14 June 2018
EMA/PRAC/394603/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 14-17 May 2018

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

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

The Chairperson opened the 14-17 May 2018 meeting by welcoming all participants.

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

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

The PRAC Chairperson welcomed John Joseph Borg as the new member for Malta and noted that Benjamin Micallef is the new alternate for Malta, replacing Jon Joseph Borg.

In addition, the Chairperson announced the delegation of tasks by Slovakia to Czech Republic for the duration of the current meeting in accordance with Article 103 of Directive 2001/83/EC and Article 5 of the PRAC Rules of Procedure.

The Chairperson also announced that the Commission decision (CD) on appointing independent scientific experts to the PRAC for a term of three years from 2 July 2018 had been adopted on 8 May 2018, see C(2018) 2722 final.

1.2. Agenda of the meeting on 14-17 May 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 09-12 April 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 09-12 April 2018 were published on the EMA website on 11 June 2018 (EMA/PRAC/288660/2018).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Others

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

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

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

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

Background

At its last plenary meeting, the PRAC agreed the process and timelines for the revision of the PRAC recommendation adopted in January 2018 (see PRAC minutes January 2018) for the referral procedure under Article 107i of Directive 2001/83/EC on hydroxyethyl starch (HES) solutions for infusion. For background information, see PRAC minutes April 2018).

Summary of recommendation(s)/conclusions

The PRAC discussed the feedback from the Member States and from MAHs in an oral explanation. The PRAC adopted by majority a revised PRAC recommendation addressing the European Commission's questions. The PRAC conclusions were consistent with the latest position reached in January 2018 (see PRAC minutes January 2018).

Nineteen members voted in favour of the recommendation whilst fifteen members had divergent views[2]. The Norwegian and Icelandic PRAC members agreed with the recommendation.

[1] Solution for infusion
[2] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

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

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

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

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

Background

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

Summary of recommendation(s)/conclusions

- The PRAC was presented with the list of participants and the agenda for the public hearing on quinolone- and fluoroquinolone-containing products for systemic and inhalation use to be held on 13 June 2018 during the June 2018 PRAC meeting.

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

Applicant: Bayer AG

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

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Xofigo (radium-223 dichloride) to review the results of a phase 3 study (ERA 223[3]) and assess their potential impact on the benefit-risk balance of Xofigo in the authorised indication of the treatment of castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. The review was started after analyses of uncleaned preliminary data from this clinical trial, evaluating Xofigo in combination with abiraterone acetate and prednisone/prednisolone in chemotherapy-naïve patients with asymptomatic or mildly symptomatic bone predominant metastatic castrate-resistant prostate cancer, found that the incidences of treatment emergent fractures and deaths were increased in the treatment arm (radium-223 dichloride plus abiraterone acetate and prednisone/prednisolone) compared to the control arm (placebo plus abiraterone acetate and prednisone/prednisolone). For further background, see PRAC minutes December 2017 and PRAC minutes March 2018.

Summary of recommendation(s)/conclusions

- The PRAC discussed a draft list of experts (LoE) for the Inter-Committee Scientific Advisory Group (SAG) on Oncology (SAG-O) meeting scheduled on 19 June 2018.
- In addition, the PRAC discussed a list of questions (LoQ) to the SAG-O.

Post meeting note: On 4 June 2018, the PRAC adopted the final LoQ for the SAG-O by written procedure.

3.3. Procedures for finalisation

3.3.1. Daclizumab – ZINBRYTA[4] – 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

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for Zinbryta (daclizumab), conducted to further investigate the risk of immune-mediated encephalitis and assess its impact on the benefit-risk balance of the medicinal product, is to be concluded. The review was initiated following cases of serious immune-mediated adverse reactions in the central nervous system (CNS), including encephalitis and encephalo-meningitis. In March 2018, the PRAC recommended provisional measures without prejudice to the final conclusions of the ongoing procedure. For further background and information on the provisional measures, see PRAC minutes March 2018. A final

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

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

Discussion

The PRAC reviewed the totality of the available data, including data provided by the MAH in writing from clinical trials and post-marketing in relation to the overall risk of immune-mediated disorders, including adverse drug reactions with CNS involvement associated with treatment with Zinbryta.

In addition, PRAC also considered the known serious immune-mediated liver toxicity associated with Zinbryta as well as other immune-mediated disorders affecting other organs than the brain or the liver.

The PRAC concluded that Zinbryta (daclizumab beta) is associated, during treatment and for several months (i.e. at least 6 months) after the end of treatment, with an unpredictable and potentially fatal risk of immune-mediated disorders including CNS, liver and other organs. In view of the above, the PRAC confirmed its initial recommendation that the benefit-risk balance of Zinbryta is no longer favourable.

Summary of recommendation(s)/conclusions

- The PRAC confirmed its initial recommendation that the benefit-risk balance of Zinbryta is no longer favourable.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) and reviewed its content together with a communication plan.
- The PRAC noted the European Commission decision on withdrawal of the marketing authorisation for Zinbryta (daclizumab beta) issued on 27 March 2018.

Post-meeting note: the press release entitled 'EMA review of Zinbryta confirms medicine's risks outweigh its benefits - Multiple sclerosis medicine no longer authorised and has been recalled from hospitals and pharmacies' (EMA/286850/2018) was published on the EMA website on 18 May 2018.

3.3.2. 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 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, is to be concluded. For further background, see PRAC minutes December 2017, PRAC minutes February 2018 and PRAC minutes March 2018.

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

Discussion

The PRAC reviewed the totality of the data regarding the risk for liver injury with Esmya (ulipristal acetate) provided by the MAH, including data from clinical trials and non-clinical studies including in vitro testing, data provided at an oral explanation at the current meeting, and data by National Competent Authorities on cases of liver injury and liver transplantation reported since the initial marketing authorisation of the product. The PRAC also considered the views expressed by experts at an ad-hoc expert group meeting convened on 3 May 2018.

The PRAC concluded that Esmya (ulipristal acetate) may carry a rare risk for serious liver injury. While uncertainties around causality remain, PRAC recognised the very serious outcome of the reported cases of liver injury. Balancing this against the benefits of Esmya (ulipristal acetate) in the treatment of moderate to severe symptoms of uterine fibroids, the PRAC concluded that the indicated population should be restricted for safety reasons. Furthermore, measures to minimise the risk of liver injury should be implemented.

The PRAC recommended that intermittent treatment of moderate to severe symptoms of uterine fibroids with Esmya (ulipristal acetate) should be restricted to adult women of reproductive age who are not eligible for surgery. The PRAC clarified that Esmya (ulipristal acetate) can be used as one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The PRAC also recommended that the initiation and supervision of treatment with Esmya (ulipristal acetate) should be restricted to physicians experienced in the diagnosis and treatment of uterine fibroids.

The PRAC further concluded that Esmya (ulipristal acetate) should be contraindicated in patients with underlying hepatic disorder. In addition, the PRAC recommended the performance of liver function tests before starting each treatment course with Esmya (ulipristal acetate), during treatment as well as two to four weeks after discontinuation of treatment. Guidance on treatment initiation and discontinuation based on the results of these tests is to be included in the product information for Esmya (ulipristal acetate). Treatment should be stopped in patients showing signs or symptoms compatible with liver injury and the patient should be investigated immediately.

The PRAC also found it necessary to introduce a patient card to be provided in each package of Esmya (ulipristal acetate) to ensure that patients are adequately informed of the possible risks of liver injury and the risk minimisation measures. In addition, the existing physician's guide to prescribing should be updated accordingly.

The PRAC was also of the opinion that mechanistic studies should be conducted, to further investigate a possible mechanism for hepatic toxicity. In addition, observational studies should be performed to further characterise the hepatic risk and to evaluate the effectiveness of the risk minimisation measures implemented.

In view of the above, the Committee considered that the benefit-risk balance of Esmya (ulipristal acetate) remains favourable subject to the agreed amendments to the product information[5] and the additional risk minimisation measures.

[5] Sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.2 of the SmPC and Annex II. The package leaflet is updated accordingly

Summary of recommendation(s)/conclusions

- The PRAC adopted, by majority[6], a recommendation to vary the marketing authorisation for Esmya (ulipristal acetate) to be considered by CHMP for an opinion – See EMA Press Release (EMA/289137/2018) entitled 'PRAC recommends new measures to minimise risk of rare but serious liver injury with Esmya for fibroids - Regular liver function testing required during treatment'.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC). The Committee reviewed its content together with a communication plan.

Twenty-eight members voted in favour of the recommendation whilst three members had divergent views[7]. The Icelandic PRAC member agreed with the recommendation whilst the Norwegian PRAC member disagreed.

Post-meeting note: the press release 'Esmya: new measures to minimise risk of rare but serious liver injury - EMA concludes review of medicine for uterine fibroids' representing the opinion provided by the CHMP (EMA/355940/2018) was published on the EMA website on 1 June 2018.

3.4. Re-examination procedures[8]

None

3.5. Others

None

4. Signals assessment and prioritisation[9]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Daclatasvir - DAKLINZA (CAP); dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir - ZEPATIER (CAP); glecaprevir, pibrentasvir - MAVIRET (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, periteprevir, ritonavir - VIEKIRAX (CAP); sofosbuvir - SOVALDI (CAP); sofosbuvir, velpatasvir - EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP)

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

PRAC Rapporteur: Julie Williams

[6] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded
[7] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded
[8] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[9] 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

Scope: Signal of dysglycaemia

EPITT 19234 – New signal

Background

Direct-acting antiviral (DAAV) agents target specific non-structural proteins of the hepatitis C virus (HCV) and result in disruption of viral replication and infection. DAAVs provide interferon-free treatment options and a high efficacy rate offering rapid clearance of HCV. Among these, Sovaldi, a centrally authorised medicine containing sofosbuvir, is estimated to have been administered to approximately 448,563 to 897,126 patients (based on 24- or 12-week course) in the post-marketing setting in the period from first authorisation in January 2014 to December 2017.

During the assessment of the most recent PSUR (PSUSA/00010134/201712) for Sovaldi (sofosbuvir), a signal of dysglycaemia was identified by the Rapporteur, based on five literature articles (*Alem et al* 2017[10], *Pavone et al* 2016[11], *Dawood et al* 2017[12], *Li et al* 2017[13], *Lyman et al* 2016[14]) on studies which reported hypoglycaemia in diabetic patients treated with HCV DAAVs. Of note, these studies included DAAVs other than sofosbuvir, and the proposed mechanism for the effect can be considered applicable to all HCV DAAVs. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the evidence from EudraVigilance and the literature, the PRAC agreed that the MAHs for DAAV-containing products for the treatment of hepatitis C should provide a cumulative review of blood glucose disorders and relevant terms as well as discuss the need for any potential amendment to the product information and/or the risk management plan.

The PRAC appointed Julie Williams as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for direct-acting antivirals against hepatitis C (Daklinza (daclastavir), Epclusa (sofosbuvir/velpatasvir), Exviera (dasabuvir), Harvoni (ledipasvir/sofosbuvir), Maviret (glecaprevir/pibrentasvir), Sovaldi (sofosbuvir), Viekirax (ombitasvir/peritepreviir/ritonavir), Vosevi (sofosbuvir/velpatasvir/voxilaprevir), Zepatier (elbasvir/grazoprevir) should submit to EMA, within 60 days, a cumulative review of blood glucose disorders and relevant terms (e.g. MedDRA SMQs[15] 'hypoglycaemia' and 'hyperglycaemia/new onset diabetes mellitus'). The review should include an analysis of non-clinical and clinical trial data regarding blood glucose disorders and outcomes in diabetic patients, case report data from the MAHs'

[10] Abdel Alem S, Elsharkawy A, Fouad R, et al. Improvement of glycemic state among responders to sofosbuvir based treatment regimens: single centre experience. J Med Virol. 2017;89:2181–2187. https://doi.org/10.1002/jmv.24897
[11] Pavone, P; d'Ettorre, G; Lichtner, M; Tieghi, T; Marocco, R; Mezzaroma, I; Passavanti, G; Mastroianni, C; Vullo, V (Rome, Italy). Improving of glycaemic control associated with DAAV HCV treatment persists at SVR12. Poster P273. HIV Drug Therapies 2016 (Glasgow)
[12] Dawood AA, Nooh MZ, Elgamal AA. Factors associated with improved glycemic control by direct-acting antiviral agent treatment in egyptian type 2 diabetes mellitus patients with chronic hepatitis C genotype 4. Diabetes Metab J. 2017 Aug;41(4):316-321. doi: 10.4093/dmj.2017.41.4.316
[13] Jia Li. Does hepatitis C eradication lead to improved glucose metabolism, renal and cardiovascular outcomes in diabetic patients? AASLD Liver Learning; Oct 21 2017; 194531
[14] Backus LI, Belperio PS, Shahoumian TA, Mole LA. The impact of achieving virologic response from hepatitis C direct-acting antivirals on diabetes control. Hepatology. 2017 Jul 27. doi: 10.1002/hep.29408
[15] Medical dictionary for regulatory activities – Standardised MedDRA Queries

databases, a literature review and review of data from epidemiological sources (e.g. HCV-TARGET[16] and ANRS HEPATHER[17] cohorts). The MAHs should also discuss the need for any amendment to the product information and/or the risk management plan.

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

4.1.2. Dolutegravir – TIVICAY (CAP); abacavir sulfate, dolutegravir sodium, lamivudine – TRIUMEQ (CAP)

Applicant(s): ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

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

EPITT 19244 – New signal

Background

Tivicay (dolutegravir) is an antiviral agent for systemic use indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV) infected adults, adolescents and children above 6 years of age. Triumeq (abacavir/dolutegravir/lamivudine) is an antiviral for systemic use indicated for the treatment of HIV infected adults and adolescents above 12 years of age weighing at least 40 kg.

Recent estimates up to 31 December 2017 provided by the MAH report a total cumulative post-approval exposure for dolutegravir and dolutegravir/abacavir/lamivudine of over 900,000 patient years, assuming a standard daily dose for dolutegravir of 50 mg once daily.

