes May 2017](#).

The collection of data and analysis of the above-mentioned study started in May 2017. At its February 2018 meeting (see [PRAC minutes February 2018](#)), the PRAC was updated on the preliminary data analysis in preparation for the PRAC consultation on the preliminary study report and on 19 February 2018, the EMA Secretariat circulated to the PRAC the draft report of the ‘EMA and Member States report to the European Commission on the experience with the list of products subject to additional monitoring’ for comments.

At the current meeting, the PRAC finalised its discussion on the report of the ‘EMA and Member States report to the European Commission on the experience with the list of products subject to additional monitoring’ as consolidated with comments received.

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 28/03/2018 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. EudraVigilance – annual report 2017

The EMA secretariat presented to the PRAC the 2017 EudraVigilance annual report for the European Parliament, the Council and the Commission in line with Regulation (EC) No. 726/2004, Article 24(2), paragraph 2. Following the next EMA Management Board meeting in March 2018, the report will be submitted to the EU institutions and published on the EMA website in Q1 2018.

Post-meeting note: On 15 March 2018, the EudraVigilance annual report 2017 ([EMA/7552/2018](#)) was published on the EMA website.

12.13.3. EudraVigilance operational plan – milestones 2018 to 2020

At the organisational matters teleconference on 22 March 2018, following previous discussions (see [PRAC minutes June 2017](#), [PRAC minutes July 2017](#), [PRAC minutes September 2017](#), [PRAC minutes November 2017](#) and [PRAC minutes December 2017](#)), and the go-live of the new EudraVigilance system on 22 November 2017, the EMA Secretariat presented to the PRAC in line with the PRAC work plan 2018 ([EMA/PRAC/139104/2018](#)) the draft EudraVigilance operational plan that describes key activities and developments that will potentially impact EudraVigilance and its stakeholders from a technical and operative perspective during the next three years from 2018 to 2020.

12.13.4. EudraVigilance (EV) - processing large volumes of cases made available through EV to MAHs

Following requests for clarification from MAHs and discussion at the EudraVigilance Expert Group ([EV-EWG](#)), the EMA Secretariat proposed to the PRAC options to define a common approach as regards the processing of large volumes of cases made available through EudraVigilance to MAHs. The PRAC gave an orientation on the most appropriate option and advised also to consult with the Pharmacovigilance Inspectors Working Group ([PhV IWG](#)).

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.16.2. Referral road map project – call for interest

At the organisational matters teleconference on 22 March 2018, the EMA Secretariat presented to the PRAC the 'referral roadmap', a project recently launched in order to create a cross-committee platform to discuss ways of sharing experience of and improving operational aspects on the preparation, initiation, conduct and implementation of a referral. Of note, this activity is reflected in the PRAC work plan 2018 ([EMA/PRAC/139104/2018](#)). The EMA Secretariat launched a call for expression of interest amongst PRAC members to participate. Four PRAC delegates expressed interest in joining the working group on safety referrals.

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

12.18.3. Policy on scientific publication and representation for EMA's scientific committees and their members

The PRAC welcomed the overview given by the EMA Secretariat on the current policy on scientific publication and representation for EMA's scientific committees and their members

([EMA/231477/2005 rev. 1](#)) to facilitate external communication activities from the EMA scientific committees as a whole or by individual members.

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

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

The EMA Secretariat presented to the PRAC the revised draft Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population- specific considerations IV: Paediatric population further to the public consultation undertaken from August to October 2017. A follow-up discussion for finalisation of the draft will be held at the PRAC April/May 2018 meeting.

12.20.2. Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population-specific considerations V: ‘Medicines used by the older population’

The topic was deferred. The PRAC will be updated in due course.

12.20.3. Public hearing – outcome report

At the organisational matters teleconference on 22 March 2018, the PRAC welcomed the presentation by the EMA Secretariat of the ‘outcome report’ of the public hearing held on 26 September 2017 in the context of the referral procedure under Article 31 of Directive 2001/83/EC for valproate-containing medicines ([EMEA/H/A-31/1454](#)). The ‘outcome report’ provides an overview of the entire public hearing process from beginning to end, based on feedback received from the various parties involved and aims at improving the process to ensure the conduct of future hearings is optimal. Overall, the public hearing provided valuable insight and information, adding value to the outcome of the referral. The speakers’ interventions helped to focus and define where the real problems in managing the risk of valproate are and also gave some indications for possible solutions. Furthermore, the public hearing allowed different stakeholders to provide their point of view, listen and learn from each other. In addition the public hearing increased transparency and understanding of the regulatory procedure for the safety of medicines in Europe (referral procedure). The PRAC endorsed the report and its findings which would be taken on board for future public hearings.

Post-meeting note: the ‘outcome report’ will be presented to the EMA Management Board at its June 2018 meeting and published afterwards on the EMA website.

12.20.4. Scientific meeting on long-term pregnancy outcomes, EMA, London, 28-29 June 2018 - Agenda

The EMA Secretariat presented to the PRAC the agenda of the planned scientific meeting on long-term pregnancy outcomes to be held on 28-29 June 2018. The PRAC contributed in further structuring the agenda and defining the areas for which the development of some guidance is anticipated.

13. Any other business

Next meeting on: 09-12 April 2018

14. Annex I – Signals assessment and prioritisation⁴⁴

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 timetables⁴⁵.

14.1.1. Clopidogrel – CLOPIDOGREL APOTEX (CAP), CLOPIDOGREL BGR (CAP), CLOPIDOGREL HCS (CAP), CLOPIDOGREL KRKA (CAP), CLOPIDOGREL KRKA D.D. (CAP), CLOPIDOGREL MYLAN (CAP), CLOPIDOGREL RATIOPHARM (CAP), CLOPIDOGREL RATIOPHARM GMBH (CAP), CLOPIDOGREL TAD (CAP), CLOPIDOGREL TEVA (CAP), CLOPIDOGREL ZENTIVA (CAP), GREPID (CAP), ISCOVER (CAP), PLAVIX (CAP), ZYLLT (CAP); NAP Clopidogrel, acetylsalicylic acid - CLOPIDOGREL/ACETYLSALICYLIC ACID ZENTIVA (CAP), DUOPLAVIN (CAP); NAP

