14 February 2019
EMA/PRAC/190876/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of meeting on 14-17 January 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 14-17 January 2019 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 noted that Alexandra Spurni was the new alternate for Romania, replacing Andreia Rulea. In addition, the PRAC Chair announced that it was the last PRAC meeting for Jolanta Gulbinovic as the member for Lithuania. The PRAC thanked her for her valuable contribution to the work of the PRAC.

Finally, the PRAC welcomed the new Romanian presidency of the Council of the EU.

1.2. Agenda of the meeting on 14-17 January 2019

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 26-29 November 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 26-29 November 2018 were published on the EMA website on 08 February 2019 (EMA/PRAC/109243/2019).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

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

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

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for methotrexate-containing medicines (oral and parenteral formulations) following reports of overdose toxicity as a consequence of daily intake in error instead of weekly intake. The ongoing review also assesses the risk minimisation measures taken nationally over recent years to fully elucidate the issue and to take appropriate measures. For further background see PRAC minutes April 2018 and PRAC minutes October 2018.

Summary of recommendation(s)/conclusions

- The PRAC discussed and concurred on the need to engage with patients, carers and healthcare professionals and agreed with the organisation of a stakeholders meeting scheduled on 26 February 2019. The PRAC discussed a draft list of questions (LoQ) to the stakeholders.

Post-meeting note: On 8 February 2019, the PRAC adopted the LoQ to for the meeting with stakeholders.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[1]

None

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

3.5. Others

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Acetylsalicylic acid (NAP)

Applicant(s): various

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of data on cancer-related mortality from a single study in elderly adults

EPITT 19317 – New signal

Lead Member State(s): HU

Background

Acetylsalicylic acid is an analgesic and antithrombotic agent indicated for the treatment of headache, toothache, migraine, neuralgia and other pains and in some Member States for the prevention of thrombotic cerebrovascular or cardiovascular disease.

The exposure for acetylsalicylic acid is estimated to have been more than 1 billion patients worldwide, in the period from first authorisation in 1942 to 2016.

Following publications by *McNeil JJ et al*[3] in the New England Journal of Medicine, a signal of increased cancer-related mortality in elderly adults was identified by Germany. Hungary confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information from the published clinical trial which included 19,114 healthy persons with a median age of 74 years. A higher all-cause mortality and cancer-related mortality was observed in participants treated with daily low dose acetylsalicylic acid compared to placebo. The PRAC discussed the evidence in the context of other available studies as well as the authorised indications of acetylsalicylic acid.

The PRAC appointed Julia Pallos as Rapporteur for the signal.

[2] 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

[3] McNeil JJ et al. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med. 2018;379(16):1499-1508
McNeil JJ et al. Effect of Aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379(16):1509-1518
McNeil JJ et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med. 2018;379(16):1519-1528

Summary of recommendation(s)

- The originator MAH Bayer for acetylsalicylic acid-containing products should submit to the EMA responses to the list of questions (LoQs) agreed by the PRAC in the next PSUR with a data lock point (DLP) set on 01/02/2019 due for submission no later than 02/05/2019.

4.2.2. Dipeptidyl peptidase-4 (DPP-4) inhibitors: alogliptin – VIPIDIA (CAP); linagliptin – TRAJENTA (CAP); saxagliptin – ONGLYZA (CAP); sitagliptin – JANUVIA (CAP), RISTABEN (CAP), TESAVEL (CAP), XELEVIA (CAP); vildagliptin – GALVUS (CAP), JALRA (CAP), XILIARX (CAP); Glucagon-like peptide-1 (GLP-1) receptor agonists: albiglutide – EPERZAN (CAP); dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP); lixisenatide – LYXUMIA (CAP); semaglutide – OZEMPIC (CAP)

Applicant(s): AstraZeneca AB (Bydureon, Byetta, Onglyza), Boehringer Ingelheim (Trajenta), Eli Lilly Nederland B.V. (Trulicity), GlaxoSmithKline Trading Services limited (Eperzan), Merck Sharp & Dohme B. V. (Januvia, Ristaben, Tesavel, Xelevia), Novartis Europharm Limited (Galvus, Jalra, Xiliarx), Novo Nordisk A/S (Ozempic, Saxenda, Victoza), Sanofi-aventis groupe (Lyxumia), Takeda Pharma A/S (Vipidia)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of increased risk of cholangiocarcinoma in adults with type 2 diabetes mellitus (T2DM)