On 8 May 2018, the MAH provided information about a signal that had arisen from preliminary data from an observational study: the Tsepamo study[18] on birth outcomes in HIV-infected women in Botswana, relating to safety of use during pregnancy. The United Kingdom confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC considered the available evidence from the preliminary data from the Tsepamo study conducted in Botswana. The PRAC noted the findings of this study, which suggested a potential increased risk of neural tube defects associated with the use of dolutegravir-containing medicines prior to conception. The PRAC considered that these findings merited prompt evaluation and communication to alert healthcare professionals to the findings of this study. It was also agreed that these study findings should be considered in the broader context of the available data. Further data on dolutegravir use during pregnancy should be requested from the MAH of dolutegravir-containing products (single ingredient and fixed combinations) to this purpose.

[16] Hepatitis C Therapeutic Registry and Research Network (HCV TARGET)
[17] French National Institute for Health and Medical Research-French National Agency for Research on acquired immune deficiency syndrome (AIDS) and Viral Hepatitis (Inserm-ANRS) - Therapeutic option for hepatitis B and C: a French cohort (HEPATHER)
[18] Observational study capturing birth outcomes data at 8 government hospitals throughout Botswana (~45% of all deliveries) starting August 2014

The PRAC appointed Julie Williams as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH (ViiV Healthcare) should distribute a direct healthcare professional communication (DHPC) to inform prescribers of this risk and to recommend that dolutegravir is not used in women planning a pregnancy and that women of child bearing potential who take dolutegravir should use effective contraception.
- The MAH should submit to EMA, within 8 days, a review of safety of dolutegravir use during pregnancy including information on pregnancy outcomes, categorised according to exposure (prior to conception, first trimester, second or third trimester), from all available data sources (including clinical trials, post-marketing experience and relevant literature), as well as considering the findings from the Tsepamo study in the context of these broader data. The MAH should discuss further data sources and/or studies that can further inform risk characterisation and management in relation to this issue including consideration of mechanistic studies. Finally, the submission should include a proposal for amending the product information and the risk management plan.
- A 15-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Hydroxycarbamide – SIKLOS (CAP), NAP

Applicant(s): Addmedica S.A.S., various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19210 – New signal

Background

Siklos (hydroxycarbamide) is an antineoplastic agent indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic Sickle cell syndrome. Nationally authorised indications of hydroxycarbamide-containing products include chronic myeloid leukaemia (CML) in the chronic or accelerated phase of the disease and myeloproliferative diseases such as essential thrombocythaemia and polycythaemia vera.

The exposure for Siklos, a centrally authorised medicine containing hydroxycarbamide, is estimated to have been more than 12,242 patient-years worldwide, in the period from first authorisation in June 2007 to June 2017. In addition, the cumulative number of patients treated with hydroxycarbamide[19] is estimated to have been approximately 1,421,190 in the period from July 1989 to June 2017.

During routine signal detection activities, a signal of progressive multifocal leukoencephalopathy (PML) was identified by the EMA, based on 4 cases retrieved from EudraVigilance and a fifth case retrieved from the literature. Belgium confirmed that the signal needed initial analysis and prioritisation by the PRAC.

[19] Centrally authorised product(s) excluded

Discussion

Having considered the evidence from case reports in EudraVigilance and from the literature, the PRAC agreed that the MAHs of hydroxycarbamide-containing products should provide additional information for a further assessment of the signal of PML as part of the relevant PSUSA procedures. The MAHs involved in PSUSA procedure PSUSA/00009182/201712[20] should provide their responses within 30 days via the ongoing PSUSA procedure. The MAH (Addmedica) of Siklos (hydroxycarbamide) should submit on 06/09/2018 the responses in the next PSUR for PSUSA procedure PSUSA/00001692/201806 with a data lock point (DLP) on 28/06/2018.

The PRAC appointed Laurence de Fays as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for hydroxycarbamide-containing products should submit to EMA in the relevant PSUSA procedures a cumulative review and analysis of cases of PML and other disorders caused by JC[21] virus from all sources, i.e. spontaneous reports, literature and clinical trials as well as a proposal for amending the product information, their risk minimisation plan and risk minimisation measures. The MAHs should provide estimates of the cumulative patient exposure, background incidence of PML in the treated population as well as incidence in the non-immunocompromised population and discuss the biological plausibility of hydroxycarbamide in the development of opportunistic infections including PML. Finally, the analysis should provide information on the authorised indications together with a description of the current product information wording in relation to serious/opportunistic infections, haematological (including lymphocyte) effects, including any wording relating to an association of haematological/immune cell effects with serious/opportunistic infections and all haematological/immune cell monitoring requirements.
- The assessment of this review will be performed in the relevant PSUSA procedures.

4.2. New signals detected from other sources

See Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/SDA/030

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of tubulointerstitial nephritis

EPITT 19127 – Follow-up to January 2018

Background

For background information, see PRAC minutes January 2018.

[20] hydroxycarbamide (except for centrally authorised product(s)) – recommendation due in July 2018
[21] John Cunningham

The MAH for Eliquis (apixaban) replied to the request for information on the signal of tubulointerstitial nephritis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the cumulative review provided by the MAH for Eliquis (apixaban), the PRAC agreed that the evidence of a causal relationship between treatment with apixaban and tubulointerstitial nephritis is not sufficiently strong at this stage to warrant regulatory action.

Summary of recommendation(s)

- No further action is deemed warranted at this stage. However, the MAH for Eliquis (apixaban) should continue to monitor this event as part of routine safety surveillance, and present new relevant data in future PSURs.

4.3.2. Apixaban – ELIQUIS (CAP) - EMEA/H/C/002148/SDA/031; edoxaban – LIXIANA (CAP) - EMEA/H/C/002629/SDA/010, ROTEAS (CAP) - EMEA/H/C/004339/SDA/002; Serotonin and noradrenaline reuptake inhibitors (SNRI): desvenlafaxine (NAP); duloxetine - ARICLAIM (CAP), CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP); milnacipran (NAP); venlafaxine (NAP) Selective serotonin reuptake inhibitors (SSRI): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP)

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

PRAC Rapporteur: Julie Williams

Scope: Signal of drug interaction between apixaban or edoxaban and selective serotonin reuptake inhibitors (SSRI) and/or serotonin and noradrenaline reuptake inhibitors (SNRI) leading to increased risk of bleeding

EPITT 19139 – Follow-up to January 2018

Background

For background information, see PRAC minutes January 2018.

The MAHs Bristol-Myers Squibb (for Eliquis (apixaban)) and Daiichi Sankyo Europe GmbH (for Lixiana, Roteas (edoxaban)) replied to the request for information on the signal of drug interaction between apixaban or edoxaban and selective serotonin reuptake inhibitors (SSRI) and/or serotonin and noradrenaline reuptake inhibitors (SNRI) leading to increased risk of bleeding and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the available evidence from EudraVigilance and the literature, including the response from the MAH of Eliquis (apixaban) and the MAH for Lixiana and Roteas (edoxaban), as well as the biological plausibility of an interaction between apixaban or edoxaban and SSRIs or SNRIs resulting in an increased risk of bleeding. In the light of this evidence, the PRAC agreed that the MAHs of apixaban- and edoxaban-containing

products should amend their product information to add the interaction with SSRIs or SNRIs and the potential impact on haemostasis.

Summary of recommendation(s)

- The MAH(s) of apixaban- and edoxaban-containing products should submit to EMA, within 60 days, a variation for amending the product information[22].

For the full PRAC recommendation, see EMA/PRAC/287231/2018 published on 11/06/2018 on the EMA website.

4.3.3. Hormonal contraceptives: Chlormadinone, estradiol (NAP); chlormadinone acetate, ethinylestradiol (NAP); conjugated estrogens, medrogestone (NAP); conjugated estrogens, medroxyprogesterone acetate (NAP); conjugated estrogens, norgestrel (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel ,ethinylestradiol (NAP); dienogest, estradiol[23] (NAP); dienogest, ethinylestradiol (NAP); drospirenone, estradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, estriol, levonorgestrel (NAP); estradiol, gestodene (NAP); estradiol, levonorgestrel (NAP); estradiol, medroxyprogesterone acetate (NAP); estradiol, nomegestrol acetate (NAP); estradiol, norethisterone (NAP); estradiol, norgestimate (NAP); estradiol (17-beta), progesterone (NAP); estradiol (17-beta), trimegestone (NAP); estradiol valerate, norgestrel (NAP); ethinylestradiol, etonogestrel (NAP); ethinylestradiol, etynodiol (NAP); ethinylestradiol, gestodene[24] (NAP); ethinylestradiol, gestodene[25] (NAP); ethinylestradiol, levonorgestrel (NAP); ethinylestradiol, lynestrenol (NAP); ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol[26] (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); mestranol, norethisterone (NAP); nomegestrol (NAP); nomegestrol acetate, estradiol – ZOELY (CAP); norelgestromin, ethinyl estradiol – EVRA (CAP), NAP; norethisterone (NAP)

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

PRAC Rapporteur: Doris Stenver

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

EPITT 19144 – Follow-up to January 2018

Background

For background information, see PRAC minutes January 2018.

A further assessment of the study (*Skovlund et al.* 2017)[27], including clarifications provided by the study authors, was performed by the Rapporteur.

Discussion

Having considered the available evidence arising from a recent publication on the signal of suicidality associated with hormonal contraceptives and the additional clarifications on the

[22] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly
[23] Contraception indication
[24] All route of administrations except transdermal
[25] Transdermal application
[26] Combination pack
[27] Skovlund, C. W., Morch, L. S., Kessing, L. V., Lange T., Lidegaard, O. 2017. Association of hormonal contraception with suicide attempts and suicides. Am J Psychiatry, appiajp201717060616

study findings provided by the study authors, the PRAC concluded that this issue merits further investigation.

Therefore, the MAHs for the innovator hormonal contraceptive-containing products should provide additional information in order to better perform an in-depth analysis of the data and assess the need for further actions on this issue.

Summary of recommendation(s)

- The MAHs for the innovator hormonal contraceptive-containing products should submit to EMA, within 75 days, a critical appraisal of the most recent publications (*Skovlund et al.* 2016[28], *Skovlund et al.* 2017[27]) on depression/suicide in relation to hormonal contraceptive use, the most recent data on systemic exposure associated with the use of oral and non-oral hormonal contraception, especially comparing patch, rings and oral forms, a discussion on the magnitude of the absolute as well as the relative risk of these suspected reactions associated with hormonal contraceptives based on the review of data on depression/suicide/self-injury/mood change events and related events as well as a discussion on the need for any risk minimisation measures including relevant updates of the product information as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.4. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/000717/SDA/049

Applicant(s): Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19130 – Follow-up to January 2018

Background

For background information, see PRAC minutes January 2018.

The MAH for Revlimid (lenalidomide) replied to the request for information on the signal of progressive multifocal leukoencephalopathy (PML) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of PML, the PRAC agreed that the MAH of Revlimid (lenalidomide) should submit a variation to amend the product information to include a special warning and precaution for use in relation to the risk of PML.

Summary of recommendation(s)

- The MAH for Revlimid (lenalidomide) should submit to EMA, within 60 days, a variation for amending the product information[29].

For the full PRAC recommendation, see EMA/PRAC/287231/2018 published on

[28] Skovlund, C. W., Morch, L. S., Kessing, L. V., Lidegaard, O. 2016. Association of hormonal contraception with depression. JAMA Psychiatry, 73, 1154-1162

[29] Recommendation to update of SmPC section 4.4. The package leaflet is to be updated accordingly

11/06/2018 on the EMA website.

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

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

PRAC Rapporteur: Patrick Batty

Scope: Signal of pulmonary haemorrhage

EPITT 19181 –Follow-up to April 2018

Background

For background information, see PRAC minutes April 2018.

The MAHs for pegfilgrastim-, lenograstim- and lipegfilgrastim-containing medicinal products replied to the request for comments on the proposed wording for the update of the product information further to the signal of pulmonary haemorrhage and the responses were assessed by the Rapporteur.

Discussion

Having considered the evidence from EudraVigilance, the possibility of a class effect and the responses from MAHs, the PRAC recommended that the MAHs of pegfilgrastim-, lenograstim- and lipegfilgrastim-containing products should update their product information to add haemoptysis and pulmonary haemorrhage as undesirable effects of uncommon[30] and rare frequency[31] respectively.

Summary of recommendation(s)

- The MAHs[32] of pegfilgrastim-, lenograstim-[33] and lipegfilgrastim-containing products should submit to EMA, within 60 days, a variation for amending the product information[34].

For the full PRAC recommendation, see EMA/PRAC/287231/2018 published on 11/06/2018 on the EMA website.

4.3.6. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/017

Applicant(s): Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of aseptic meningitis

EPITT 19115 – Follow-up to January 2018

Background

For background information, see PRAC minutes January 2018.

[30] Stated frequency is applicable for pegfilgrastim-containing products; for lipegfilgrastim- and lenograstim-containing products the frequency is to be calculated by the MAHs
[31] Stated frequency is applicable for pegfilgrastim-containing products; for lipegfilgrastim- and lenograstim-containing products the frequency is to be calculated by the MAHs
[32] Applicants for products under evaluation should update their product information accordingly during evaluation
[33] To include pulmonary haemorrhage and haemoptysis for both cancer patients and healthy donors
[34] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

The MAH for Keytruda (pembrolizumab) replied to the request for information on the signal of aseptic meningitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the MAH for Keytruda (pembrolizumab) should amend its product information to add meningitis (aseptic) as an undesirable effect with a frequency 'rare'.

Summary of recommendation(s)

- The MAH for Keytruda (pembrolizumab) should submit to EMA, within 60 days, a variation for amending the product information[35].

For the full PRAC recommendation, see EMA/PRAC/287231/2018 published on 11/06/2018 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

See also Annex I 15.1.