Applicant(s): Apotex Europe BV (Clopidogrel Apotex), Archie Samuel s.r.o. (Clopidogrel ratiopharm GmbH), HCS bvba (Clopidogrel HCS), Laboratoires Biogaran (Clopidogrel BGR), Krka, d.d. (Clopidogrel Krka, Clopidogrel Krka d.d., Zyllt), Mylan S.A.S. (Clopidogrel Mylan), Pharmathen S.A. (Grepid), Sanofi-aventis groupe (Clopidogrel Zentiva, Clopidogrel/Acetylsalicylic acid Zentiva), Sanofi Clir SNC (Duoplavin, Plavix), TAD Pharma GmbH (Clopidogrel TAD), Teva B.V. (Clopidogrel ratiopharm, Clopidogrel Teva), various

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of insulin autoimmune syndrome

EPITT 19155 – New signal

Lead Member State: PT

14.1.2. Pembrolizumab – KEYTRUDA (CAP)

Applicant(s): Merck Sharp & Dohme

PRAC Rapporteur: Sabine Straus

Scope: Signal of cholangitis sclerosing

EPITT 19154 – New signal

Lead Member State: NL

⁴⁴ 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

⁴⁵ 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

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.2. 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 Q1 2013 to Q1 2018, 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. Anidulafungin - ECALTA (CAP) - EMEA/H/C/000788/II/0036

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Updated RMP (version 12.1) in order to include new safety information: an update of incidence and prevalence of hepatotoxicity categorised as an important identified risk and a re-categorisation of convulsions from an important potential risk to important identified risk based on ongoing study A8851008: a prospective, open-label study to assess the pharmacokinetics, safety and efficacy of anidulafungin when used to treat children with invasive candidiasis, including candidemia, PASS A8851030: a retrospective

cohort study of the risk of severe hepatic injury in hospitalised patients treated with echinocandins for candida infections, the 'global antifungal surveillance programme' and the MAH's review and analysis of cumulative exposure data up to the data lock point (DLP) of 31 August 2017

15.2.3. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0018

Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: Updated RMP (version 10.0) in order to introduce changes in the pharmacovigilance activities related to the use of apremilast in pregnancy and to remove 'use in patients of different racial origin' from the safety concerns

15.2.4. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/II/0036

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Julie Williams

Scope: Updated RMP (version 16) to include the new population (children from the age of 2 months) as approved in variation II/22. In addition, to amend the statement concerning additional monitoring following renewal procedure in which the black triangle symbol was removed from the product information. Furthermore, the updated RMP includes a re-categorisation of the following important identified risk as not important: hypersensitivity/anaphylaxis and *C. difficile*-associated diarrhea

15.2.5. Cetorelix - 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

15.2.6. Darunavir - PREZISTA (CAP) - EMEA/H/C/000707/WS1355/0094; Darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/WS1355/0024

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Amelia Cupelli

Scope: Updated RMP (version 25.4 for Prezista, version 4.4 for Rezolsta) in order to amend the due date for the final report for study GS-US-216-0128: 'a phase 2/3, multicentre, multicohort, two-part study evaluating pharmacokinetics (PK), safety, and efficacy of cobicistat-boosted atazanavir (ATV/co) or cobicistat-boosted darunavir (DRV/co), administered with background regimen (BR) in human immunodeficiency virus-1 (HIV-1) infected, treatment-experienced, virologically suppressed paediatric subjects' from Q1 2022 to Q1 2024

15.2.7. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0040/G, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of an updated RMP (version 9.1) in order to: 1) include a feasibility assessment of experiments and/or studies to further understand the effect of ibrutinib on various components and functions of the adaptive and humoral immune system; 2) include the completed non-clinical in vitro rabbit ventricular and atrial wedge study (under review in procedure IB/0039) in the table of completed studies in the RMP annex; 3) include a targeted follow-up questionnaire for cardiac arrhythmias as part of routine pharmacovigilance activities; 4) update the text for clarification purposes, to modify the important potential risk of 'infections (excluding progressive multifocal leukoencephalopathy (PML))' to 'infections (including viral reactivation)' (PML is already listed as a separate important potential risk); 5) replace the three post-authorisation measures (PAMs) for study PCYC-1103-CA: 'a long term safety study of Bruton's tyrosine kinase (Btk) inhibitor ibrutinib in B cell lymphoma and chronic lymphocytic leukaemia', study PCI32765CAN3001: 'a phase 3b, multicentre, open-label, ibrutinib long term extension study' and study PCYC-1116-CA: 'an open label extension study in patients 65 years or older with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) who participated in study PCYC-1115-CA (ibrutinib version chlorambucil)', all related to long-term safety (> 2 years) of ibrutinib, with a single long-term safety PAM for study 3038-1: a long term study to characterize the safety of long term exposure to ibrutinib based on data and pooled analyses from trials of patients with mantle cell lymphoma and CLL

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include children aged one month and older to the authorised population for the treatment of adults with Philadelphia chromosome-negative

relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to include the new population, update the posology and the safety information. The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.2. 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. Brivaracetam - BRIVIACT (CAP) - EMEA/H/C/003898/II/0010/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped application consisting of: 1) extension of indication to include adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy 4 years of age and older. As a consequence, sections 4.1, 4.2, 4.7, 5.1 and 5.2 of the SmPC are updated; 2) submission of a 5mL oral syringe and adaptor for the paediatric population. The package leaflet, labelling and the RMP (version 6.1) are updated accordingly. The submission also includes a final environmental risk assessment (ERA) for the inclusion of the paediatric population in accordance with the new proposed indication

15.3.4. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0003

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include to treatment of advanced renal cell carcinoma the 'treatment-naïve adults with intermediate or poor risk per International Metastatic Renal Carcinoma Database (IMDC) criteria'. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add a warning on dose reductions and dose interruptions and to update the safety information. The final report of study A031203: a randomized phase 2 study comparing cabozantinib with commercially supplied sunitinib in patients with previously untreated locally advanced or metastatic renal cell carcinoma is submitted in support of this application. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes in the product information

15.3.5. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0065

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of plaque psoriasis in adult patients. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 13) are updated accordingly

15.3.6. [Daratumumab - DARZALEX \(CAP\) - EMEA/H/C/004077/II/0011, Orphan](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include the combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.1) are updated accordingly. In addition, the MAH took the opportunity to update the contact details of the Lithuanian and Slovenian local representatives in the package leaflet