EPITT 19343 – New signal

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

Background

Dipeptidyl peptidase-4 (DPP-4) inhibitors alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin are centrally authorised products indicated, under certain conditions, for the treatment of adult patients with type 2 diabetes mellitus (T2DM) to improve glycaemic control, alone or in combinations with other medicines. Glucagon-like peptide-1 (GLP-1) receptor agonists albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide and semaglutide are centrally authorised products indicated, alone or in combinations with other medicines and under certain conditions for the treatment of T2DM. Saxenda (liraglutide) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients.

The exposure for Vipidia (alogliptin) is estimated to have been more than 932,033 patient-years cumulatively worldwide, in the period from first authorisation in 2010 to 2018. The exposure for Trajenta (linagliptin) is estimated to have been more than 10.41 million patient-years cumulatively worldwide, in the period from first authorisation in 2011 to 2018. The exposure for Onglyza (saxagliptin) is estimated to be approximately 3.24 million patient-years worldwide, in the period from first authorisation in 2009 to 2017. The exposure for Januvia (sitagliptin), Ristaben (sitagliptin), Tesavel (sitagliptin), Xelevia (sitagliptin) is estimated to have been more than 47.57 million patient-years worldwide, in the period from first authorisation in 2006 to 2017. The exposure for Galvus (vildagliptin), Jalra (vildagliptin), Xiliarx (vildagliptin) is estimated to have been more than 8.86 million patient-years worldwide, in the period from first authorisation in 2007 to 2018. The exposure for Eperzan

(albiglutide) is estimated to have been more than 134,825 patient-years worldwide, in the period from first authorisation in 2014 to 2018. The exposure for Trulicity (dulaglutide) is estimated to have been more than 2.9 million patient-years worldwide, in the period from first authorisation in 2014 to 2018. The exposure for Bydureon (exenatide) and Byetta (exenatide) is estimated to have been more than 4.9 million patient-years worldwide, in the period from first authorisation in 2005 to 2018. The exposure for Saxenda (liraglutide) and Victoza (liraglutide) is estimated to have been more than 8.3 million patient-years worldwide, in the period from first authorisation in 2009 to 2017. The exposure for Lyxumia (lixisenatide) is estimated to have been more than 98,869 patient-years worldwide, in the period from first authorisation in 2013 to 2016. The exposure for Ozempic (semaglutide) is estimated to have been more than 42,355 patient-years worldwide, in the period from first authorisation in 2017 to 2018.

Following the publication in BMJ by *Abrahami et al*[4], a signal of cholangiocarcinoma was identified by the Netherlands, suggesting that compared with use of other second or third line antidiabetic drugs, the use of DPP-4 inhibitors and possibly GLP-1 receptor agonists might be associated with an increased risk of cholangiocarcinoma in adults with T2DM. The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information presented in the study and agreed that this signal merits further investigation. The PRAC agreed to seek further clarifications from the study authors as well as to request the MAHs to provide a discussion on the available evidence.

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

Summary of recommendation(s)

- The MAHs for Bydureon and Byetta (exenatide), Onglyza (saxagliptin), Trajenta (linagliptin), Trulicity (dulaglutide), Eperzan (albiglutide), Januvia, Ristaben, Tesavel and Xelevia (sitagliptin), Galvus, Jalra, Xiliarx (vildagliptin), Ozempic (semaglutide), Saxenda and Victoza (liraglutide), Lyxumia (lixisenatide) and Vipidia (alogliptin) should submit to the EMA, within 60 days, a discussion on the publication by *Abrahami et al* and any other relevant publications, clinical studies and non-clinical data. The MAHs should also discuss the need for risk minimisation measures and propose to amend the product information as warranted.
- The study authors *Abrahami et al.* are requested to submit to the EMA, within 60 days, additional clarifications on the study, as formulated in a list of questions (LoQ).
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Apixaban – ELIQUIS (CAP) - EMEA/H/C/002148/SDA/032

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

PRAC Rapporteur: Menno van der Elst

[4] Abrahami D et al. Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study. BMJ 2018;363:k4880

Scope: Signal of pancreatitis

EPITT 19265 – Follow up to September 2018

Background

For background information, see PRAC minutes September 2018.