5.1.1. Binimetinib - EMEA/H/C/004579

Scope: Treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, in combination with encorafenib

5.1.2. Durvalumab - EMEA/H/C/004771

Scope: Treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC)

5.1.3. Encorafenib - EMEA/H/C/004580

Scope: Treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, in combination with binimetinib

5.1.4. Eravacycline - EMEA/H/C/004237

Scope: Treatment of complicated intra-abdominal infections (cIAI) in adults

5.1.5. Glycopyrronium, formoterol fumarate dihydrate - EMEA/H/C/004245

Scope: Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

5.1.6. Lenalidomide - EMEA/H/C/004857

Scope: Treatment of multiple myeloma

[35] Update of SmPC section 4.8. The package leaflet is updated accordingly

5.1.7. Melatonin – EMEA/H/C/004425, PUMA[36]

Scope: Treatment of insomnia in children with autism spectrum disorders and neurogenetic diseases

5.1.8. Meropenem, vaborbactam - EMEA/H/C/004669

Scope: Treatment of complicated urinary tract infection (cUTI), including pyelonephritis, intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), bacteraemia, infections due to bacterial organisms

5.1.9. Mexiletine hydrochloride - EMEA/H/C/004584, Orphan

Applicant: Lupin (Europe) Limited

Scope: Treatment of myotonic disorders

5.1.10. Pegfilgrastim - EMEA/H/C/003961

Scope: Treatment of neutropenia

5.1.11. Tildrakizumab – EMEA/H/C/004514

Scope: Treatment of adults with moderate-to-severe plaque psoriasis

5.1.12. Viable T-cells - EMEA/H/C/002397, Orphan

Applicant: Kiadis Pharma Netherlands B.V., ATMP[37]

Scope: Adjunctive treatment in haematopoietic stem cell transplantation (HSCT) for a malignant disease

5.1.13. Voretigene neparvovec - EMEA/H/C/004451, Orphan

Applicant: Spark Therapeutics Ireland Ltd, ATMP[38]

Scope: Treatment of patients with vision loss due to Leber congenital amaurosis or retinitis pigmentosa inherited retinal dystrophy

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. Darunavir - PREZISTA (CAP) - EMEA/H/C/000707/WS1312/0093; Darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/WS1312/0023;

[36] Paediatric-use marketing authorisation(s)
[37] Advanced therapy medicinal product
[38] Advanced therapy medicinal product

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 from 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 for 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 the RMP template (version 2) for 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 the 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)

Background

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the human immunodeficiency virus 1 (HIV-1) protease. Cobicistat is a mechanism-based inhibitor of cytochrome P450 of the CYP3A subfamily. Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and a nucleoside analogue of 2'-deoxycytidine. Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Darunavir alone or in combination as darunavir/cobicistat or darunavir/cobicistat/emtricitabine/tenofovir alafenamide is indicated for the treatment of HIV-1 infection under certain conditions.

The CHMP is evaluating a worksharing variation application for Prezista, Rezolsta and Symtuza, centrally authorised products containing darunavir, darunavir/cobicistat and darunavir/cobicistat/emtricitabine/tenofovir alafenamide respectively, to reflect data from study TMC114HIV3015: a single arm, open label study to assess the pharmacokinetics of darunavir and ritonavir, darunavir and cobicistat, etravirine, and rilpivirine in HIV-1 infected pregnant women. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes March 2018.

Summary of advice

- The RMP for Prezista (darunavir), Rezolsta (darunavir/cobicistat) and Symtuza (darunavir/cobicistat/emtricitabine/tenofovir alafenamide) in the context of the variation under evaluation could be considered acceptable provided that an update to RMP version 25.6, version 4.6 and version 4.0 respectively and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the safety concern 'use in pregnant and breastfeeding women' should be removed from the RMP and the outcomes of the product information changes reflected in the risk minimisation measures (RMM).

- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) in order to warn healthcare professionals (HCPs) of an increased risk of treatment failure and an increased risk of mother to child transmission of HIV infection due to low exposure values of darunavir and cobicistat during the second and third trimesters of pregnancy. Therefore, HCPs should switch women who become pregnant to an alternative drug regimen. The PRAC agreed the content of the DHPC together with a communication plan.

5.3.2. Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/II/0033, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to reflect the results from the paediatric study DACOGENAML2004: 'a phase 1-2 safety and efficacy study of Dacogen (decitabine) in sequential administration with cytarabine in children with relapsed or refractory acute myeloid leukaemia' as per the requirement of Article 46 of Regulation (EC) No1901/2006. The RMP (version 3.1), in line with revision 2 of the RMP template, is updated accordingly. In addition, the MAH took the opportunity to update section 4.4 of the SmPC to align the safety warning related to the sodium excipient with the Annex to the revised European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The package leaflet is updated accordingly. Moreover, the contact details of the local representative in Slovenia are updated in the package leaflet

Background

Decitabine is a cytidine deoxynucleoside analogue indicated for the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.

The CHMP is evaluating a variation application for Dacogen, a centrally authorised product containing decitabine, to reflect the results from a paediatric study entitled DACOGENAML2004 (listed as a category 3 in the RMP): a phase 1-2 safety and efficacy study of Dacogen (decitabine) in sequential administration with cytarabine in children with relapsed or refractory acute myeloid leukaemia. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Dacogen (decitabine) in the context of the procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 3.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC noted that no clinically meaningful anti-leukaemic efficacy with the sequential combination was observed in children and the study was terminated early. In addition, reported adverse events were consistent with the known safety profile of Dacogen (decitabine) in adults. The PRAC agreed with removing the planned paediatric study from the RMP pharmacovigilance plan of the RMP.

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. Arsenic trioxide - TRISENOX (CAP) - PSUSA/00000235/201709

Applicant: Teva B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Trisenox (arsenic trioxide) is an antineoplastic agent indicated for induction of remission, and consolidation in adult patients with acute promyelocytic leukaemia (APL) (white blood cell count, ⩽ 10 x 103/µl) in combination with all-trans-retinoic acid (ATRA), and adult patients with relapsed/refractory APL (previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the T(15;17) translocation and/or the presence of the pro-myelocytic leukaemia/retinoic-acid-receptor-alfa (PML/RAR-alfa) gene.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Trisenox, a centrally authorised medicine containing arsenic trioxide, 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 Trisenox (arsenic trioxide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on 'encephalopathy' to patients with vitamin B1 deficiency and to add 'encephalopathy' and 'Wernicke encephalopathy' as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[39].

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. Cariprazine - REAGILA (CAP) - PSUSA/00010623/201712

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

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

Reagila (cariprazine) is a psycholeptic indicated for the treatment of schizophrenia in adult patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Reagila, a centrally authorised medicine containing cariprazine, 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 Reagila (cariprazine) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should closely monitor cases of severe cutaneous adverse reactions (SCARs).

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. Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/201711

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Genvoya (cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide) is a combination of antivirals for systemic use indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in adults and adolescents aged from 12 years and with body weight at least 35 kg, and in children aged from 6 years and with body weight at least 25 kg for whom alternative regimens are unsuitable due to toxicities.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Genvoya, a centrally authorised medicine containing cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide, 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 Genvoya (cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to contraindicate the concomitant use of lurasidone as it may result in increased plasma concentrations of

lurasidone which are associated with potentially serious adverse reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[40].

- In the next PSUR, the MAH should submit a detailed review of cases of suicidal ideation, behaviour and completed suicide and discuss the need for an update of the product information. In addition, an update on the outcome of the procedure reviewing the signal of decreased exposure in pregnancy and its implications on the known efficacy/safety profile of Genvoya (cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide) should be provided.

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. Deferasirox - EXJADE (CAP) - PSUSA/00000939/201710

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Exjade (deferasirox) is an oral active iron chelating agent indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. It is also indicated for the treatment of chronic iron overload due to blood transfusions in paediatric patients with beta thalassaemia major due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years. Furthermore, deferasirox is indicated in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older, and in adult and paediatric patients with other anaemias aged 2 years and older, when deferoxamine therapy is contraindicated or inadequate. Moreover, it is indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Exjade, a centrally authorised medicine containing deferasirox, 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 Exjade (deferasirox) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the drug-drug interaction with busulfan, to amend the current warnings on renal and hepatic functions to add that some cases were associated with loss of consciousness in the context of hyperammonaemic encephalopathy with specific focus on paediatric patients, and to recommend early measurement of ammonia levels in patients

[40] 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

developing unexplained changes in mental status. In addition, a reference to severe forms of hepatic and acute renal failure associated with encephalopathy and changes in consciousness in hyperammonaemia context is added as part of the undesirable effect section. Therefore, the current terms of the marketing authorisation(s) should be varied[41].

- In the next PSUR, the MAH should provide a detailed review of cases where 'increased dose administered' and/or overdose was reported. In addition, the MAH should provide detailed reviews of cases reporting 'neonates' and 'congenital malformation', as well as paediatric cases of severe forms of hepatic and/or renal failure with hyperammonaemia. In addition, the MAH should provide a detailed cumulative review and analysis of cases with interaction with or concomitant use of magnesium.

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. Edoxaban - LIXIANA (CAP); ROTEAS (CAP) - PSUSA/00010387/201710 (with RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Lixiana, Roteas (edoxaban) is an inhibitor of factor Xa indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors. It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lixiana and Roteas, centrally authorised medicines containing edoxaban, 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 Lixiana and Roteas (edoxaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'thrombocytopenia' as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[42].
- In the next PSUR, the MAH should include a review of cases of musculoskeletal and connective tissue disorders to establish the association with the underlying disease and whether edoxaban may have a contributory role. In addition, the MAH should provide further details on cases of vitreous detachment. Furthermore, the MAH should

[41] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[42] 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

provide a detailed description of patients who discontinued treatment or died due to treatment emergent adverse events (TEAEs) in study DU176b-D-U311[43], and patients who discontinued treatment due to TEAEs in studies DU176b-C-E314[44] and DU176b-C-J316[45].

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

6.1.6. Iloprost[46] - VENTAVIS (CAP) - PSUSA/00001724/201709

Applicant: Bayer AG

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Ventavis (iloprost) is a synthetic prostacyclin analogue indicated for the treatment of adult patients with primary pulmonary hypertension (PPH).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ventavis, a centrally authorised medicine containing iloprost, 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 Ventavis (iloprost) 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 60 days a detailed review of all available data on pregnancy including a discussion on the need to amend the product information as applicable.
- In the next PSUR, the MAH should provide an analysis of pregnancy cases with a display of time evolution of the number of cases of pregnancies that have been reported since the marketing authorisation approval of Ventavis (iloprost) to determine whether a significant increase in exposure during pregnancy is observed.

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

6.1.7. Micafungin - MYCAMINE (CAP) - PSUSA/00002051/201710

Applicant: Astellas Pharma Europe B.V.

[43]Multinational, prospective, randomized, open-label, blind-evaluator, non-inferiority study comparing edoxaban with dalteparin for prevention of the combined outcome of recurrent venous thromboembolism (VTE) or major bleeding in patients with VTE associated with cancer
[44] Multicentre, randomized, double blind study with blinded evaluation of endpoints by an independent clinical event committee
[45] Randomized, double-blind, placebo-controlled, parallel-group, multicentre, event-driven study conducted to evaluate efficacy and safety of 15 mg in patients with non-valvular atrial fibrillation aged 80 years or older who are ineligible for available oral anticoagulants
[46] Nebuliser solution only

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Mycamine (micafungin) is an antimycotic for systemic use that inhibits the synthesis of 1,3-β-D-glucan indicated for the prophylaxis of candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/µl) for 10 or more days. Mycamine (micafungine) is also indicated for the treatment of invasive candidiasis, and for the treatment of oesophageal candidiasis in patients 16 years of age or older for whom intravenous therapy is appropriate.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mycamine, a centrally authorised medicine containing micafungin, 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 Mycamine (micafungin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'anaphylactic and anaphylactoid shock' as undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[47].
- In the next PSUR, the MAH should closely monitor cases of pancreatitis.

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

6.1.8. Nintedanib[48] - VARGATEF (CAP) - PSUSA/00010318/201710

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: Evaluation of a PSUSA procedure

Background

Vargatef (nintedanib) is a triple angiokinase inhibitor indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

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

Summary of recommendation(s) and conclusions

[47] 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
[48] Oncology indications only

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Vargatef (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the warning of 'gastrointestinal perforations' and to add a new warning on 'renal impairment/failure', according to new reported safety data, as well as to include 'myocardial infarction' and 'renal failure' as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[49].
- In the next PSUR, the MAH should provide a cumulative and interval analysis of cases of arthralgia. In addition, the MAH should submit the follow up and analysis of interstitial lung disease (ILD)/pneumonitis cases, and an update of the product information, if applicable. However, if upon completion of the follow-up for these cases a new signal arises, the MAH should follow the relevant procedures, before the next PSUR.

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

6.1.9. Nintedanib[50] - OFEV (CAP) - PSUSA/00010319/201710

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Ofev (nintedanib) is a triple angiokinase inhibitor indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ofev, a centrally authorised medicine containing nintedanib, 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 Ofev (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on 'renal impairment/failure' according to new reported safety data and to add 'rash' as an undesirable effect with a frequency 'common', 'pruritus' with a frequency 'uncommon' and 'renal failure' with a frequency 'unknown'. Therefore, the current terms of the marketing authorisation(s) should be varied[51].
- In the next PSUR, the MAH should provide a detailed analysis of all reported cases of ischaemic central nervous system vascular conditions and autoimmune haemolytic anaemia. In addition, the MAH should provide an analysis of new cases of

[49] Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[50] Respiratory indication only
[51] Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

hepatotoxicity, to assess the effectiveness of the product information update on this topic, and provide an analysis of cases of glomerulonephritis and cases where pirfenidone and nintedanib were used in combination.

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

6.1.10. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/201710

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Imlygic (talimogene laherparepvec) is an oncolytic immunotherapy indicated for the treatment of adults with unresectable melanoma regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Imlygic, a centrally authorised medicine containing talimogene laherparepvec, 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 Imlygic (talimogene laherparepvec) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the possibility of quantitative polymerase chain reaction (qPCR)-testing for talimogene laherparepvec following accidental exposure to Imlygic. Therefore, the current terms of the marketing authorisation(s) should be varied[52].
- In the next PSUR, the MAH should provide data on the potential increase in frequency and seriousness of immune-mediated reactions for combination therapy studies[53] with checkpoint-inhibitors.