15.3.7. [Darunavir - PREZISTA \(CAP\) - EMEA/H/C/000707/WS1312/0093;](#) [Darunavir, cobicistat - REZOLSTA \(CAP\) - EMEA/H/C/002819/WS1312/0023;](#) [Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA \(CAP\) - EMEA/H/C/004391/WS1312/0005](#)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4, 4.6, 5.1 and 5.2 of the SmPCs for Prezista, Rezolsta and Symtuza to reflect the data of study TMC114HIV3015 (listed as a category 3 study in the RMP): a single arm, open label study to assess the pharmacokinetics of darunavir and ritonavir, darunavir and cobicistat, etravirine, and rilpivirine in human immunodeficiency virus-1 (HIV-1) infected pregnant women. The package leaflet of Symtuza and the RMPs (version 25.3 for Prezista, version 4.3 for Rezolsta and version 2.1 for Symtuza) are updated accordingly. In addition, the MAH took the opportunity to implement RMP template (version 2) for the Prezista and Rezolsta RMPs, the removal of the fulfilled category 4 data collection on adverse events of anti-HIV drugs (D:A:D) study from the Prezista and Rezolsta RMPs, removal of observational study on growth in children and 'growth abnormalities in the paediatric population' as an important potential risk in the Prezista RMP as well as the addition of the missing information 'safety in patients with cardiac conduction disorders' in the Rezolsta RMP (alignment with Tybost (cobicistat) RMP)

15.3.8. [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 consisting of: 1) submission of 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 RMPs for Prezista (darunavir) and Rezolsta (darunavir/cobicistat)

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

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.10. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/II/0005/G

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) submission of the final report from study ELX-PH-08 (listed as a category 3 study in the RMP). This is an in vitro evaluation study aimed to investigate the effects on treating primary cultures of cryopreserved human hepatocytes with eluxadoline on the expression of cytochrome P450 (CYP) enzymes; 2) submission of the final report from study 3030-102-002 (listed as a category 3 study in the RMP). This is a randomised, open label study aimed to evaluate the effect of eluxadoline as a potential time dependent inhibitor of CYP3A4⁴⁶ with the substrate midazolam. The RMP (version 2.0) is updated to refine the important identified risk of 'sphincter of Oddi (SO) spasm' to 'SO spasm (sphincter of Oddi dysfunction, SOD)' and to include pancreatitis as an important identified risk as agreed in the conclusions of PSUSA/00010528/201703 finalised at PRAC/CHMP in October 2017

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

Applicant: Techdow Europe AB

PRAC Rapporteur: Menno van der Elst

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

⁴⁶ Cytochrome P 450 3A4

15.3.12. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/X/0044/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped application consisting of: 1) extension application to introduce a new strength of hard capsules (0.25 mg) to the currently approved presentations of Gilenya; 2) extension of indication to add a new indication for the treatment of paediatric patients of 10 years of age and above with relapsing multiple sclerosis (RMS). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3, 6 and 8 of the SmPC are updated. The package leaflet, labelling and the RMP (version 13.0) are updated accordingly. In addition, Annex II is updated to be brought in line with the latest QRD template (version 10)

15.3.13. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/II/0047

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final clinical study report (CSR) for study D2399 (listed as a category 3 study in the RMP): a single arm, open-label, multicentre study evaluating the long-term safety and tolerability study of fingolimod 0.5 mg/day administered orally once daily in approximately 5,000 patients with relapsing multiple sclerosis. The RMP (version 14.0) is updated accordingly

15.3.14. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0085

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of study EPI-HPV-069: a meta-analysis assessing the risk of three autoimmune diseases following vaccination with Cervarix: autoimmune thyroiditis (AIT), Guillain-Barre syndrome (GBS) and inflammatory bowel disease (IBD). The RMP (version 18) is updated accordingly and includes minor updates related to other studies

15.3.15. 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 CYP3A4⁴⁷ 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

⁴⁷ Cytochrome P450 3A4

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

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.17. Levetiracetam - KEPRA (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

15.3.18. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/II/0016

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study NN8022-4192 (listed as a category 3 study in the RMP). This is a randomised, placebo-controlled trial on subjects with obesity or overweight who were otherwise healthy, to compare the effect of liraglutide 3.0 mg with placebo on postprandial gallbladder dynamics after 12 weeks of treatment. This variation fulfils post-authorisation measure MEA 009.2. The RMP (version 29) is updated accordingly

15.3.19. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0013/G

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of extension of indication to include children and adolescents aged 6 to 17 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC and sections 1, 2, 3, 4 and information for healthcare professionals in the package leaflet are updated accordingly. In addition to the proposed SmPC/package leaflet updates

specific to the paediatric indication, the MAH proposed to include some wording to ensure the name and batch number of the administered product should be clearly recorded in the patient file. The RMP (version 3) is updated accordingly; as well as quality variations

15.3.20. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/II/0002, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.5 and 5.2 of the SmPC in order to reflect the results from study R1600721: 'assessment of PKC412 (midostaurin) and its metabolites (CGP052421 and CGP062221) as inhibitors of human bile salt export pump (BSEP)' and study R1701192: 'in vitro assessment of cytochrome P450 3A4 and 3A5 enzyme inhibition by PKC412, CGP52421 and CGP62221', in fulfilment of the post-authorisation measures MEA 011 and REC 014. In addition, the MAH took the opportunity to update section 5.2 of the SmPC to correct figures as per study A2107 (amendment 02), an open label study on absorption, distribution, metabolism and excretion (ADME) already assessed and to make editorial changes in the SmPC. The RMP (version 2.0) is updated accordingly. In addition, the search criteria for the important identified risk pulmonary toxicity (including pleural effusion and interstitial lung disease) was updated to include the MedDRA PT⁴⁸ 'pleural effusion'

15.3.21. 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 4, 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

15.3.22. Nitric oxide - INOMAX (CAP) - EMEA/H/C/000337/II/0051

Applicant: Linde Healthcare AB

PRAC Rapporteur: Julie Williams

Scope: Quality variation to introduce an additional container closure system. The RMP (version 6.0) is updated to reflect post-authorisation experience with the new cylinder closure system

⁴⁸ Medical dictionary for regulatory activities – Preferred term

15.3.23. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/II/0047](#)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on the nivolumab use in patients who have previously undergone allogeneic hematopoietic stem cell transplantation (HSCT) and the increased risk of rapid onset and severe graft versus host disease (GVHD) based on evidence from spontaneous case reports, literature case reports, and from 2 multicentre case series. Annex II.D and the package leaflet are updated accordingly. The RMP (version 7.8) is also updated to include the 'risk of GVHD with nivolumab after allogeneic HSCT' as an important potential risk based on the RMP template (revision 2). In addition, the MAH took the opportunity to make some minor editorial corrections to the product information