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

Discussion

Having considered the available evidence, including a case review submitted by the MAH, the PRAC agreed to request further clarifications on case causality of several cases from the MAH within 30 days.

Summary of recommendation(s)

- The MAH for Eliquis (apixaban) should submit to the EMA, within 30 days, further information on the cases included in the review.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.2. Biotin (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of interference with clinical laboratory tests

EPITT 19156 – Follow up to June 2018

Background

For background information, see PRAC minutes June 2018.

The MAHs Quiris Healthcare GmbH & Co. KG, Dr. Kleine Pharma GmbH, Kräuterhaus Sanct Bernhard KG, BIO-H-TIN Pharma GmbH & Co. KG, FAR.G.IM, Alfasigma S.p.A., Bayer, Essential Pharmaceuticals Ltd, Fresenius Kabi and Baxter replied to the list of questions (LoQ) on the signal of interference with clinical laboratory tests and the responses were assessed by the Rapporteur.

Discussion

Based on the assessment of the available data (i.e. literature and EudraVigilance data), as well as additional information from the MAHs Quiris Healthcare GmbH & Co. KG, Dr. Kleine Pharma GmbH, Kräuterhaus Sanct Bernhard KG, BIO-H-TIN Pharma GmbH & Co. KG, FAR.G.IM, Alfasigma S.p.A., Bayer, Essential Pharmaceuticals Ltd, Fresenius Kabi and Baxter, the PRAC considered that there is sufficient evidence on the interference with clinical laboratory tests to warrant updating the product information of biotin-containing medicinal products. This applies to medicinal products for oral use containing ≥150 microgram biotin per dose unit and medicinal products for parenteral use containing ≥60 microgram biotin per dose unit. The PRAC also agreed on the key elements for communication at the discretion of the National Competent Authorities (NCAs).

Summary of recommendation(s)

- The MAHs for biotin-containing products for oral use containing ≥150 microgram biotin per dose unit and products for parenteral use containing ≥60 microgram biotin per dose unit should submit to the relevant NCAs of the Member States, within 90 days, a variation to amend their product information[5].
- The MAHs for mono-component and fixed dose combinations of biotin-containing products should provide, in future periodic safety update reports (PSURs)[6] submitted in accordance with the 'list of Union reference dates and frequency of submission of PSURs' ('EURD list'), new pharmacokinetic (PK) data with potentially relevant information in the context of the risk of interference and the evaluation of new cases of interference including those related to off-label use. MAHs should also evaluate the appropriateness of the agreed cut-off for inclusion of the warning in the product information.
- The PRAC also agreed on the key elements for communication at the discretion of the NCAs.

For the full PRAC recommendation, see EMA/PRAC/905027/2019 published on 11/02/2019 on the EMA website.

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

Applicant(s): ViiV Healthcare B.V. (Tivicay), ViiV Healthcare UK Limited (Juluca, Triumeq)

PRAC Rapporteur: Julie Williams

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

EPITT 19244 – Follow-up to October 2018

Background

For background information, see PRAC minutes October 2018.

The Safety Working Party (SWP) provided responses to the PRAC list of questions (LoQ) in the context of the evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the SWP responses including expert advice on the MAH's proposals for further in-vitro studies as well as additional non-clinical investigations to further substantiate the causality of dolutegravir in the occurrence of neural tube defects. The PRAC agreed that the ongoing mechanistic studies that were being conducted by the MAH were sufficient and that additional non-clinical investigations were not warranted. Nevertheless, the PRAC

[5] Update of SmPC section 4.4. The package leaflet is to be updated accordingly
[6] With data lock points (DLP) set on 01/01/2019, 01/01/2025 and 01/01/2035 respectively, due for submission no later than 01/04/2019, 01/04/2025 and 01/04/2035

considered that the MAH should provide further updates on the data from the Tsepamo study[7] when available, and to provide responses to outstanding questions in the next PSUR.