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

6.1.11. Thalidomide - THALIDOMIDE CELGENE (CAP) - PSUSA/00002919/201710

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

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

[53] Including study 20110264: a phase 1b/2, multicentre, open-label trial to evaluate the safety and efficacy of talimogene laherparepvec and ipilimumab compared to ipilimumab alone in subjects with unresected, stage IIIB-IV melanoma

Thalidomide Celgene (thalidomide) is an immunosuppressant indicated in combination with melphalan and prednisone for the treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Thalidomide Celgene, a centrally authorised medicine containing thalidomide, 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 Thalidomide Celgene (thalidomide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'leukocytoclastic vasculitis' as an undesirable effect with a frequency 'unknown'. Therefore, the current terms of the marketing authorisation(s) should be varied[54].
- The MAH should submit to EMA within 40 days a cumulative review and analysis of cases of progressive multifocal leukoencephalopathy (PML).
- In the next PSUR, the MAH should provide a cumulative review of cases of drug reaction with eosinophilia and systemic symptoms (DRESS) and discuss whether there is a need to update the product information, and a review of cases of human chorionic gonadotropin (hCG) increased with a further discussion on additional actions to be taken.

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

6.1.12. Toremifene - FARESTON (CAP) - PSUSA/00002999/201709

Applicant: Orion Corporation

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Fareston (toremifene) is a nonsteroidal triphenylethylene derivative indicated for the treatment of hormone-dependent metastatic breast cancer in postmenopausal patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fareston, a centrally authorised medicine containing toremifene, 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 Fareston (toremifene) in the approved indication(s) remains unchanged.

[54] 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

- Nevertheless, the product information should be updated to include 'hepatic steatosis' as undesirable effect with a frequency 'unknown'. Therefore, the current terms of the marketing authorisation(s) should be varied[55].

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

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

6.2.1. Sodium oxybate[56] - XYREM (CAP); NAP - PSUSA/00010612/201710

Applicants: UCB Pharma Limited (Xyrem), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Sodium oxybate is a central nervous system depressant indicated for the treatment of narcolepsy with cataplexy in adults, and for the treatment of alcohol dependence under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xyrem, a centrally authorised medicine containing sodium oxybate, and nationally authorised medicines containing sodium oxybate, 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 sodium oxybate-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'nocturia' as undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[57].
- In the next PSUR, the MAHs should closely monitor cases of off label use as well as cases of respiratory arrest in long-term use.

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.

[55] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[56] Oral use only
[57] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

See also Annex I 16.3.

6.3.1. Adapalene, benzoyl peroxide (NAP) - PSUSA/00000059/201709

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Adapalene is a retinoid and benzoyl peroxide is an antibacterial agent. In combination, it is indicated for the treatment of acne vulgaris when comedones, papules and pustules are present.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing adapalene/benzoyl peroxide 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 adapalene/benzoyl peroxide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'application site burn' as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[58].

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. Calcium carbonate, famotidine, magnesium hydroxide (NAP) - PSUSA/00001351/201709

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Calcium carbonate and magnesium hydroxide are antacids, famotidine is an H2-receptor antagonist. In combination, calcium carbonate/famotidine/magnesium hydroxide is indicated for short-term symptomatic treatment of heartburn or acid regurgitation.

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

[58] 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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of calcium carbonate/famotidine/magnesium hydroxide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on phosphatemia in haemodialysis patients due to the risk of loss of efficacy of calcium-phosphate binders when combined with famotidine. Therefore, the current terms of the marketing authorisation(s) should be varied[59].

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. Etomidate (NAP) - PSUSA/00001330/201709

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Etomidate is a short-acting hypnotic indicated for the induction of general anaesthesia under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing etomidate 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 etomidate-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on 'transient adrenal insufficiency' and on 'decreased serum cortisol levels' associated with single doses of etomidate. In addition, the product information should be updated to include 'cortisol decreased' as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied[60].

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. Famotidine (NAP) - PSUSA/00001350/201709

Applicant(s): various

[59] 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

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

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Famotidine is a histamine type 2 receptor antagonist (H2RA) indicated for the prevention of relapse of duodenal or benign gastric ulcer, and of symptoms and erosions or ulcerations associated with gastroesophageal reflux disease (GERD). It is also indicated for the treatment of heartburn, dyspepsia, duodenal ulcer, benign gastric ulcer, hypersecretory conditions, as well as symptomatic relief of GERD and healing of esophageal erosion or ulceration associated with GERD.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing famotidine 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 famotidine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the risk of loss of efficacy of calcium carbonate when co-administered as phosphate binder with famotidine in haemodialysis patients. Therefore, the current terms of the marketing authorisation(s) should be varied[61].
- In the next PSUR, the MAH should provide a cumulative review on cases of QT prolongation and discuss a product information update if applicable. In addition, the MAHs should discuss evidence related to interaction with cyanocobalamine, tyrosine kinase inhibitors (excluding vandetanib, imatinib) and ulipristal.

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

6.3.5. Fluoxetine (NAP) - PSUSA/00001442/201709

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of major depression with or without associated anxiety, for the treatment of obsessive compulsive disorder (OCD) and panic disorder. It is also indicated for the treatment of bulimia nervosa and premenstrual dysphoric disorder (PMDD). Lastly, fluoxetine is indicated in combination with olanzapine for depressive episodes associated with bipolar disorder and treatment of adult patients with treatment-resistant depression.

[61] 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 assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing fluoxetine 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 fluoxetine-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The PRAC considered that the risk of autism spectrum disorders (ASD) and the risk of neurodevelopmental disorder other than ASD, after in utero exposure to SSRI in general and to fluoxetine in particular, as well as the risk of cardiac valve disorders needed to be further assessed. Further consideration is to be given at the level of the CMDh.
- In addition, the PRAC considered the issue of persistent sexual dysfunction and noted that a work sharing variation was to be submitted by the MAH addressing the issue as an undesirable effect.
- In the next PSUR, the MAH Eli Lilly should provide a detailed cumulative review of cases of drug reaction with eosinophilia and systemic symptoms (DRESS), a cumulative review of cases of type 2 diabetes and discuss if a further update of the product information is needed.

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. Fluvastatin (NAP) - PSUSA/00001457/201708

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Fluvastatin is a synthetic statin which competitively inhibits β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase indicated for the prevention of coronary heart disease and for the treatment of dyslipidaemia in adults. In addition, fluvastatin is indicated for the treatment of heterozygous familial hypercholesterolaemia in children and adolescents aged nine years and older.

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

- Nevertheless, the product information should be updated to include 'diarrhoea' as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[62].
- In the next PSUR, the MAHs should provide a cumulative review of cases new-onset diabetes mellitus and tendinopathy associated with the use of fluvastatin (not as a class effect).

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. Minocycline (NAP) - PSUSA/00002065/201708

Applicant(s): various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Minocycline is a tetracycline indicated for the prevention of asymptomatic meningococcal carriers, and of pre- and post-operative infections. In addition, minocycline is indicated for the treatment of acne (including tetracycline resistant acne), skin and soft tissue infections, ophthalmological infections, acute and chronic bronchitis, bronchiectasis, lung abscess, ear, nose and throat infections, pelvic inflammatory disease, nocardiosis, urinary tract infections, gonorrhoea, non-gonococcal urethritis and prostatitis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing minocycline 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 minocycline-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 foetal exposure and utilisation during pregnancy 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.

6.3.8. Sodium oxybate[63] (NAP) - PSUSA/00010613/201710

Applicant(s): various

[62] 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
[63] Intravenous use only

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Sodium oxybate is the sodium salt of an analogue of the neurotransmitter gamma-aminobutyric acid (GABA) indicated for induction of anaesthesia and narcosis. It is also indicated as anaesthetic adjuvant and for sedation under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing sodium oxybate 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 sodium oxybate-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, all MAHs are requested to discuss the most recent literature published regarding the excretion of sodium oxybate into breast milk and to propose an update of the product information as appropriate with considerations to be given to the pharmacokinetic properties and posology of the product and whether a time interval is necessary after the administration of sodium oxybate.

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)[64]

See also Annex I 17.1.

7.1.1. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG (Medikinet Retard)

PRAC Rapporteur: Valerie Strassmann

Scope: Protocol for a multicentre, observational, prospective PASS study to evaluate the safety concerns of long-term cardiovascular and psychiatric risks within the adult attention deficit/hyperactivity disorder (ADHD) population taking Medikinet Retard (methylphenidate hydrochloride) according to normal standard clinical practice

The PRAC appointed Valerie Strassmann as Rapporteur for this procedure.

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

7.1.2. Teicoplanin (NAP) - EMEA/H/N/PSA/S/0029

Applicant: Sanofi (Targocid)

PRAC Rapporteur: Valerie Strassmann

Scope: Revised protocol following substantial amendments to a protocol previously agreed by PRAC in June 2015 and amended in May 2017 for a PASS study: a prospective, observational cohort study, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12 mg/kg twice a day), and comparison with external historical comparator data

Background

Teicoplanin is a glycopeptide antibiotic used for parenteral treatment of infections. Targocid is a nationally authorised medicine containing teicoplanin (MRP procedures with DE and DK acting as RMSs). Following the conclusion of a referral under Directive 2001/83/EC a PASS study to evaluate the safety of Targocid (teicoplanin) in adults with Gram-positive infections who are exposed to the higher loading dose of 12mg/kg twice a day (24 mg/kg/day) was included as an obligation in the marketing authorisation (Annex IV of the EC decision). In June 2015, the PRAC adopted a protocol for a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12mg/kg twice a day), and comparison with external historical comparator data. For further background, see PRAC minutes April 2014, PRAC minutes September 2014, and PRAC minutes June 2015.

Further to the MAH's submission of a substantial protocol amendment to extend the recruitment period by about 6 months to reach the anticipated study size of 300 patients following a review of actual recruitment. The amended protocol (version 1 including the protocol amendment No 02) was reviewed by the PRAC.

Endorsement/Refusal of the protocol

- The PRAC, having considered the protocol amendment No 02 version 1, dated 26 February 2018, and in accordance with Article 107o of Directive 2001/83/EC, endorsed the amended protocol.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[65]

See also Annex I 17.2.

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

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 007 [protocol for study SB2-G41-AS; SB2-G42-CD: a prospective observational cohort study in ankylosing spondylitis (AS) and Crohn's disease

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

(CD) for two years to observe safety, efficacy and immunogenicity of Flixabi with active comparator in AS and CD] as per the request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

Background

Flixabi is a centrally authorised medicine containing infliximab, a tumour necrosis factor alfa (TNF-α) inhibitor indicated in rheumatoid arthritis in combination with methotrexate under conditions, in adult CD under conditions, in paediatric CD under conditions, in ulcerative colitis under conditions, in ankylosing spondylitis (AS) under conditions, in psoriatic arthritis under conditions and in psoriasis under certain conditions.

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

Summary of advice

- The PRAC re-discussed the proposed study protocols and agreed that given the limited data that can be gathered within the proposed AS study, this study should be removed from the RMP. In addition, the PRAC agreed the observational study on CD as currently designed could be useful provided that the MAH makes some smaller amendments. The MAH should submit to EMA within 90 days further discussion and justification on the matter.

7.3. Results of PASS imposed in the marketing authorisation(s)[66]

7.3.1. Magnesium sulfate heptahydrate, sodium sulfate anhydrous, potassium sulfate (NAP) - EMEA/H/N/PSR/S/0016

Applicant(s): Ipsen Pharma (Eziclen, Izinova)

PRAC Rapporteur: Caroline Laborde

Scope: Results for a multicentre, European, observational, drug utilisation study (DUS) of Eziclen/Izinova (BLI800) (magnesium sulfate heptahydrate/sodium sulfate anhydrous/potassium sulfate) as a bowel cleansing preparation to document the misuse of BLI800, defined as non-compliance in terms of sufficient liquid intake, during the post approval period in the real life setting; and to describe the safety profile of BLI800 in routine clinical practice, overall and in cases of misuse defined as non-compliance in terms of sufficient liquid intake, and identify any immediate/acute adverse events

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

associated with the use of BLI800 in special populations (i.e. the elderly and patients at risk for electrolyte shifts)

Background

In January 2013, Eziclen/Izinova, an oral solution composed of sulfate salts of sodium, potassium and magnesium, was authorised in adults, via the decentralised procedure (DCP), for bowel cleansing prior to any procedure requiring a clean bowel (e.g. bowel visualisation including endoscopy and radiology or surgical procedures). The post-marketing commitments that accompanied the approval included the requirement for the MAH to conduct a drug utilisation study (DUS) to assess drug utilisation in the real life setting in a representative sample of the European target population. The PASS protocol version 4 was endorsed by PRAC in March 2015 (see PRAC minutes March 2015).

The final study report dated 2 February 2018 was submitted to EMA by the MAH Ipsen Pharma SAS on 6 March 2018. 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 'a multicentre, European, observational, DUS of BLI800 as a bowel cleansing preparation', the PRAC considered that supplementary information was required before a recommendation could be made on the benefit-risk balance of medicinal products containing sulfate salts of sodium, potassium and magnesium concerned by the PASS final report. The MAH should provide within 60 days further clarifications on the statistical method, the participants and the adverse events/adverse reactions. A 60 day-assessment timetable will be applied.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[67]

See Annex I 17.4.

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

See also Annex I 17.5.

7.5.1. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/ANX 002.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to ANX 002.4 [first interim results for PASS D7120R00003 (previously RO-2455-403-RD): a long-term post-marketing observational study exploring the safety of roflumilast in the treatment of chronic obstructive pulmonary disease (COPD), combined data results from Sweden, Germany and the US (Annex II-D condition) [final clinical study report (CSR) expected in March 2031]] as per the request for supplementary information (RSI) adopted in January 2018

Background

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

Roflumilast is a phosphodiesterase type 4 (PDE4) inhibitor, a non-steroidal anti-inflammatory agent used for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

The MAH had committed to conduct a long-term comparative observational safety study to compare the incidences of all-cause mortality, major cardiovascular events, new diagnosis of cancer, all-cause hospitalisation, hospitalisation related to respiratory disease, suicide or hospitalisation for suicide attempt, and new diagnosis of depression, tuberculosis or viral hepatitis B or C in roflumilast-treated COPD patients compared with COPD patients not treated with roflumilast according to the conditions included in the Annex II of the marketing authorisation. A revised protocol following substantial amendment 7 to the protocol agreed in October 2011 by CHMP for this imposed PASS study (D7120R00003, previously RO-2455-403-RD) entitled 'a long-term comparative observational safety study to evaluate mortality rate, including cardiovascular, suicide and cancer death rates and incidence rate of hospitalisations in treated chronic obstructive pulmonary disease (COPD) patients compared to match COPD patients not treated with roflumilast' was endorsed by PRAC in February 2017 (see PRAC minutes February 2017). The interim results of this imposed PASS study (D7120R00003, previously RO-2455-403-RD) were submitted by the MAH, AstraZeneca, and assessed by the Rapporteur for PRAC review.