15.3.24. [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

15.3.25. [Rituximab - BLITZIMA \(CAP\) - EMEA/H/C/004723/WS1333/0007; RITEMVIA \(CAP\) - EMEA/H/C/004725/WS1333/0007; RITUZENA \(CAP\) - EMEA/H/C/004724/WS1333/0008; TRUXIMA \(CAP\) - EMEA/H/C/004112/WS1333/0008](#)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Doris Stenver

Scope: Submission of the clinical study report (CSR) of final results (up to 76 weeks) of study CT-P10 3.2: 'a randomised, controlled, double-blind, parallel-group, phase 3 study to compare the pharmacokinetics, efficacy, and safety between CT-P10 (rituximab), Rituxan and MabThera in patients with rheumatoid arthritis'. In addition, results up to week 24 of study CT-P10 3.3: 'a phase 3, randomised, parallel-group, active-controlled, double-blind study to demonstrate equivalence of pharmacokinetics and non-inferiority of efficacy for CT-P10 (rituximab) in comparison with Rituxan each administered in combination with cyclophosphamide, vincristine, and prednisone (CVP) in patients with advanced follicular lymphoma' are updated in this variation. The RMP (version 9.0) is updated accordingly

15.3.26. [Trastuzumab - HERCEPTIN \(CAP\) - EMEA/H/C/000278/II/0140](#)

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC for Herceptin 150mg powder for concentrate for solution for infusion and sections 4.4, 4.8 and 5.1 of the SmPC for Herceptin 600mg solution for injection in vial, in order to update the safety information based on the final results from study BO22227 (Hannah) (listed as a category 3 study in the RMP): a phase 3, randomised, open-label study to compare pharmacokinetics, efficacy and safety of subcutaneous (SC) Herceptin with intravenous (IV) Herceptin administered in women with HER2 positive early breast cancer (EBC). The RMP (version 19.0) is updated accordingly

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

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

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

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

16.1.1. Aflibercept⁴⁹ - ZALTRAP (CAP) - PSUSA/00010019/201708

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.2. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (Δ LNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS (CAP) - PSUSA/00010530/201708 (with RMP)

Applicant: MolMed SpA, ATMP⁵⁰

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.3. Asenapine - SYCREST (CAP) - PSUSA/00000256/201708

Applicant: N.V. Organon

⁴⁹ Oncological indication(s) only

⁵⁰ Advanced therapy medicinal product

PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.4. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/201708

Applicant: Eli Lilly Nederland B.V.
PRAC Rapporteur: Patrick Batty
Scope: Evaluation of a PSUSA procedure

16.1.5. Brimonidine⁵¹ - MIRVASO (CAP) - PSUSA/00010093/201708

Applicant: Galderma International
PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.6. Caffeine⁵² - PEYONA (CAP) - PSUSA/00010615/201707

Applicant: Chiesi Farmaceutici S.p.A.
PRAC Rapporteur: Daniela Philadelphy
Scope: Evaluation of a PSUSA procedure

16.1.7. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/201708

Applicant: Pfizer Ireland Pharmaceuticals
PRAC Rapporteur: Jolanta Gulbinovic
Scope: Evaluation of a PSUSA procedure

16.1.8. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/201708

Applicant: Actelion Registration Limited
PRAC Rapporteur: Ghania Chamouni
Scope: Evaluation of a PSUSA procedure

16.1.9. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/201708

Applicant: Roche Registration Limited
PRAC Rapporteur: Sabine Straus
Scope: Evaluation of a PSUSA procedure

⁵¹ Centrally authorised product(s) only

⁵² Indicated in premature apnoea of premature newborns, centrally authorised product(s) only

16.1.10. Copper (⁶⁴Cu) chloride - CUPRYMINA (CAP) - PSUSA/00010040/201708

Applicant: Sparkle S.r.l.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.11. Corifollitropin alfa - ELONVA (CAP) - PSUSA/00000875/201707

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.12. Crizotinib - XALKORI (CAP) - PSUSA/00010042/201708

Applicant: Pfizer Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.13. Dabrafenib - TAFINLAR (CAP) - PSUSA/00010084/201708

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.14. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) - VAXELIS (CAP) - PSUSA/00010469/201708

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.15. Eliglustat - CERDELGA (CAP) - PSUSA/00010351/201708

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.16. Emtricitabine, rilpivirine, tenofovir disoproxil - EVIPLERA (CAP) - PSUSA/00009142/201708

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.17. **Enzalutamide - XTANDI (CAP) - PSUSA/00010095/201708**

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.18. **Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/201708**

Applicant: Chiesi Farmaceutici S.p.A., ATMP⁵³

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.19. **Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/201708**

Applicant: Shield TX (UK) Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.20. **Fluticasone, salmeterol⁵⁴ - AERIVIO SPIROMAX (CAP), AIREXAR SPIROMAX (CAP) - PSUSA/00010531/201708**

Applicant: Teva B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.21. **Human alpha₁-proteinase inhibitor⁵⁵ - RESPREEZA (CAP) - PSUSA/00010410/201708**

Applicant: CSL Behring GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.22. **Human coagulation factor VIII, human von Willebrand factor⁵⁶ - VONCENTO (CAP) - PSUSA/00010102/201708**

Applicant: CSL Behring GmbH

⁵³ Advanced therapy medicinal product

⁵⁴ Centrally authorised product(s) only

⁵⁵ Centrally authorised product(s) only

⁵⁶ Centrally authorised product(s) only

PRAC Rapporteur: Sabine Straus
Scope: Evaluation of a PSUSA procedure

16.1.23. Ioflupane (¹²³I) - DATSCAN (CAP) - PSUSA/00001767/201707

Applicant: GE Healthcare Ltd
PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.24. Lenvatinib - KISPLYX (CAP), LENVIMA (CAP) - PSUSA/00010380/201708

Applicant: Eisai Europe Ltd.
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

16.1.25. Linaclotide - CONSTELLA (CAP) - PSUSA/00010025/201708 (with RMP)

Applicant: Allergan Pharmaceuticals International Limited
PRAC Rapporteur: Valerie Strassmann
Scope: Evaluation of a PSUSA procedure

16.1.26. Loxapine⁵⁷ - ADASUVE (CAP) - PSUSA/00010113/201708

Applicant: Ferrer Internacional s.a.
PRAC Rapporteur: Sabine Straus
Scope: Evaluation of a PSUSA procedure

16.1.27. Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - PSUSA/00002017/201707