Summary of recommendation(s)

- The MAHs for Tivicay (dolutegravir), Juluca (dolutegravir, rilpivirine) and Triumeq (abacavir sulfate, dolutegravir sodium, lamivudine), respectively should provide, in the next PSUR with a data lock point (DLP) set on 15/05/2019 and 16/01/2019, respectively, due for submission no later than 24/07/2019 and 27/03/2019, respectively, responses to the outstanding LoQ.

4.3.4. Gabapentin (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of dysphagia

EPITT 19296 – Follow up to September 2018

Background

For background information, see PRAC minutes September 2018.

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

Discussion

Having considered all the available evidence from literature, clinical trials and case reports from the post-marketing setting, the PRAC agreed that there is sufficient evidence for a causal association of dysphagia with gabapentin treatment. The PRAC agreed that dysphagia should be added as an adverse drug reaction to the product information of all gabapentin-containing medicinal products.

Summary of recommendation(s)

- The MAHs for gabapentin-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend their product information[8].

For the full PRAC recommendation, see EMA/PRAC/905027/2019 published on 11/02/2019 on the EMA website.

4.3.5. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/SDA/032

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of scleroderma

EPITT 19282 – Follow up to September 2018

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

[8] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

Background

For background information, see PRAC minutes September 2018.

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

Discussion

Having considered the available evidence from the cumulative review provided by the MAH for Opdivo (nivolumab), the PRAC agreed that the likelihood of a causal relationship is not sufficiently strong at this stage. Therefore, the PRAC concurred that no regulatory action is currently warranted.

Summary of recommendation(s)

- The MAH for Opdivo (nivolumab) should continue to monitor these events as part of routine safety surveillance.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Autologous CD34^{+} cell enriched population that contains haematopoietic stem cells transduced with LentiGlobin BB305 lentiviral vector encoding the beta-A-T87Q-globin gene - EMEA/H/C/003691, Orphan

Applicant: Bluebird bio GmbH, ATMP[9]

Scope (accelerated assessment): Treatment of transfusion-dependent β-thalassaemia (TDT)

5.1.2. Cemiplimab - EMEA/H/C/004844

Scope: Treatment in monotherapy of patients with metastatic cutaneous squamous cell carcinoma

5.1.3. Glutamine - EMEA/H/C/004734, Orphan

Applicant: Emmaus Medical Europe Ltd

Scope: Treatment of Sickle cell disease (SCD)

[9] Advanced therapy medicinal product

5.1.4. Quizartinib - EMEA/H/C/004468, Orphan

Applicant: Daiichi Sankyo Europe GmbH

Scope (accelerated assessment): Treatment of acute myeloid leukaemia (AML)

5.1.5. Risankizumab - EMEA/H/C/004759

Scope: Treatment of psoriasis in adults

5.1.6. Trientine dihydrochloride - EMEA/H/C/004111, Orphan

Applicant: Univar BV

Scope: Treatment of Wilson's disease

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

See also Annex I 15.2.

5.2.1. Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/WS1509/0138; emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/WS1509/0158

Applicant(s): Bristol-Myers Squibb and Gilead Sciences Ltd. (Atripla), Gilead Sciences Ireland UC (Truvada)