Summary of advice

- Based on the PRAC review of the PASS interim report, the PRAC considered that additional information, i.e. characteristics of patients, clarifications on controls, discussion on the limitations of the databases, categories of exposure, clarifications on variables, and results of all the secondary outcomes, should be provided. A revised interim report should be submitted to EMA within 60 days and will follow a 60 days review procedure by the PRAC.

7.6. Others

See also Annex I 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

8.3.1. Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/R/0023 (with RMP)

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

Background

Fortacin is a medicine centrally authorised in 2013 containing a combination of lidocaine and prilocaine, local anaesthetics. Fortacin (lidocaine/prilocaine) is indicated for the treatment of primary premature ejaculation in adult men.

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

Summary of advice

- Based on the review of the available pharmacovigilance data for Fortacin (lidocaine/prilocaine) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds relating to exposure of an insufficient number of patients due to the recent marketing and limited period on the market of the medicinal product.
- In addition, the PRAC supported updating the product information[68] to remove the drug utilisation study (DUS) designed to characterize real clinical practice and the patients who are prescribed the product.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

[68] Update of Annex II

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. Dolutegravir – TIVICAY (CAP) - EMEA/H/C/002753/II/0034 Dolutegravir, abacavir, lamivudine – TRIUMEQ (CAP) - EMEA/H/C/002754/II/0053

Applicant(s): ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams; PRAC representative of the CHMP Rapporteur's delegation: Qun-Ying Yue

Guzman

Scope: Consultation on type II variations to update section 4.8 of the SmPC to add the new adverse drug reactions (ADRs) 'acute hepatic failure' and 'weight increase' based on post-marketing and clinical trial data. The package leaflet is updated accordingly

Background

Tivicay is a centrally authorised medicine containing dolutegravir (DTG), a 2-metal binding integrase inhibitor, and is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV) infected adults, adolescents and children above 6 years of age.

Triumeq is a centrally authorised medicine containing a combination of dolutegravir, a 2-metal binding integrase inhibitor, abacavir sulphate (ABC), a nucleoside reverse transcriptase inhibitor (NRTI) and lamivudine (3TC), a nucleoside reverse transcriptase inhibitor (NRTI). Triumeq (DTG/ABC/3TC) is indicated for the treatment of HIV infected adults and adolescents above 12 years of age weighing at least 40 kg.

A type II variation proposing to update the product information of Tivicay (DTG) and Triumeq (DTG/ABC/3TC) to add the undesirable effects weight increased and liver hepatic failure with a frequency 'uncommon' and 'rare' respectively is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, with regard to the issue of hepatic failure, the PRAC agreed on the addition of the undesirable effect together with clarification of the proposed frequency. Of note, the risk of hepatobiliary disorders is also listed in the RMP and the risk is being further characterised within the

EuroSIDA[69] cohort. Considering that the utility of a specific hepatic function monitoring strategy is not evident, a new wording on the matter in the product information (PI) was not supported for the time being.

- Regarding the issue of weight increase, based on the review of the available information, the PRAC considered that data were insufficient to conclude on any association between a DTG-containing anti-retroviral therapy (ART) regimen and weight increase. The PRAC advised that the MAH should continue to monitor this issue in the next PSURs with a focus on additional clinical trial data.

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. Tretinoin[70] (NAP)

Applicant: Cheplapharm Arzneimittel GmbH (Vesanoid)

PRAC Lead: Martin Huber

Scope: Consultation on the need for updated communication materials for tretinoin-containing products following the completion of the referral procedure on retinoids under Article 31 of Directive 2001/83/EC in March 2018 (EMEA/H/A-31/1446)

Background

A referral procedure under Article 31 of Directive 2001/83/EC was concluded at PRAC in February 2018 for retinoid[71]-containing medicines indicated for the treatment of several conditions mainly affecting the skin such as acne, severe chronic hand eczema

[69] A prospective observational cohort study to assess the impact of antiretroviral drugs on the outcome of the general population of HIV-infected patients living in Europe
[70] For oral use, in oncology indication(s) only
[71] Acitretin; adapalene; alitretinoin; bexarotene; isotretinoin; tazarotene; tretinoin

unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders[72], evaluating measures currently in place for oral and topical retinoids for pregnancy prevention and the possible risk of neuropsychiatric disorders (EMEA/H/A-31/1446). In its conclusions, the PRAC recommended to vary[73] the terms of the marketing authorisations for retinoid-containing medicines (see EMA Press Release (EMA/69925/2018) entitled 'PRAC recommends updating measures for pregnancy prevention during retinoid use - Warning on possible risk of neuropsychiatric disorders also to be included for all oral retinoids') and agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan. For further background, see PRAC minutes February 2018).

Following conclusion of a variation procedure recently finalised (FR/H/xxxx/WS/52), the absolute contraindication of use during pregnancy was deleted from the product information of Vesanoid (oral tretinoin) and replaced with a recommendation that it must not be used during pregnancy unless the woman's condition requires treatment for certain oncological conditions. Of note, Vesanoid (oral tretinoin) is only indicated in the treatment of acute promyelocytic leukaemia (APL) whereas topical tretinoin is indicated in the treatment of acne.

Following an enquiry by the MAH of Vesanoid (oral tretinion) to EU NCAs, Germany anticipated some issues regarding the implementation of the direct healthcare professional communication (DHPC) agreed as an outcome of the referral procedure for Vesanoid (oral tretinoin). The MAH requested the NCAs that Vesanoid (oral tretinoin) should be excluded from the DHPC.

In this context, Germany requested PRAC advice on its assessment that overall the conclusion of the Article 31 referral procedure for retinoids was unchanged and proposals for minor updates of the DHPC.

Summary of advice

- Based on the review of the available information, the PRAC considered that the overall conclusions of the referral (EMEA/H/A-31/1446) under Article 31 of Directive 2001/83/EC on retinoids as set out in the PRAC assessment report adopted at its February 2018 meeting (see PRAC minutes February 2018) do not require any amendment following the conclusions of the procedure FR/H/xxxx/WS/52 amending the product information of Vesanoid (oral tretinoin).
- Indeed, although pregnancy is no longer listed as a contraindication to the use of Vesanoid in the product information[74], it is indicated in the section[75] on fertility, pregnancy and lactation that tretinoin is teratogenic and Vesanoid (oral tretinoin) must not be used during pregnancy, especially during the first trimester, and in women of childbearing potential not using contraception, unless the clinical condition of the woman (severity of the patient's condition, urgency of the treatment) requires

[72] Tretinoin may also be used to treat promyelocytic leukaemia
[73] For all oral retinoids containing acitretin, alitretinoin and isotretinoin: update of SmPC section 4.4. The package leaflet and the labelling are updated accordingly. For all oral retinoids containing acitretin, tretinoin and bexarotene: update of SmPC section 4.4. The package leaflet is updated accordingly. For all oral retinoids products containing alitretinoin and isotretinoin: update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. For all topical retinoids containing adapalene, alitretinoin, isotretinoin, tretinoin and tazarotene: update of SmPC sections 4.3 and 4.6. The package leaflet is updated accordingly
[74] SmPC section 4.3
[75] SmPC section 4.6

tretinoin for the treatment of newly diagnosed, relapsed or APL which is refractory to chemotherapy.

- The wording of the DHPC agreed as the outcome of the referral procedure remains correct. The PRAC therefore considers that no changes to the DHPC are necessary at European level. Amendments could however be introduced at national level for clarity if considered necessary by the national competent authorities. Concerning the DHPC communication plan, it was reiterated that all MAHs involved in the referral procedure should disseminate the DHPC. The primary recipients for the DHPC are general practitioners (GPs), dermatologists, psychiatrists, pharmacists, gynaecologists and obstetricians. Unless requested at national level, hemato-oncologists are not expected to receive the DHPC.

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

None

12.4. Cooperation within the EU regulatory network

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

The EMA Secretariat provided the PRAC with a status update on the Brexit preparedness business continuity plan, including Committees' operational preparedness activities in view of the withdrawal of the UK from the European Union.

12.4.2. PRAC strategic review and learning meeting (SRLM) – results from the questionnaire on adverse drug reactions (ADR) to vaccines and pharmacovigilance newsletter

PRAC lead: Eva Jirsová

Following the April 2018 PRAC strategic review and learning meeting (SRLM) held in Prague, Czech Republic, under the Bulgarian Presidency, the Czech PRAC member presented to the PRAC the results of a questionnaire survey made amongst the PRAC delegates on 'adverse drug reactions (ADRs) to vaccines and pharmacovigilance newsletters'.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q1 2018 and predictions

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

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the GPAG progress highlights including the ongoing review by the group of the dedicated section on PSURs of the 'GVP Product- or Population-Specific Considerations IV: Paediatric population' and the proposal in relation to the PSUR periodicity.

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 May 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 May 2018, the updated EURD list was adopted by the CHMP and CMDh at their May 2018 meetings and published on the EMA website on 17/05/2018, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the SMART Working Group (SMART WG) meeting held on 14 May 2018 and the follow-up discussions on practices to establish the periodicity of monitoring of medicinal products. The vast majority of NCAs determine the frequency following the risk-based principles stablished in 'GVP Module IX on signal management' (EMA/827661/2011 Rev 1*).

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on 30/05/2018 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

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

As a follow-up to the March 2018 PRAC discussion (see PRAC minutes March 2018), the EMA Secretariat presented the revised draft Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population- specific considerations IV: Paediatric population and this was adopted by the PRAC. Should there be any further comments from EMA committees, the PRAC will be informed accordingly before publication of the final document on the EMA website.

12.20.2. Initial marketing authorisation applications (MAA) and Generics MAA – review of rapporteur assessment report templates – roll out Spring 2018

The EMA Secretariat presented to the PRAC the results of a review performed by EMA of the 'Rapporteurs assessment reports templates' for marketing authorisation applications (MAA) and Generics MAA. Of note, the RMP part has been revised in line with the RMP template Revision 2. PRAC delegates were invited to provide written comments to by 30 May 2018.

13. Any other business

Next meeting on: 11-14 June 2018

14. Annex I – Signals assessment and prioritisation[76]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[77].

14.1.1. Apixaban – ELIQUIS (CAP)

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of neutropenia

EPITT 19187 – New signal

Lead Member State: NL

14.1.2. Dulaglutide – TRULICITY (CAP)

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

PRAC Rapporteur: Carmela Macchiarulo

Scope: Signal of acute kidney injury

EPITT 19204 – New signal

Lead Member State: IT

14.1.3. Ipilimumab – YERVOY (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Signal of cytomegalovirus gastrointestinal infection

EPITT 19207 – New signal

Lead Member State: NL

14.1.4. Meningococcal group b vaccine (rDNA, component, adsorbed) – BEXSERO (CAP)

Applicant(s): GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

[76] [76] 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

[77] 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

Scope: Signal of meningism

EPITT 19224 – New signal

Lead Member State: SE

14.1.5. Niraparib – ZEJULA (CAP)

Applicant(s): Tesaro UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Signal of potential occurrence of embolic and thrombotic events

EPITT 19206 – New signal

Lead Member State: UK

14.1.6. Nivolumab – OPDIVO (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of cholangitis sclerosing

EPITT 19203 – New signal

Lead Member State: DE

14.1.7. Teriflunomide – AUBAGIO (CAP)

Applicant(s): Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Signal of dyslipidaemia

EPITT 19227 – New signal

Lead Member State: DE

14.1.8. Tocilizumab – ROACTEMRA (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of noninfectious encephalitis

EPITT 19197 – New signal

Lead Member State: DE

14.1.9. Trastuzumab – HERCEPTIN (CAP), HERZUMA (CAP), ONTRUZANT (CAP); trastuzumab emtansine - KADCYLA (CAP); pertuzumab – PERJETA (CAP)

Applicant(s): Celltrion Healthcare Hungary Kft. (Herzuma), Roche Registration GmbH (Herceptin, Kadcyla, Perjeta), Samsung Bioepis UK Limited (SBUK) (Ontruzant)

PRAC Rapporteur: To be appointed

Scope: Signal of multiple sclerosis relapse

EPITT 19208 – New signal

Lead Member States: DE, DK

14.2. New signals detected from other sources

14.2.1. Oxybutynin – KENTERA (CAP), NAP; carbamazepine (NAP)

Applicant(s): Nicobrand Limited (Kentera), various

PRAC Rapporteur: To be appointed

Scope: Signal on drug interaction between oxybutynin and carbamazepine resulting in seizures and carbamazepine overdose secondary to carbamazepine plasma level variations

EPITT 19233 – New signal

Lead Member State: BE

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Deferiprone - EMEA/H/C/004710

Scope: Treatment of iron overload in thalassemia major

15.1.2. Gefitinib - EMEA/H/C/004826

Scope: Treatment of non-small cell lung cancer (NSCLC)

15.1.3. Paclitaxel - EMEA/H/C/004441

Scope: Treatment of metastatic breast cancer

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. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0060

Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 8.0) to introduce the new RMP template, update some milestones of the pharmacovigilance plan and delete some safety concerns from the educational material to healthcare professionals

15.2.2. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0051

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 8.0) to introduce the new RMP template, update some milestones of the pharmacovigilance plan and delete some safety concerns from the educational material to healthcare professionals

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

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

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

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

15.2.5. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS1364/0092; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS1364/0021

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of the RMP (version 12.0) in order to include the changes requested in the conclusions of EMEA/H/C/PSUSA/00002511/201701 procedure finalised in September 2017, updating the safety specifications and risk minimisation measures. The pharmacovigilance plan is also updated. The draft protocol for a non-interventional non-imposed PASS (A0081359) entitled 'a population-based cohort study of pregabalin to

characterize pregnancy outcomes' is submitted. The MAH took the opportunity to include minor updates and to align the RMP to the most recent template (revision 2)