Applicant: Roche Registration Limited
PRAC Rapporteur: Eva Segovia
Scope: Evaluation of a PSUSA procedure

16.1.28. Nonacog alfa - BENEFIX (CAP) - PSUSA/00002183/201708

Applicant: Pfizer Limited
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

⁵⁷ Pre-dispensed inhalation powder only

16.1.29. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/201708

Applicant: Novartis Europharm Limited
PRAC Rapporteur: Patrick Batty
Scope: Evaluation of a PSUSA procedure

16.1.30. Pyronaridine, artesunate - PYRAMAX (Art 58⁵⁸) - EMEA/H/W/002319/PSUV/0017

Applicant: Shin Poong Pharmaceutical Co., Ltd.
PRAC Rapporteur: Caroline Laborde
Scope: Evaluation of a PSUR procedure

16.1.31. Reslizumab - CINQAERO (CAP) - PSUSA/00010523/201708

Applicant: Teva Pharmaceuticals Limited
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

16.1.32. Safinamide - XADAGO (CAP) - PSUSA/00010356/201708

Applicant: Zambon S.p.A.
PRAC Rapporteur: Almath Spooner
Scope: Evaluation of a PSUSA procedure

16.1.33. Saxagliptin - ONGLYZA (CAP) - PSUSA/00002685/201707

Applicant: AstraZeneca AB
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

16.1.34. Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/201708

Applicant: Alexion Europe SAS
PRAC Rapporteur: Qun-Ying Yue
Scope: Evaluation of a PSUSA procedure

16.1.35. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/201708

Applicant: Shire Pharmaceuticals Ireland Limited

⁵⁸ 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: Doris Stenver
Scope: Evaluation of a PSUSA procedure

16.1.36. Vemurafenib - ZELBORAF (CAP) - PSUSA/00009329/201708

Applicant: Roche Registration Limited
PRAC Rapporteur: Ulla Wändel Liminga
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. Catridecacog - NOVOTHIRTEEN (CAP); NAP - PSUSA/00010034/201707

Applicants: Novo Nordisk A/S (NovoThirteen), various
PRAC Rapporteur: Ghania Chamouni
Scope: Evaluation of a PSUSA procedure

16.2.2. Ribavirin⁵⁹ - REBETOL (CAP); NAP - PSUSA/00010007/201707

Applicants: Merck Sharp & Dohme Limited (Rebetol), various
PRAC Rapporteur: Caroline Laborde
Scope: Evaluation of a PSUSA procedure

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

16.3.1. Almotriptan (NAP) - PSUSA/00000101/201706

Applicant(s): various
PRAC Lead: Dolores Montero Corominas
Scope: Evaluation of a PSUSA procedure

16.3.2. Amorolfine (NAP) - PSUSA/00000185/201706

Applicant(s): various
PRAC Lead: Julia Pallos
Scope: Evaluation of a PSUSA procedure

⁵⁹ Oral formulations only

16.3.3. Caffeine⁶⁰ (NAP) - PSUSA/00000482/201707

Applicant(s): various

PRAC Lead: Daniela Philadelphy

Scope: Evaluation of a PSUSA procedure

16.3.4. Ceftibuten (NAP) - PSUSA/00000611/201707

Applicant(s): various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

16.3.5. Demeclocycline, triamcinolone (NAP) - PSUSA/00010415/201707

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.6. Enalapril, hydrochlorothiazide (NAP) - PSUSA/00001212/201707

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.7. Epirubicin (NAP) - PSUSA/00001234/201706

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.8. Fluticasone propionate, formoterol fumarate dihydrate (NAP) - PSUSA/00010339/201707

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.9. Human coagulation factor XIII (NAP) - PSUSA/00001622/201706

Applicant(s): various

⁶⁰ Indicated in apnoea, non-centrally authorised product(s) only

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.10. Hydrochlorothiazide, moexipril (NAP) - PSUSA/00002082/201706

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.3.11. Ketorolac⁶¹ (NAP) - PSUSA/00001810/201707

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.12. Ketorolac⁶² (NAP) - PSUSA/00001811/201707

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.13. Ketotifen⁶³ (NAP) - PSUSA/00001812/201706

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.14. Landiolol (NAP) - PSUSA/00010570/201708

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.15. Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide (NAP) - PSUSA/00010390/201707

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

⁶¹ Ophthalmic formulations only

⁶² Systemic formulations only

⁶³ Ophthalmic formulations only

16.3.16. Magnesium sulfate, sodium sulfate, potassium sulfate (NAP) - PSUSA/00010239/201708

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.17. Octreotide (NAP) - PSUSA/00002201/201706

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.3.18. Triamcinolone⁶⁴ (NAP) - PSUSA/00003017/201707

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.19. Triamcinolone⁶⁵ (NAP) - PSUSA/00003017/201707

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.20. Trimetazidine (NAP) - PSUSA/00003043/201708

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.3.21. Typhoid vaccine (live, attenuated) (NAP) - PSUSA/00003067/201707

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

⁶⁴ Topical and nasal formulations only

⁶⁵ Topical and nasal formulations only

16.4. Follow-up to PSUR procedures

16.4.1. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/LEG 035

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Review of cases of T cell-lymphoma reported in the post marketing setting including a discussion on the potential dechallenge effect, as requested in the conclusions of PSUSA/00001393/201702 adopted by PRAC at its October 2017 meeting

16.4.2. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/LEG 036

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Review of cases of tumefactive lesions reported in the literature and in post marketing setting, as requested in the conclusions of PSUSA/00001393/201702 adopted by PRAC at its October 2017 meeting

16.4.3. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/LEG 004

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Analysis of all available data relating to myocardial infarction, including a review of all post-marketing cases, as requested in the conclusions of PSUSA/00010319/201704 adopted by PRAC at its November 2017 meeting

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁶⁶

17.1.1. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/PSA/S/0026

Applicant: Shire Pharmaceuticals

PRAC Rapporteur: Almath Spooner

Scope: Amended PASS protocol for registry PARADIGM on subjects with chronic hypoparathyroidism to explore physicians advancing disease knowledge in

⁶⁶ In accordance with Article 107n of Directive 2001/83/EC

hypoparathyroidism including an amended statistical analysis plan (SAP), to the protocol previously agreed at the December 2017 PRAC meeting (PSP/S/0058.1)