PRAC Rapporteur: Martin Huber

Scope: Worksharing variation consisting of an update of the RMPs (version 17.1 for Atripla and version 15.5 for Truvada) in order to: 1) reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template); 2) remove the additional risk minimisation measures (RMMs) for tenofovir disoproxil fumarate in the form of education materials regarding renal toxicity and bone events, with the resulting amendment of Annex II of the product information; 3) add clinical data from study GS-US-104-0352: a phase 3, randomized, open-label study comparing the safety and efficacy of switching stavudine or zidovudine to tenofovir disoproxil fumarate versus continuing stavudine or zidovudine in virologically suppressed human immunodeficiency virus (HIV)-infected children taking highly active antiretroviral therapy; 4) revise the due dates for study GS-US-276-0103 (listed as category 3 study in the RMP): a prospective, observational study of individuals who seroconvert while taking Truvada (emtricitabine/tenofovir disoproxil) for pre exposure prophylaxis (PrEP), and study GS-EU-276-4027 (listed as category 3 study in the RMP): a cross-sectional post authorisation safety study to assess healthcare provider's level of awareness of risk minimisation materials for Truvada (emtricitabine/tenofovir disoproxil) for PrEP in the European Union; 5) implement already approved administrative changes

Background

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI), emtricitabine a nucleoside analogue of cytidine and tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. In combination, efavirenz/emtricitabine/tenofovir disoproxil is indicated as Atripla for the

treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 ribonucleic acid (RNA) levels of < 50 copies/mL on their current combination antiretroviral therapy for more than three months. In combination as emtricitabine/tenofovir disoproxil, it is indicated as Truvada in antiretroviral combination therapy for the treatment of HIV-1 infected adults as well for the treatment of HIV-1 infected adolescents, with nucleoside reverse transcriptase inhibitor (NRTI) resistance or toxicities precluding the use of first line agents. Emtricitabine/tenofovir disoproxil is also indicated, as Truvada, in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk.

The PRAC is evaluating a type II worksharing variation procedure for Atripla and Truvada, centrally authorised medicines containing efavirenz/emtricitabine/tenofovir disoproxil and emtricitabine/tenofovir disoproxil respectively, to update the RMP to remove, in particular, additional risk minimisation measures (aRMM) for tenofovir disoproxil fumarate in the form of education materials regarding renal toxicity and bone events, with the resulting amendment of Annex II of the product information. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation.

Summary of advice

- The RMPs for Atripla (efavirenz/emtricitabine/tenofovir disoproxil) and Truvada (emtricitabine/tenofovir disoproxil) in the context of the variation under evaluation could be considered acceptable provided that an update to RMP version 17.1 for Atripla and version 15.5 for Truvada and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC supported the discontinuation of the requirement for the educational material to healthcare professionals (HCPs) on renal toxicity and bone events as an aRMM as the knowledge gathered over the years amongst healthcare professionals is considered sufficient to mitigate the relevant risk in clinical practice, as shown in particular in the results of a HCP survey. Therefore, the PRAC advised to manage renal safety concerns in HIV-1 infected adults through routine RMM. The PRAC supported the MAH's proposal to maintain the aRMM for paediatric patients for Truvada (emtricitabine/tenofovir disoproxil). Annex II should be updated accordingly.

5.2.2. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/II/0038

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of the RMP (version 20.0) in order to streamline and improve the educational programme and communication to prescribing physicians as requested in the conclusion of variation II/0035 adopted in June 2018

Background

Micafungin is an echinocandin antifungal indicated for the treatment of invasive candidiasis, treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate and for the prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia for 10 or more days, under certain conditions.

The PRAC is evaluating a type II variation procedure for Mycamine, a centrally authorised medicine containing micafungin, to update the RMP in order to streamline and improve the educational programme and communication to physicians prescribing Mycamine (micafungin). The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation. For further background, see PRAC minutes September 2018 and PRAC minutes November 2018 (29-31 October 2018).

Summary of advice

- The RMP (version 22.0) for Mycamine (micafungin) in the context of the variation under evaluation is considered acceptable.
- The PRAC considered the further measures to improve physicians' knowledge on important potential risk of liver tumours and supported the update of the prescriber checklist to focus on the specific important risks focusing on hepatic events, haemolytic events, renal events and potential risk of liver tumour formation. In addition, the PRAC supported the deletion of the 'administration and monitoring guide' as no additional benefit of this material is expected any longer since relevant information is included in the 'prescriber checklist' and in the product information. Annex II is to be updated accordingly.

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

See also Annex I 15.3.