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

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

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

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

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

15.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0007/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Grouped variations consisting of: 1) extension of indication to include in combination with bevacizumab, paclitaxel and carboplatin the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC), based on the interim results of study GO29436: a phase 3, open-label, randomized study of atezolizumab in combination with carboplatin+paclitaxel with or without bevacizumab compared with carboplatin+paclitaxel +bevacizumab in chemotherapy-naïve patients with stage IV NSCLC (IMpower 150). As a consequence sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated; 2) update of section 4.8 of the SmPC in order to update the monotherapy safety data and reflect the largest pooled monotherapy population available (including data from study IMvigor211: a phase 3, open-label, multicentre, randomized study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy, and study PCD4989g: a phase 1, open-label, dose-escalation study of the safety and pharmacokinetics of atezolizumab administered intravenously as a single agent to patients with locally advanced or metastatic solid tumours or hematologic malignancies). The package leaflet and the RMP (version 4.0) are updated accordingly. In addition, the MAH took the opportunity to make small corrections and formatting changes throughout the SmPC

15.3.3. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0055, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the frontline treatment of adult patients with CD30+ advanced Hodgkin lymphoma (HL) in combination with chemotherapy, based on data from ECHELON-1 (C25003): a phase 3 multicentre, randomised, open-label study comparing the modified progression-free survival (mPFS) obtained with brentuximab vedotin, doxorubicin, vinblastine and dacarbazine versus the mPFS obtained with doxorubicin, bleomycin, vinblastine and dacarbazine. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 13) are updated accordingly. Furthermore, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

15.3.4. 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 5 mL 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

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

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

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

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

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

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

double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM. The package leaflet and the RMP (version 7.2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest QRD template (version 10)

15.3.7. Trametinib - MEKINIST (CAP) - EMEA/H/C/002643/WS1274/0023; Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/WS1274/0031

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the combination adjuvant treatment with trametinib and dabrafenib of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the Mekinist and Tafinlar SmPCs are updated. The package leaflet and the RMP (version 14.0 for Mekinist and version 9.0 for Tafinlar) are updated accordingly. In addition, the MAH took the opportunity to correct some typos throughout the Mekinist and Tafinlar product information, to include a cross reference to the Mekinist SmPC in section 4.6 of the Tafinlar SmPC regarding fertility as well as to update the list of local representatives for Bulgaria, Hungary, Estonia, Latvia and Lithuania in the package leaflet of both products

15.3.8. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1344/0025; FORXIGA (CAP) - EMEA/H/C/002322/WS1344/0044

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include the treatment of insufficiently controlled type 1 diabetes mellitus (T1DM) as an adjunct to insulin, when insulin does not provide adequate glycaemic control, for Forxiga and Edistride (dapagliflozin). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and RMP (version 16) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the SmPC and package leaflet

15.3.9. Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/II/0059

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include a paediatric indication for Philadelphia chromosome positive acute lymphoblastic leukaemia. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 16.0) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the product information

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 CYP3A4[78] 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. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0039/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include patients with non-metastatic castration-resistant prostate cancer (CRPC). As a consequence, sections 4.1 and 5.1 of the SmPC are updated based on the supportive clinical study results of study MDV3100-14 (PROSPER): a phase 3 randomized controlled study, designed to investigate the safety and efficacy of enzalutamide in patients with non-metastatic castration-resistant prostate cancer; study MDV3100-09 (STRIVE): a multicentre phase 2 study to investigate the safety and efficacy of enzalutamide versus bicalutamide in men with non-metastatic or metastatic castration-resistant prostate cancer; and based on supportive non-clinical data from 7 new reports. The package leaflet and the RMP (version 12.1) are updated accordingly; 2) update of sections 4.4, 4.7, 4.8 and 5.2 of the SmPC in order to amend the warning on possible association with seizure, the effects on driving or operating machines, the identified adverse reactions and to amend the 'race' subsection regarding pharmacokinetic properties based on the results from the completed study PROSPER and study PREVAIL: a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral enzalutamide in chemotherapy-naive subjects with progressive metastatic prostate cancer who have failed androgen deprivation therapy; as well as the updated integrated clinical safety database. The package leaflet is updated accordingly

15.3.12. Febuxostat - ADENURIC (CAP) - EMEA/H/C/000777/II/0047

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to reflect the results of preclinical study MRPO-2015-PKM-005: 'a pharmacokinetic study of azathioprine in the rat after one-week daily oral treatment at three different dosages and with the concomitant oral administration of febuxostat or allopurinol' and clinical study REP-POPPK-MRP-2015-PKM-005: 'a population-based pharmacokinetic (Pop-PK) extrapolation

[78] Cytochrome P 450 3A4

model analysis from preclinical MRPO-2015-PKM-005, investigating the drug-drug interaction with azathioprine when co-administered with febuxostat. The RMP (version 6.0) is updated accordingly. In addition, the MAH took the opportunity to correct typing errors and to bring the product information in line with the latest QRD template (version 10)

15.3.13. Fidaxomicin - DIFICLIR (CAP) - EMEA/H/C/002087/II/0032/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 5.1 of the SmPC in order to update the safety information following final results from study ANEMONE listed as an additional pharmacovigilance activity in the RMP: a drug utilisation study (DUS) of the use of oral fidaxomicin in routine clinical settings. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet; 2) update of sections 4.4 and 5.2 of the SmPC in order to update the safety information based on the results from study PROFILE: an open label study designed to evaluate the pharmacokinetics of fidaxomicin in inflammatory bowel disease (IBD) subjects with *Clostridium difficile* infection (CDI). The package leaflet and the RMP (version 9.0) are updated accordingly

15.3.14. 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

15.3.15. Florbetapir (^{18}F) - AMYVID (CAP) - EMEA/H/C/002422/II/0029

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Update of section 4.4 of the SmPC following the final report from study I6E-MC-AVBF (listed as a category 3 study in the RMP): a non-interventional category 3 study, a European drug usage survey to assess the usage pattern of Amyvid (florbetapir (^{18}F)) in the EU. The RMP (version 3.1) is updated accordingly

15.3.16. Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP) - EMEA/H/C/004781/WS1369/0001; TRELEGY ELLIPTA (CAP) - EMEA/H/C/004363/WS1369/0001

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to modify the current approved chronic obstructive

pulmonary disease (COPD) therapeutic indication to 'maintenance treatment in adult patients with moderate to severe COPD'. As a consequence, sections 4.1, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 02) are updated accordingly. This is based on the results of study CTT116855: a phase 3, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with COPD; study 200812: a phase 3B, 24-week randomised, double-blind study to compare 'closed' triple therapy (FF/UMEC/VI) with 'open' triple therapy (FF/VI + UMEC) in subjects with COPD; and the population pharmacokinetics (PK) report 208059

15.3.17. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP) - EMEA/H/C/000703/WS1349/0076/G; SILGARD (CAP) - EMEA/H/C/000732/WS1349/0064/G

Applicant: MSD Vaccins

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations consisting of an update of section 5.1 of the SmPC following the final results from two long-term follow-up (LTFU) studies, namely: study V501-020-21 (listed as a category 3 study in the RMP): 1) an extension of study V501-020, the pivotal efficacy study of the quadrivalent human papillomavirus (qHPV) vaccine in young men 16 to 26 years of age, in order to assess the effectiveness and immunogenicity of the qHPV vaccine for up to 10 years of follow-up (fulfilment of Gardasil MEA 070.3 and Silgard MEA 069.3); 2) extension study V501-16: extension of a base study MSD-sponsored randomized clinical trial assessing the immunogenicity of a 2 dose schedule of qHPV in adolescents 9 to 13 years of age compared to a 3-dose schedule in young women 16 to 26 years of age. The study provides additional immunogenicity follow-up through 5 years post-vaccination (fulfilment of Gardasil REC 083 and Silgard REC 080).The RMP (version 12) is updated accordingly. In addition, the MAH took the opportunity to bring the product information (PI) in line with the latest QRD template (version 10)

15.3.18. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0209

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

15.3.19. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS1278/0042; Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS1278/0053

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Opdivo and Yervoy SmPCs are updated. The package leaflet and the RMP (version 19.0 for Yervoy and version 13.0 for Opdivo) are updated accordingly. In addition, the MAH took the opportunity to correct some typos throughout the Yervoy (ipilimumab) and Opdivo (nivolumab) product information

15.3.20. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0063/G, Orphan

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variations consisting of: 1) extension of indication to include the combination regimen of the ivacaftor 150 mg evening dose and Symkevi (tezacaftor/ivacaftor); to add a blister card pack presentation containing 28-tablets for the 150 mg film-coated tablets (EU/1/12/782/005); 2) addition of a blister pack presentation containing 28-tablets for the 150 mg film-coated tablets (EU/1/12/782/006). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 6.5 and 8 of the SmPC are updated. Annex A, the package leaflet, labelling and RMP (version 6.0) are updated accordingly

15.3.21. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/II/0064

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of section 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the safety and efficacy information based on interim results from study GS-US-334-0154 (listed as a category 3 study in the RMP): a study to evaluate the safety, efficacy and pharmacokinetics in patients treated with ledipasvir/sofosbuvir fixed-dose combination for 12 weeks in genotype 1 or 4 hepatitis C virus (HCV)-infected subjects with renal insufficiency. The package leaflet and the RMP (version 3.2) are updated accordingly

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

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Update of Annex II to amend the key elements of the risk minimisation programme with information on prescription duration and to revise due dates of two post-authorisation non-interventional, safety studies CC-5013-MDS-10 and CC-5013-MDS-1 on patients with myelodysplastic syndromes (MDS) treated with lenalidomide to gather safety data on the use of lenalidomide in MDS patients and monitor off-label use. Section 4.4 of the SmPC is updated accordingly. The RMP (version 35) is updated in line

with GVP module V on 'Risk management systems' revision 1, in order to reclassify and/or rename known safety concerns associated with the use of Revlimid (lenalidomide). As a consequence, Annex IID is updated

15.3.23. 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

15.3.24. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0023, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Patrick Batty

Scope: Update of section 5.1 of the SmPC in order to update the overall survival data based on the final results from study BO21004/CLL11 (listed as a category 3 study in the RMP): a pivotal study evaluating the efficacy and safety of obinutuzumab as therapy for patients with previously untreated chronic lymphocytic leukaemia (CLL) with comorbidities. The RMP (version 4.0) is updated accordingly. In addition, the MAH took the opportunity to format the listing of 'other side effects' and correct the term 'heart attack to heart failure' in section 4 of the package leaflet

15.3.25. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to include information on vaccination based on interim results from study BN29739 (listed as a category 3 study in the RMP): a phase 3b, multicentre, randomised, parallel-group, open-label study to evaluate the effects of ocrelizumab on immune response in patients with relapsing forms of multiple sclerosis (MS). The package leaflet and the RMP (version 2.0) are updated accordingly. The RMP version 2.0 has also been submitted

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

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

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

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

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

15.3.28. Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/II/0016/G

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of an update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1 5.2 and 5.3 of the SmPC with the final results from 2 studies, namely: 1) study DFCI 11-001 (listed as a category 3 study in the RMP): a phase 2, open-label, randomized, multicentre study to determine the safety and feasibility of administering an investigational asparaginase product (asparaginase formulation) compared with Oncaspar (pegaspargase) in subjects aged 1 to <22 years with newly diagnosed acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma; 2) study AALL07P4 (listed as a category 3 study in the RMP): a multicentre, open label, randomized, active-controlled, parallel design clinical pilot study conducted to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, immunogenicity and efficacy of an investigational asparaginase product in comparison with Oncaspar (pegaspargase) in patients aged 1 to <31 years newly diagnosed with high risk B-precursor ALL. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.29. Plerixafor - MOZOBIL (CAP) - EMEA/H/C/001030/II/0034, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include paediatric patients aged 1 to 18 years for Mozobil (plerixafor). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 10) are updated accordingly

15.3.30. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0058

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include the prevention of stroke, myocardial infarction and cardiovascular death, and for the prevention of acute limb ischaemia and mortality in adult patients with coronary artery disease (CAD) or peripheral artery disease (PAD) for Xarelto 2.5 mg co-administered with acetylsalicylic acid. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The package leaflet, labelling and the RMP (version 11.1) are updated accordingly. In addition, section 4.8 of the SmPC is updated for all other dose strengths (10/15/20 mg) of Xarelto with relevant exposure information based on the provided clinical data

15.3.31. Rufinamide - INOVELON (CAP) - EMEA/H/C/000660/II/0045, Orphan

Applicant: Eisai Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include the treatment of seizures associated with Lennox Gastaut syndrome in patients of 1 year of age and older as adjunctive therapy. As a consequence, sections 4.1, 4.2, 4.5, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 10.0) are updated accordingly. In addition, the MAH took the opportunity to include minor corrections in the product information and to update the name and contact details of the local representative in Belgium and Luxembourg. Furthermore, the product information is brought in line with the latest QRD template (version 10)

15.3.32. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0033/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include information on dose up-titration for psoriatic arthritis (PsA) and update the radiographic sub-section for PsA based on results from the 24-week data from study CAIN457F2342: a phase 3, randomized, double-blind, placebo controlled multicentre study of subcutaneous secukinumab (150 mg and 300 mg) in prefilled syringe to demonstrate efficacy (including inhibition of structural damage), safety, and tolerability up to 2 years in subjects with active psoriatic arthritis (FUTURE 5), the pooled data from PsA phase 3 studies, the pooled data from patients who up-titrated their secukinumab dose in the following studies, namely: study CAIN457F2306E1: a three-year extension study to evaluate the long term efficacy, safety and tolerability of secukinumab in patients with active PsA; study CAIN457F2312: efficacy at 24 weeks with long term safety, tolerability and efficacy up to 5 years of secukinumab in patients of active psoriatic arthritis (FUTURE 2) as well as study CAIN457F2318: 24 week efficacy and 3-year safety and efficacy of secukinumab in active psoriatic arthritis, and long-term study observations which demonstrate higher rates of discontinuation for patients on secukinumab 150 mg compared to patients on secukinumab 300 mg. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of

local representatives in the package leaflet and to bring it in line with the latest approved SmPC as per procedure IB/0028 finalised in July 2017; 2) the RMP (version 3.0) is updated to include suicidal ideation and behaviour as an important potential risk in the RMP and including minor administrative/editorial changes (LEG 005.2)

15.3.33. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/II/0002/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped quality variations. The RMP (version 2.0) is updated accordingly