17.1.2. Telavancin - VIBATIV (CAP) - EMEA/H/C/PSA/S/0027

Applicant: Theravance Biopharma Ireland Ltd

PRAC Rapporteur: Julie Williams

Scope: Amended protocol (version 4.0) for a non-interventional imposed PASS: a multicentre, multinational, post-marketing, retrospective chart review on the use of intravenous Vibativ (telavancin) in clinical settings to the protocol previously agreed in June 2014 (MEA 006.3); including a request to extend the submission of the final results and/or a PASS study review to 31 December 2020 due to the extremely low usage of the product and difficulties in patient enrolment

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁷

17.2.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 008.3

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 008.2 [assessment of a protocol for a retrospective, observational new user cohort study, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with medicines containing sodium-glucose co-transporter-2 (SGLT2) inhibitors or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

17.2.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 007.3

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.2 [assessment of a protocol for a retrospective, observational new user cohort study, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with medicines containing sodium-glucose co-transporter-2 (SGLT2) inhibitors or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

17.2.3. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/MEA 002.3

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

⁶⁷ 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

Scope: MAH's response to MEA 002.2 [PASS protocol for a multiple sclerosis (MS) pregnancy exposure registry study 109MS402 (listed as a category 3 in the RMP) aiming at evaluating prospectively pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product] as per the request for supplementary information (RSI) adopted the November 2017 PRAC meeting

17.2.4. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001

Applicant: Almirall S.A

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study M-41008-40: a PASS in European psoriasis registries (listed as a category 3 in the RMP) to evaluate the long-term safety of Skilarence (dimethyl fumarate) used for the treatment of patients with moderate to severe psoriasis [future due date(s): end of data collection: Q1 2027; study report: within a year of availability of the final data set] (from initial MAA/opinion)

17.2.5. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 002

Applicant: Almirall S.A

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study M-41008-44: a PASS retrospective chart review to assess the effectiveness of Skilarence (dimethyl fumarate) risk minimisation activities in daily practice (from initial MAA/opinion)

17.2.6. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/MEA 006.3

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised protocol for drug utilisation study (DUS) ELIGL C06912 conducted in the US population using the MarketScan database to assess adherence to the labelling with regard to drug-drug interactions (DDI) and to genotyping assessment prior to the initiation of eliglustat therapy. The aim of the protocol revision is to propose a new additional database: the 'International Collaborative Gaucher Group' (ICGG) Gaucher registry database to achieve the first study objective 'to estimate the proportion of patients in the U.S. who have been genotyped for CYP2D6⁶⁸ prior to the initiation of eliglustat therapy'

17.2.7. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 045.4

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 045.2 [PASS protocol for study GS-EU-276-4027, a drug

⁶⁸ Cytochrome P450 2D6

utilisation study (DUS) to characterize: 1) prescribers' level of knowledge about the key risks of Truvada for a pre-exposure prophylaxis (PrEP) indication and assess the effectiveness of risk minimisation measures; 2) prescribing practices in routine clinical practice of Truvada for PrEP by describing the demographics of human immunodeficiency virus 1 (HIV-1) uninfected individuals who were prescribed Truvada for PrEP, and the prescribed dosing schedule for Truvada for PrEP as reported by the prescriber, as a result of variation II/126 finalised at CHMP/PRAC in July 2016 to extend the indication to PrEP] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

17.2.8. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.4

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second progress report for study MRK-2859: ulcerative colitis (UC) Nordic registry: a non-interventional observational longitudinal PASS of Simponi (golimumab) in the treatment of UC using Nordic national health registries, including the MAH's response to MEA 026.3 [first progress report for study MRK-2859] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

17.2.9. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 002.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 002 [protocol for a study/survey (listed as a category 3 study in the RMP): a cross-sectional multinational, multichannel survey conducted among healthcare professionals and patients to measure the effectiveness of Suliqua (insulin glargine/lixisenatide) educational materials set up to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

17.2.10. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 001.5

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Updated protocol for study 178-CL-114 (version 10.0): a long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (individual and composite outcomes) in patients administered mirabegron, following FDA's request for supplementary information

17.2.11. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: PASS protocol for a safety surveillance programme using existing EU rheumatoid arthritis (RA) registries conducted in four countries: Germany (German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (OBS15180)), Spain (Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER) (6R88-RA-1720)), Sweden (Register for Antirheumatic Therapies in Sweden (ARTIS) (OBS15220)) and UK (British Society for Rheumatology Biologicals Register (BSRBR) (6R88-RA-1634)) (from initial MAA/opinion)

17.3. Results of PASS imposed in the marketing authorisation(s)⁶⁹

17.3.1. Domperidone (NAP) - EMEA/H/N/PSR/J/0010

Applicant: Janssen Pharmaceutical

PRAC Rapporteur: Caroline Laborde

Scope: Results for a PASS assessing the effectiveness of the risk minimisation measures of domperidone to characterise prescribers' knowledge, understanding and extent of awareness regarding new safety information for domperidone following the change in SmPC and the distribution of a direct healthcare professional communication (DHPC), as imposed in the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2013, as per the request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

17.3.2. Domperidone (NAP) - EMEA/H/N/PSR/J/0015

Applicant: Janssen Pharmaceutical

PRAC Rapporteur: Caroline Laborde

Scope: Results of a drug utilisation study (DUS) of domperidone in Europe using databases to investigate the effectiveness of risk minimisation measures and to describe the prescribing patterns before and after the changes to the domperidone label in routine clinical practice in selected European countries, as required in the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2013

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁷⁰

17.4.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0173

Applicant: AbbVie Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study BSRBR-RA (British Society for Rheumatology Biologics Registers Rheumatoid Arthritis): a registry in the UK, evaluating

⁶⁹ In accordance with Article 107p-q of Directive 2001/83/EC

⁷⁰ 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

the influence of tumour necrosis factor (TNF) inhibitor treatment on cancer incidence in rheumatoid arthritis (RA) patients with a history of malignancy. No changes to the product information are proposed

17.4.2. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/II/0037

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of the final report from PASS CLE-20098-094 study on agomelatine and the risk of hospitalisation for acute liver injury. This is a large, multinational, retrospective longitudinal cohort and nested case-control study to compare the risk of acute liver injury (ALI) in patients initiating treatment with agomelatine and other antidepressants with the risk in patients initiating treatment with citalopram

17.4.3. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/II/0038

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: Submission of the final report from PASS CLE-20098-094 study of agomelatine and the risk of hospitalisation for acute liver injury. This is a large, multinational, retrospective longitudinal cohort and nested case-control study to compare the risk of acute liver injury (ALI) in patients initiating treatment with agomelatine and other antidepressants with the risk in patients initiating treatment with citalopram

17.4.4. 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

17.4.5. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/WS1326/0145; Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/WS1326/0184

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Caroline Laborde

Scope: Submission of the final report from study GS-EU-104-0433 (listed as a category 3 study in the RMP). This is an observational, drug utilisation study (DUS) of Viread in children and adolescents with human immunodeficiency virus-1 (HIV-1) infection, in fulfilment of a post-authorisation measure (PAM) for Viread (MEA 46) and Truvada (MEA 276)

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. 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

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation⁷¹

17.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 053.5

Applicant: Genzyme Europe BV

PRAC Rapporteur: Caroline Laborde

Scope: Second interim study report for PASS study ALGMYC07390 evaluating the

⁷¹ In line with the revised variations regulation for any submission before 4 August 2013

prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions, including MAH's response to MEA 053.4 on first interim report as per the request for supplementary information adopted in July 2017 [final clinical study report (CSR): due 31 August 2019]

17.5.2. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.9

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Fourth annual interim report for study C1CL670E2422: an observational, multicentre study to evaluate the safety of deferasirox in the treatment of paediatric non-transfusion dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate

17.5.3. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/MEA 006.2

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Second interim report for drug utilisation study (DUS) ELIGL C06912 conducted in the US population using the MarketScan database to assess adherence to the labelling with regard to drug-drug interactions (DDI) and to genotyping assessment prior to the initiation of eliglustat therapy

17.5.4. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 005

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: First interim report for an enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMEA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR): Q4/2021]

17.5.5. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 005

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: First interim report for an enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMEA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR): Q4/2021]

17.5.6. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 002

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: First interim report for an enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMEA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR): Q4/2021]

17.5.7. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 045.3

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Enrolment progress report for study GS-EU-276-4027: a cross-sectional PASS to assess healthcare provider's level of awareness of risk minimisation materials for Truvada (emtricitabine/tenofovir disoproxil) for pre-exposure prophylaxis (PrEP) in the European Union

17.5.8. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.7

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 002.6 [second interim study report for a US category 3, non-interventional PASS (B2311060 study): active surveillance of conjugated oestrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data] as per the request for supplementary information (RSI) adopted in November 2017

17.5.9. Florbetaben (¹⁸F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 005.1

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 005 [interim results for PASS study FBB-01_02_13: a prospective observational study to assess the effectiveness of the training and risk minimisation measures recommended for the usage of the diagnostic agent Neuraceq in post-authorisation clinical settings [final clinical study report (CSR): Q1/2019]] as per the request for supplementary information (RSI) adopted at the October 2017 PRAC meeting

17.5.10. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 027.5

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual progress report of the ENEIDA registry (study MK-8259-042): a long-term, non-interventional observational study of patients with inflammatory bowel disease (IBD) in Spain to evaluate whether the use of golimumab is associated with a risk of colectomy for intractable disease, advanced neoplasia (colorectal cancer or high grade dysplasia), and hepatosplenic T-cell lymphoma (HSTCL) in patients with ulcerative colitis (UC) as compared with alternative therapies for similar severity of disease

17.5.11. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/LEG 188.5

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Annual report for 2017 on a review of second primary malignancies (SPM), including a data analysis plan, in order to compare incidence rates of SPM among patients treated with Glivec (imatinib) with expected incidence based on the rates among the general population

17.5.12. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/ANX 191.6

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Fourth progress report for study CSTI571I2201: a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Philadelphia positive (Ph+) acute lymphoblastic leukaemia (ALL) patients treated with chemotherapy + imatinib ± haematopoietic stem cell treatment (±HSCT)

17.5.13. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 133.12

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Tenth annual paediatric inflammatory bowel disease (IBD) registry (DEVELOP) report on long-term safety and efficacy of infliximab and other therapies, safety and efficacy of variable infliximab dosing intervals, episodic therapy, monotherapy (initiated de novo or following discontinuation of concomitant immunomodulators), combined infliximab and immunomodulator therapy (azathioprine/6-mercaptopurine (AZA/6-MP) or methotrexate (MTX))

17.5.14. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 005

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Julie Williams

Scope: First annual progress report for a patient registry of lixisenatide use in adult patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and

databases in Italy and Belgium [due date: final report due in December 2020] (from initial MAA/opinion)

17.5.15. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 013.4

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Annual interim results for study GS-EU-337-1820: a prospective observational drug utilisation study (DUS) of ledipasvir/sofosbuvir (LDV/SOF) in adults with hepatitis C virus/human immunodeficiency virus (HCV/HIV) coinfection [final clinical study report (CSR): Q3/Q4 2019]

17.5.16. Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/MEA 008.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: First annual progress report for a patient registry of lixisenatide use in adult patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and databases in Italy and Belgium

17.5.17. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/001252/ANX 002.10

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Eighth interim report of the observational safety study on Bronchitol (inhaled mannitol) using the UK cystic fibrosis (CF) Trust registry aiming at comparing the rate of identified and potential risks for Bronchitol in patients with CF between Bronchitol-exposed patients vs. an unexposed patient group matched (via propensity score modelling) for age, disease severity, concomitant medications and presence of chronic *Pseudomonas*

17.5.18. Nalmefene - SELINCRO (CAP) - EMEA/H/C/002583/MEA 001.3

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Interim baseline study report for PASS 14910A (EUPAS5678): a non-interventional multi-country prospective cohort study investigating patterns of use of Selincro (nalmefene) and frequency of adverse drug reactions in routine clinical practice

17.5.19. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 002.3

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Study progress report (EVM-17123, November 2017, version 2.0) for PASS D3820R00006 (previously D2288R00081): a post-marketing observational drug utilisation study (DUS) of Moventig (naloxegol) conducted in selected European populations in order to describe demographic, clinical, and treatment characteristics in the baseline of patients treated with naloxegol as well as to describe treatment pattern characteristics of naloxegol utilisation at initiation and follow-up (from initial MAA/opinion)

17.5.20. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/LEG 087.5

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Fifth annual review on pregnancy cases, including cumulative data up to September 2017

17.5.21. Perampanel - FYCOMPA (CAP) - EMEA/H/C/002434/MEA 004.7

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Complementary data to the 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

17.5.22. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/ANX 033.2

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Second interim report on drug utilisation studies evaluating rivaroxaban use and potential adverse outcomes, namely study 16159 (EUPAS11145) – namely study 16159 (EUPAS11145) in routine clinical practice in Germany; study 16646 (EUPAS11141) in routine clinical practice in the Netherlands; study 16647 (EUPAS11299) in routine clinical practice in the UK; study 17543 (EUPAS9895) in routine clinical practice in Sweden