15.3.34. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0005/G

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Grouped variations consisting of: 1) extension application (line extension) to introduce a new strength (10 mg film coated tablets); 2) extension of indication to include 'the induction and maintenance of treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent'. The RMP (version 2.0) is updated accordingly

15.3.35. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/II/0048/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of section 5.3 of the SmPC with information on mean bioavailability of vemurafenib at steady state based on study GO28395: a phase 1, open-label, absolute bioavailability study of vemurafenib in patients with BRAFV600 mutation-positive malignancies; 2) Submission of the clinical study report (CSR) for study GO27826: a phase 3, randomised, double-blind, placebo-controlled study of vemurafenib (RO5185426) adjuvant therapy in patients with surgically resected, cutaneous BRAF-mutant melanoma at high risk for recurrence. The RMP (version 11.0) is updated accordingly. The MAH took the opportunity to include some minor editorial changes have been included in the product information (PI)

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. Bexarotene - TARGRETIN (CAP) - PSUSA/00000404/201709

Applicant: Eisai Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.2. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/201710

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.3. Ceftaroline fosamil - ZINFORO (CAP) - PSUSA/00010013/201710

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.4. Ceritinib - ZYKADIA (CAP) - PSUSA/00010372/201710

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.5. Cerliponase alfa - BRINEURA (CAP) - PSUSA/00010596/201710

Applicant: BioMarin International Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.6. Cetuximab - ERBITUX (CAP) - PSUSA/00000635/201709

Applicant: Merck KGaA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.7. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - PSUSA/00010590/201710

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.8. Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/201710

Applicant: Pharming Group N.V

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.9. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/201710

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.10. Delamanid - DELTYBA (CAP) - PSUSA/00010213/201710

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.11. Dinutuximab beta - QARZIBA (CAP) - PSUSA/00010597/201711

Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.12. Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed) - TRITANRIX HB (Art 58[79]) - EMEA/H/W/003838/PSUV/0010

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné; PRAC Co-rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUR procedure

16.1.13. Flutemetamol (^{18}F) - VIZAMYL (CAP) - PSUSA/00010293/201710

Applicant: GE Healthcare Ltd

[79] 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: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.14. Granisetron[80] - SANCUSO (CAP) - PSUSA/00010101/201710

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.15. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/201710

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.16. Insulin glargine - ABASAGLAR (CAP); LANTUS (CAP); LUSDUNA (CAP); TOUJEO (CAP) - PSUSA/00001751/201710

Applicant(s): Eli Lilly Nederland B.V. (Abasaglar), Sanofi-Aventis Deutschland GmbH (Lantus, Toujeo), Merck Sharp & Dohme Limited (Lusduna)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.17. Irinotecan[81] - ONIVYDE (CAP) - PSUSA/00010534/201710

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.18. Lurasidone - LATUDA (CAP) - PSUSA/00010114/201710

Applicant: Aziende Chimiche Riunite Angelini Francesco S.p.A.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.19. Macitentan - OPSUMIT (CAP) - PSUSA/00010115/201710

Applicant: Actelion Registration Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

[80] Transdermal patch only
[81] Liposomal formulations only

16.1.20. Melatonin - CIRCADIN (CAP) - PSUSA/00001963/201709

Applicant: RAD Neurim Pharmaceuticals EEC Ltd.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.21. Miglustat - ZAVESCA (CAP) - PSUSA/00002062/201710

Applicant: Actelion Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.22. Obinutuzumab - GAZYVARO (CAP) - PSUSA/00010279/201710

Applicant: Roche Registration GmbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.23. Ocriplasmin - JETREA (CAP) - PSUSA/00010122/201710

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.24. Ofatumumab - ARZERRA (CAP) - PSUSA/00002202/201710

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.25. Olaratumab - LARTRUVO (CAP) - PSUSA/00010541/201710

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.26. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – FOCLIVIA (CAP); prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - PSUSA/00010008/201710

Applicant: Seqirus S.r.l

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.27. Para-aminosalicyic acid[82] - GRANUPAS (CAP) - PSUSA/00010171/201710

Applicant: Lucane Pharma

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.28. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/201710

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.29. Pasireotide - SIGNIFOR (CAP) - PSUSA/00009253/201710

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.30. Patiromer - VELTASSA (CAP) - PSUSA/00010618/201710

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.31. Pazopanib - VOTRIENT (CAP) - PSUSA/00002321/201710

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.32. Posaconazole - NOXAFIL (CAP) - PSUSA/00002480/201710

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.33. Prucalopride - RESOLOR (CAP) - PSUSA/00002568/201710 (with RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

[82] Centrally authorised product(s) only

16.1.34. Siltuximab - SYLVANT (CAP) - PSUSA/00010254/201710

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.35. Sofosbuvir, ledipasvir - HARVONI (CAP) - PSUSA/00010306/201710

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.36. Stiripentol - DIACOMIT (CAP) - PSUSA/00002789/201711

Applicant: Biocodex

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.37. Strontium ranelate - OSSEOR (CAP); PROTELOS (CAP) - PSUSA/00009301/201709

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.38. Sulfur hexafluoride - SONOVUE (CAP) - PSUSA/00002822/201709

Applicant: Bracco International B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.39. Tofacitinib - XELJANZ (CAP) - PSUSA/00010588/201711

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

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

None

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

16.3.1. Bromazepam (NAP) - PSUSA/00000435/201708

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.2. Dermatophagoides pteronyssinus, dermatophagoides farina[83] (NAP) - PSUSA/00010582/201709

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.3. Desflurane (NAP) - PSUSA/00000958/201709

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.4. Dexibuprofen (NAP) - PSUSA/00000996/201708

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.5. Dornase alfa (NAP) - PSUSA/00001164/201709

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.6. Etidronate (NAP) - PSUSA/00001320/201709

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

[83] Allergen for therapy, oromucosal use only, products authorised via mutually recognition procedure (MRP) and decentralised procedure (DCP) only

16.3.7. Fenoterol[84] (NAP) - PSUSA/00001366/201709

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.8. Human von Willebrand factor (NAP) - PSUSA/00001642/201709

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.9. Idebenone[85] (NAP) - PSUSA/00001721/201709

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

16.3.10. Latanoprost[86] (NAP) - PSUSA/00001834/201710

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.11. Losartan (NAP) - PSUSA/00001912/201709

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.12. Lysine acetylsalicylate (NAP) - PSUSA/00001921/201709

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.13. Metronidazole, neomycin, nystatin (NAP) - PSUSA/00010508/201709

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

[84] Respiratory indications only
[85] Non-centrally authorised products only
[86] Medicinal products with paediatric indication only

16.3.14. Midazolam[87] (NAP) - PSUSA/00002057/201709

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.15. Modafinil (NAP) - PSUSA/00010242/201708

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.16. Piperacillin, tazobactam (NAP) - PSUSA/00002425/201709

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.17. Ropivacaine (NAP) - PSUSA/00002662/201709

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.18. Terbinafine (NAP) - PSUSA/00002896/201709

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.3.19. Treosulfan (NAP) - PSUSA/00009319/201708

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.20. Tretinoin[88] (NAP) - PSUSA/00003016/201708

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

[87] Except oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures
[88] Topical formulations only

16.3.21. Vigabatrin (NAP) - PSUSA/00003112/201709

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/LEG 028

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

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

16.4.2. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/LEG 029

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Detailed review on the concomitant use of apixaban and moderate inhibitors of CYP3A4[89] and P-glycoprotein in nonvalvular atrial fibrillation (NVAF) patients as requested in the conclusions of PSUSA/00000226/201705 adopted at the December 2017 PRAC

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[90]

17.1.1. Cidofovir (NAP) - EMEA/H/N/PSP/S/0052.2

Applicant: Emcure Pharma UK Ltd (Cidofovir Emcure Pharma)

PRAC Rapporteur: Julie Williams

Scope: MAH's response to PSP/S/0052.1 [protocol for 'a non-interventional, prospective, exposure (safety outcome) registry study of cidofovir to further elucidate the characteristics of the different patient populations for cidofovir use, gather details of adverse events and patient outcome following treatment in a specified indication'] as per the request for supplementary information (RSI) adopted in July 2017

[89] Cytochrome P450 3A4
[90] In accordance with Article 107n of Directive 2001/83/EC

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[91]

17.2.1. Agalsidase beta - FABRAZYME (CAP) - EMEA/H/C/000370/MEA 060.3

Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a survey to assess the effectiveness of the patient home infusion educational materials in EU countries where the material is implemented [report submission due date: March 2019]

17.2.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/MEA 010

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of a protocol for an observational study to evaluate the effectiveness of healthcare professional (HCP) educational materials, in particular the HCP brochure aiming at facilitating early recognition and intervention of the following important immune-related risks: pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus (T1DM), neuropathies, meningoencephalitis, pancreatitis, and infusion-related reactions [submission of the final clinical study report (CSR): December 2022]

17.2.3. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/MEA 002.1

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Doris Stenver

Scope: MAH's response to MEA 002 (listed as a category 3 study in the RMP) [protocol for a non-interventional cohort study to assess characteristics and management of patients with Merkel cell carcinoma in Germany [final report expected in Q1 2024]] as per the request for supplementary information (RSI) adopted in January 2018

17.2.4. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 003.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 003 [protocol for an observational safety study using an existing database, study I4V-MC-B004: a retrospective cohort study to assess the long-term safety of baricitinib compared with other therapies used in the treatment of adults with moderate-to-severe rheumatoid arthritis in the course of routine clinical care [final report due date: 31/03/2031]] as per the request for supplementary information (RSI) adopted in December 2017

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

17.2.5. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 004.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 004 [protocol for assessing the effectiveness of the patient alert card and healthcare professional educational material, study I4V-MC-B010: a rheumatologist survey to assess the effectiveness of the risk minimisation measures (RMM) for Olumiant (baricitinib); and objective 3 of study I4V-MC-B011: a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries [final report anticipated within 4 months following the end of data] as per the request for supplementary information (RSI) adopted in December 2017

17.2.6. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 005.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 005 [protocol for an observational post marketing disease registry in EU patients, study I4V-MC-B011: a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries] as per the request for supplementary information (RSI) adopted in December 2017

17.2.7. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 008.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 008 [protocol for an observational post marketing disease registry in EU patients, study I4V-MC-B012: a post-marketing safety surveillance of baricitinib in three European registers] as per the request for supplementary information (RSI) adopted in December 2017

17.2.8. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 002.1

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 002 [protocol for a long-term PASS MS 700568-0002: a prospective, observational cohort study evaluating the safety profile, in terms of incidence of adverse events of special interest, in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine [final report expected in Q2 2034] (from initial opinion/MA)] as per the request for supplementary information (RSI) adopted in January 2018

17.2.9. Colistimethate sodium - COLOBREATHE (CAP) - EMEA/H/C/001225/MEA 012

Applicant: Teva B.V.

PRAC Rapporteur: Julie Williams

Scope: Progress report on study recruitment and revised protocol for study CLB-MD-08: a cross-sectional study to evaluate the effectiveness of Colobreathe (colistimethate sodium) risk minimisation educational programme among healthcare professionals and patients

17.2.10. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 047.5

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 047.4 [amendment to the protocol of the HUBIN registry PASS: a European observational cohort of patients with type 1 diabetes mellitus (T1DM) treated via intraperitoneal route with Insuman Implantable 400 IU/mL in MedtronicMiniMed implantable pump, and an amended statistical analysis plan (SAP) following phase out process of the pump manufacturer for Insuman, previously agreed in May 2017] as per the request for supplementary information (RSI) adopted in January 2018

17.2.11. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/MEA 086.3

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to MEA 086.1 [protocol for PASS EPD172 comparing the incidence of renal failure in patients with epilepsy exposed to levetiracetam or other antiepileptic drugs (AED)] as per the request for supplementary information (RSI) adopted in December 2017

17.2.12. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/MEA 001.4

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 001.3 [revised protocols for: 1) study AMDC-204-401 (PASS): a post-authorisation observational study to evaluate the safety of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care and study; 2) study 204-403 (drug utilisation study (DUS)): a multinational retrospective medical record to evaluate utilisation patterns of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care] as per the request for supplementary information (RSI) adopted in December 2017

17.2.13. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002

Applicant: Tesaro UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Protocol for study 3000-04-001: a non-interventional PASS to evaluate the risks of myelodysplastic syndrome/acute myeloid leukaemia and secondary primary malignancies in adult patients with relapsed ovarian, fallopian tube, or primary peritoneal

cancer receiving maintenance treatment with Zejula (niraparib)

17.2.14. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) – MOSQUIRIX (Art 58[92]) - EMEA/H/W/002300/MEA 002.1

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Scientific Opinion Holder (SOH)'s response to MEA 002 [PASS protocol for study EPI-MAL-002 to estimate the incidence of adverse events of special interest (AESI) of meningitis and of other adverse events (AE) leading to hospitalisation or death, in children, prior to implementation of Mosquirix (RTS, S/AS01E)] as per the request for supplementary information (RSI) adopted in January 2018

17.2.15. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) – MOSQUIRIX (Art 58[93]) - EMEA/H/W/002300/MEA 003.1

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Scientific Opinion Holder (SOH)'s response to MEA 003 [PASS protocol for study EPI-MAL-003 to estimate the incidence of protocol-defined potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with Mosquirix] as per the request for supplementary information (RSI) adopted in January 2018

17.2.16. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 002.1

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 002 [protocol for study A3921133 (RMP category 3): a phase 3B/4 randomised safety endpoint study of 2 doses of tofacitinib in comparison to a tumour necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis (RA) [final report due date: by 31 December 2020] as per the request for supplementary information (RSI) adopted in December 2017

17.3. Results of PASS imposed in the marketing authorisation(s)[94]

None

[92] 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)
[93] 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)
[94] In accordance with Article 107p-q of Directive 2001/83/EC

17.4. Results of PASS non-imposed in the marketing authorisation(s)[95]

17.4.1. Asenapine - SYCREST (CAP) - EMEA/H/C/001177/II/0031/G

Applicant: N.V. Organon

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of the submission of final reports for the following studies (listed as category 3 studies in the RMP), namely: 1) study P08307 (EP04026.001): an observational PASS of Sycrest (asenapine) among patients aged 18 and older diagnosed with bipolar disorder [EU PAS register number: EUPAS17631];2) study P08308 (EP04026.003): an observational drug utilisation study (DUS) of Sycrest (asenapine) in the United Kingdom [EU PAS register number: EUPAS17681]; 3) study P08309 (EP04026.002): an observational post-authorisation modified prescription-event monitoring safety study to monitor the safety and utilisation of Sycrest (asenapine) In the primary care setting in England [EU PAS Register: EUPAS3603]; 4) study P08310 (EP04026.004): an observational post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of Sycrest (asenapine) in the mental health care setting in England and Wales [EU PAS Register: EUPAS3136]. No changes to the product information (PI) are proposed. The RMP (version 5.1) is updated accordingly

17.4.2. Buprenorphine, naloxone - SUBOXONE (CAP) - EMEA/H/C/000697/II/0037

Applicant: Indivior UK Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report for study PEUS005: 'a mortality study in the UK using the Health Improvement Network Database (THIN)' in order to estimate the all-cause mortality amongst patients exposed to Suboxone (buprenorphine/naloxone) in comparison to buprenorphine and methadone. The RMP (version 13.0) is updated accordingly

17.4.3. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1270/0216; LIFMIOR (CAP) - EMEA/H/C/004167/WS1270/0013

Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final report from study B1801396 (listed as a category 3 study in the RMP): a non-interventional, population-based, multi-country, observational cohort register study to evaluate the risk of adverse pregnancy outcomes in patients with rheumatoid arthritis and related inflammatory diseases, who were treated with etanercept compared to patients with the same diseases of interest who were treated with non-biologic systemic drugs, but without etanercept or other biologics during pregnancy, using merged data from Sweden, Denmark and Finland

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

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

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

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

17.4.5. Sevelamer carbonate - RENVELA (CAP) - EMEA/H/C/000993/II/0043

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Submission of the final report from study SEVELC08371: a historical cohort study of adult patients with severe chronic kidney disease (CKD) assessing the risk of bladder cancer by sevelamer exposure

17.4.6. 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): an observational, drug utilisation study (DUS) of Viread (emtricitabine/tenofovir disoproxil) in children and adolescents with human immunodeficiency virus-1 (HIV-1) infection, in fulfilment of a post-authorisation measure (PAM) for Viread (emtricitabine/tenofovir disoproxil) (MEA 46) and Truvada (tenofovir disoproxil) (MEA 276)

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[96]

17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 048.6

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Annual update report on recruitment for study IM101240: an observational registry of abatacept in patients with juvenile idiopathic arthritis (JIA registry) to explore the long-term safety of abatacept treatment for JIA in routine clinical practice (final registry report due date by 2029)

17.5.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 065.8

Applicant: AbbVie Deutschland GmbH & Co. KG

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Ninth interim report for study P10-023, a psoriasis patient registry: a 10-year, post-marketing observational study to assess the long term safety of Humira (adalimumab) in adult patients with chronic plaque psoriasis (PS)) (due date: final registry report planned in February 2023)

17.5.3. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.5

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Anette Kirstine Stark

Scope: Third annual report for study OBS13434: a prospective, multicentre, observational PASS to evaluate the long term safety profile of Lemtrada (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis (MS) and to determine the incidence of adverse events of special interest (AESIs)

17.5.4. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.12

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth annual interim report for study BEL116543/HGS1006-C1124: a long-term controlled safety registry evaluating the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus followed for a minimum of 5 years

17.5.5. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/MEA 001.3

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Third annual interim report for EuroSIDA PASS study 201177 (listed as a category 3 study in the RMP): a prospective observational cohort study in patients receiving dolutegravir to investigate the risk of hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (DAIDS) grading scale category 3 or 4)

17.5.6. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/MEA 007.3

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Third annual interim report for EuroSIDA PASS study 201177 (listed as a category 3 study in the RMP): a prospective observational cohort study in patients receiving dolutegravir to investigate the risk of hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (DAIDS) grading scale category 3 or 4)

17.5.7. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 007.3

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 007.2 [third annual report from a pregnancy research initiative to study the exposure to golimumab during pregnancy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers (CNTO148ART4001) and US health assurance claim database (CNTO148ART4002)] as per the request for supplementary information adopted at the December 2017 PRAC meeting

17.5.8. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 041.1

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Second annual interim study report of the Insuman implantable registry HUBIN-C-06380: a European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman implantable 400 IU/mL in Medtronic MiniMed implantable pump

17.5.9. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/MEA 028.6

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Sixth interim report of a PASS study (listed as a category 3 study in the RMP): a post-approval safety surveillance for monthly lot-specific adverse event review and analysis to evaluate any potential change in the frequency of hypersensitivity and immunogenicity events with the altered manufacturing process of Humalog and Liprolog (insulin lispro). This sixth report covers the batches released to the market between 15 October 2013 and 31 January 2018

17.5.10. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/MEA 021.6

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Sixth interim report of a PASS study (listed as a category 3 study in the RMP): a post-approval safety surveillance for monthly lot-specific adverse event review and analysis to evaluate any potential change in the frequency of hypersensitivity and immunogenicity events with the altered manufacturing process of Humalog and Liprolog (insulin lispro). This sixth report covers the batches released to the market between 15 October 2013 and 31 January 2018

17.5.11. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.2

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Results of a feasibility assessment conducted in US healthcare databases as per the agreed protocol (final version dated 25 May 2017) for study C38072-AS-50027: a long-term non-interventional cohort study comparing the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using secondary administrative healthcare data (listed as category 3 in the RMP]

17.5.12. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 273.3

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Caroline Laborde

Scope: Interim report for PASS study GS-EU-174-1846: a multicentre, non-interventional, retrospective cohort study of patients with chronic hepatitis B (CHB) and with moderate to severe renal impairment treated with Viread (tenofovir disoproxil)

17.6. Others

17.6.1. Canakinumab - ILARIS (CAP) - EMEA/H/C/001109/MEA 037.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Amendment to the statistical analysis plan (SAP) for study CACZ885G2403: a non-interventional study collecting safety data from systemic juvenile idiopathic arthritis (SJIA) patients enrolled in the Childhood Arthritis & Rheumatology Research Alliance (CARRA) disease registry who initiate treatment with canakinumab or comparator, with no change in the study protocol

17.6.2. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 012

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Statistical analysis plan (SAP) (edition 1.0) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes mellitus (T2DM); 2) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) study D1690C00019: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg Once daily in patients with T2DM and cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-

20/1442/C/4161)

17.6.3. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 024

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Statistical analysis plan (SAP) (edition 1.0) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes mellitus (T2DM); 2) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) study D1690C00019: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg Once daily in patients with T2DM and cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)

17.6.4. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 011

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Statistical analysis plan (SAP) (edition 1.0) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes mellitus (T2DM); 2) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) study D1690C00019: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg Once daily in patients with T2DM and cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)

17.6.5. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 014

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Statistical analysis plan (SAP) (edition 1.0) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes mellitus (T2DM); 2) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) study D1690C00019: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg Once daily in patients with T2DM and cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)

17.6.6. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/REC 030.5

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Sixth report on the monthly analysis of relevant drug event combination (DEC) for events reported with current-process Humalog (insulin lispro) compared with new-process Humalog (covering the period from 15 October 2013 to 31 January 2018) (from WS/0679)

17.6.7. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/REC 023.5

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Sixth report on the monthly analysis of relevant drug event combination (DEC) for events reported with current-process Liprolog (insulin lispro) compared with new-process Liprolog (covering the period from 15 October 2013 to 31 January 2018) (from WS/0679)

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. Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/S/0035 (without RMP)

Applicant: Noventia Pharma Srl

PRAC Rapporteur: Almath Spooner

Scope: Annual reassessment of the marketing authorisation

18.1.2. 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

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

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Doris Stenver

Scope: Conditional renewal of the marketing authorisation

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

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

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

Applicant: Noden Pharma DAC

PRAC Rapporteur: Carmela Macchiarulo

Scope: 5-year renewal of the marketing authorisation

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

Applicant: MolMed SpA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.3. Aripiprazole - ABILIFY MAINTENA (CAP) - EMEA/H/C/002755/R/0025 (with RMP)

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

18.3.4. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/R/0037 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: 5-year renewal of the marketing authorisation

18.3.5. 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

18.3.6. Etravirine - INTELENCE (CAP) - EMEA/H/C/000900/R/0052 (with RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Caroline Laborde

Scope: 5-year renewal of the marketing authorisation

18.3.7. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/R/0037 (without RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.8. Fluticasone furoate, vilanterol - REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/R/0033 (without RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.9. Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/R/0036 (with RMP)

Applicant: Noventia Pharma Srl

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.11. Macitentan - OPSUMIT (CAP) - EMEA/H/C/002697/R/0027 (with RMP)

Applicant: Actelion Registration Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.12. 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

18.3.13. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/R/0039 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

18.3.14. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/R/0025 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 14-17 May 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 - via telephone*	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova	Alternate - via telephone*	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Anette Stark	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation	3.2.1. Fluoroquinolone

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			in discussion, final deliberations and voting on:	s 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 7.3.1. Magnesium sulfate heptahydrate, sodium sulfate anhydrous, potassium sulfate (NAP) - EMEA/H/N/PSR/S/0016

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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
Sophia Trantza	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	6.1.27. Micafungin - MYCAMINE (CAP) - PSUSA/00002051/201710
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg	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,	3.2.1. Fluoroquinolones for systemic and inhalation

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			final deliberations and voting on:	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 4.3.3. Hormonal contraceptives: Chlormadinone, estradiol (NAP); chlormadinone acetate,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				ethinylestradiol (NAP); conjugated estrogens, medrogestone (NAP); conjugated estrogens, medroxyprogesterone acetate (NAP); conjugated estrogens, norgestrel (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel ,ethinylestradiol (NAP); dienogest, estradiol (NAP); dienogest, ethinylestradiol (NAP); drospirenone, estradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, estriol, levonorgestrel (NAP); estradiol, gestodene (NAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				estradiol, levonorgestrel (NAP); estradiol, medroxyprogesterone acetate (NAP); estradiol, nomegestrol acetate (NAP); estradiol, norethisterone (NAP); estradiol, norgestimate (NAP); estradiol (17-beta), progesterone (NAP); estradiol (17-beta), trimegestone (NAP); estradiol valerate, norgestrel (NAP); ethinylestradiol, etonogestrel (NAP); ethinylestradiol, etynodiol (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, levonorgestrel (NAP); ethinylestradiol, lynestrenol (NAP); ethinylestradiol,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); mestranol, norethisterone (NAP); nomegestrol (NAP); nomegestrol acetate, estradiol – ZOELY (CAP); norelgestromin, ethinyl estradiol – EVRA (CAP), 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 Dondera	Alternate	Romania	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Marina Lesičar	Expert - via telephone*	Croatia	No interests declared	Full involvement
Jana Koprušáková	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Helle Wallach Kildemoes	Expert - via telephone*	Denmark	No interests declared	Full involvement
Peggy Chocarne	Expert - via telephone*	France	No interests declared	Full involvement
Nathalie Dumarcet	Expert - in person*	France	No interests declared	Full involvement
Ines Messai	Expert - in person*	France	No interests declared	Full involvement
Thomas Grüger	Expert - via telephone*	Germany	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Nils Lilienthal	Expert - via telephone*	Germany	No interests declared	Full involvement
Jan Mueller-Berghaus	Expert - via telephone*	Germany	No interests declared	Full involvement
Tamás Szolyák	Expert - in person*	Hungary	No participation in discussion, final deliberations and voting on:	4.3.3 Hormonal contraceptives: Chlormadinone, estradiol (NAP); chlormadinone acetate, ethinylestradiol (NAP); conjugated estrogens, medrogestone (NAP); conjugated estrogens, medroxyprogesterone acetate (NAP); conjugated estrogens, norgestrel (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel ,ethinylestradiol (NAP); dienogest, estradiol (NAP); dienogest, ethinylestradiol (NAP); drospirenone, estradiol (NAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				drospirenone, ethinylestradiol (NAP); estradiol, estriol, levonorgestrel (NAP); estradiol, gestodene (NAP); estradiol, levonorgestrel (NAP); estradiol, medroxyprogesterone acetate (NAP); estradiol, nomegestrol acetate (NAP); estradiol, norethisterone (NAP); estradiol, norgestimate (NAP); estradiol (17-beta), progesterone (NAP); estradiol (17-beta), trimegestone (NAP); estradiol valerate, norgestrel (NAP); ethinylestradiol, etonogestrel (NAP); ethinylestradiol, etynodiol (NAP); ethinylestradiol, gestodene (NAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				ethinylestradiol, gestodene (NAP); ethinylestradiol, levonorgestrel (NAP); ethinylestradiol, lynestrenol (NAP); ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); mestranol, norethisterone (NAP); nomegestrol (NAP); nomegestrol acetate, estradiol – ZOELY (CAP); norelgestromin, ethinyl estradiol – EVRA (CAP), NAP; norethisterone (NAP) 6.1.12. Deferasirox - EXJADE (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				PSUSA/00000939/201710 6.3.13. Fluvastatin (NAP) - PSUSA/00001457/201708
Einar Björnsson	Expert - via telephone*	Iceland	No interests declared	Full involvement
Emma Lawless	Expert - in person*	Ireland	No interests declared	Full involvement
Anouk Neuteboom	Expert - in person*	Netherlands	No interests declared	Full involvement
Negar Babae	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Desiree Bergamin-Egenberger	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Lotte Minnema	Expert - in person*	Netherlands	No interests declared	Full involvement
Peter Mol	Expert - in person*	Netherlands	No interests declared	Full involvement
Christine Siezen	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Elizabeth van Vlijmen	Expert - in person*	Netherlands	No interests declared	Full involvement
Michal Radik	Expert - via telephone*	Slovakia	No restrictions applicable to this meeting	Full involvement
Ana Fernández Dueñas	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Kristina Dunder	Expert - via telephone*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - in person*	Sweden	No interests declared	Full involvement
Viveca Odlind	Expert - in person*	Sweden	No interests declared	Full involvement
Miriam Taekema	Expert - via telephone*	Sweden	No interests declared	Full involvement
Mari Thörn	Expert - via telephone*	Sweden	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
Marta Busana	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No interests declared	Full involvement
Karen Grant	Expert - in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Graham Lunn	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

Annex III - List of acronyms and abbreviations

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

Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event.

The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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