17.5.23. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/ANX 034.1

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report on study SN 17452 (EUPAS9977): an observational post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of Xarelto (rivaroxaban) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales

17.5.24. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/ANX 043

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Interim report on a post-authorisation programme addressing the safety of rivaroxaban in the secondary prevention of acute coronary syndrome outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all population and particularly in patients at increased risk of bleeding. The report includes findings from the drug utilisation and specific outcome studies (ANX033), specialist cohort event monitoring study (ANX 034); modified prescription event monitoring study (ANX 035)

17.6. Others

17.6.1. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/MEA 024

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to SDA 043.1 [signal of incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia, EPITT 18688] to review the instructions for use (IFU) for Bydureon (exenatide) and propose improvements of the IFU as applicable, as per the request for information adopted by PRAC in July 2017

17.6.2. Exenatide - BYETTA (CAP) - EMEA/H/C/000698/MEA 044

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to to SDA 043.1 [signal of incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia, EPITT 18688] to review the instructions for use (IFU) for Byetta (exenatide) and propose improvements of the IFU as applicable, as per the request for information adopted by PRAC in July 2017

17.6.3. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/MEA 102.4

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Annual report for study NV20234: a double-blind, randomized, stratified multicentre trial evaluating conventional and double dose oseltamivir in the treatment of immunocompromised patients with influenza exploring the safety and efficacy of oseltamivir in immunocompromised patients (final clinical study report (CSR): by end of November 2018)

17.6.4. Palonosetron - PALONOSETRON ACCORD (CAP) - EMEA/H/C/004129/LEG 002.2

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Almath Spooner

Scope: MAH's response to LEG 002.1 [six-monthly cumulative review of cases of injection site reactions classified as an important potential risk (1 October 2016-31 March 2017) as requested at the time of the opinion for marketing authorisation(s) for Palonosetron Accord 250 micrograms solution for injection until further market experience is acquired] as per the request for supplementary information (RSI) adopted in September 2017

17.6.5. Padeliporfin - TOOKAD (CAP) - EMEA/H/C/004182/REC 004

Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Submission of the outcome of the requested user testing for the patient information guide for Tookad (padeliporfin)

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0025 (without RMP)

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

18.1.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0029 (without RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.1.3. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0044 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

None

18.3. Renewals of the marketing authorisation

18.3.1. Afatinib - GIOTRIF (CAP) - EMEA/H/C/002280/R/0026 (without RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

18.3.3. Alogliptin - VIPIDIA (CAP) - EMEA/H/C/002182/R/0019 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.4. Alogliptin, metformin - VIPDOMET (CAP) - EMEA/H/C/002654/R/0024 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.5. Alogliptin, pioglitazone - INCRESYNC (CAP) - EMEA/H/C/002178/R/0023 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.6. Atosiban - ATOSIBAN SUN (CAP) - EMEA/H/C/002329/R/0012 (with RMP)

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.7. Cobicistat - TYBOST (CAP) - EMEA/H/C/002572/R/0041 (with RMP)

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.8. Fenofibrate, simvastatin - CHOLIB (CAP) - EMEA/H/C/002559/R/0017 (without RMP)

Applicant: Mylan Products Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.9. Follitropin alfa - OVALEAP (CAP) - EMEA/H/C/002608/R/0023 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.10. Indacaterol, glycopyrronium - ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/R/0024 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

18.3.11. Indacaterol, glycopyrronium - XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/R/0027 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Vericel Denmark ApS, ATMP⁷²

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.13. Mercaptamine - PROCYSBI (CAP) - EMEA/H/C/002465/R/0019 (with RMP)

Applicant: Chiesi Orphan B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

18.3.14. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/R/0025 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

18.3.15. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/R/0060 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

⁷² Advanced therapy medicinal product

18.3.16. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/R/0016 (without RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

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 05-08 March 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence Defays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Jana Lukacisnova	Alternate	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
Ghania Chamouni	Member	France	No participation in discussion, final deliberations	3.2.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	(NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); piperimidic acid (NAP) - EMEA/H/A-31/1452
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
Agni Kapou	Member - via telephone*	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Melinda Palfi	Alternate - via telephone*	Hungary	No interests declared	Full involvement
Rhea Fitzgerald	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	3.2.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452 3.2.2. Radium (223Ra) dichloride - XOFIGO (CAP) - EMEA/H/A-20/1459

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				4.3.3. Hormonal contraceptives: Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel ,eth inylestradiol (NAP); dienogest, estradiol (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, nomegestrol acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				ethinylestradiol; ethinylestradiol (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP)
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Roxana Dondera	Alternate	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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 restrictions applicable to this meeting	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Olga Roegelsperger	Expert - via telephone*	Austria	No restrictions applicable to this meeting	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Jana Koprušáková	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Radim Tobolka	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Anke Blumberg	Expert - via telephone*	Germany	No interests declared	Full involvement
Nils Lilienthal	Expert - via telephone*	Germany	No interests declared	Full involvement
George Papazisis	Expert - via telephone*	Greece	No interests declared	Full involvement
Tamás Szolyák	Expert - via telephone*	Hungary	No restrictions applicable to this meeting	Full involvement
Kate Browne	Expert - in person*	Ireland	No interests declared	Full involvement
Niamh Buckley	Expert - via telephone*	Ireland	No interests declared	Full involvement
Emma Lawless	Expert - via telephone*	Ireland	No interests declared	Full involvement
Desiree Bergamin-	Expert - via	Netherlands	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Egenberger	telephone*		declared	
Anouk Neuteboom	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Elizabeth van Vlijmen	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Silvia Duarte	Expert - via telephone*	Portugal	No interests declared	Full involvement
Mário Miguel Rosa	Expert - in person*	Portugal	No interests declared	Full involvement
Bruno Sepodes	Expert - via telephone*	Portugal	No interests declared	Full involvement
Michal Radik	Expert - in person*	Slovakia	No interests declared	Full involvement
María del Pilar Rayón Iglesias	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Annika Folin	Expert - in person*	Sweden	No interests declared	Full involvement
Miriam Taekema	Expert - in person*	Sweden	No interests declared	Full involvement
Mattia Calissano	Expert - in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - in person*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Representatives from the Medicines Evaluation Board (the Netherlands) visited the Committee				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

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

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/>