5.3.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/X/0068

Applicant: Teva B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application to add a new strength of 2 mg/mL. The RMP (version 2.0) is updated accordingly

Background

Arsenic trioxide causes morphological changes and deoxyribonucleic acid (DNA) fragmentation characteristic of apoptosis in NB4 human promyelocytic leukaemia (PML) cells *in vitro* and also causes damage or degradation of the fusion protein pro-myelocytic leukaemia/retinoic acid receptor-alpha (PML/RAR alpha). It is indicated, as Trisenox, for induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 103/µl) in combination with all-*trans*-retinoic acid (ATRA) or relapsed/refractory APL, characterised by the presence of the t(15;17) translocation and/or the presence of the PML/RAR alpha gene.

The CHMP is evaluating an extension of application to add a new strength and presentation. The RMP is proposed to be updated to include in particular 'medication errors related to possible confusion between the two presentations' as a new important potential risk and to bring in line the RMP with revision 2 of the guidance on the format of RMP in the EU (template). 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 September 2018.

Summary of advice

- The RMP for Trisenox (arsenic trioxide) in the context of the extension of application procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 2.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC discussed the MAH's responses to the RSI. The PRAC supported the distribution of a direct healthcare professional communication (DHPC). The PRAC also supported that the DHPC target audience and the distribution timelines are agreed at the level of the National Competent Authorities taking into account the situation in each Member State (e.g. time of launch of the new formulation and possible coexistence of the two formulations on the market). The MAH is requested to provide a draft DHPC for review. The PRAC also agreed with routine risk minimisation measures (RMMs) but considered that the size of the red box warning on the outer packaging should be increased and kept for at least 6 months after first distribution of the new strength (2mg/mL). Finally, the MAH is requested to submit to EMA annual reports of cases of 'medication error'.

5.3.2. Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - EMEA/H/C/000739/II/0068

Applicant: Roche Registration GmbH

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report for study BH21260 (listed as a category 3 study in the RMP): a randomized, controlled, open-label, multicentre, parallel-group study to assess all-cause mortality and cardiovascular morbidity in patients with chronic kidney disease (CKD) on dialysis and those not on renal replacement therapy under treatment with Mircera (methoxy polyethylene glycol-epoetin beta) or erythropoiesis-stimulating agents (ESAs) of reference (in fulfilment of post-approval commitment MEA 008.5). The RMP (version 12.0) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

Background

Methoxy polyethylene glycol-epoetin beta is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adult patients.

The CHMP is evaluating a type II variation for Mircera, a centrally authorised product containing methoxy polyethylene glycol-epoetin beta, in order to assess the final report for study BH21260, an interventional study assessing all-cause mortality and cardiovascular morbidity in patients with CKD on dialysis and those not on renal replacement therapy under treatment with Mircera (methoxy polyethylene glycol-epoetin beta) or ESAs of reference. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes October 2018.

Summary of advice

- The RMP for Mircera (methoxy polyethylene glycol-epoetin beta) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 12.1 is provided.

- The PRAC agreed with the removal of the completed study as an additional pharmacovigilance activity. The PRAC considered that routine pharmacovigilance activities are sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the medicinal product. With regard to safety specifications, the PRAC supported adding 'tumour growth progression' as an important potential risk and removing 'paediatric population group (<18 years)' in line with revision 2 of GVP module V on 'Risk management systems'. The PRAC also agreed on the removal of the educational material for healthcare professionals (HCP) for erythropoietin antibody-mediated pure red cell aplasia (AEAB-mediated PRCA) as an additional risk minimisation measure as it is considered that the knowledge gathered over the years amongst HCPs is sufficient to mitigate the relevant risk in clinical practice and the risk is sufficiently described in the product information. In addition, the PRAC supported the proposal to provide free AEAB testing on physician's request as a routine risk minimisation measure. As a consequence, Annex IID on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' should be updated.

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. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201807

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein with enzymatic activity. It is indicated, as Strensiq, for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Strensiq (asfotase alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add further information on immunogenicity in order to reflect the fact that the occurrence of anti-drug antibodies

can be associated with a decrease in the clinical efficacy of asfotase alfa. Therefore, the current terms of the marketing authorisation(s) should be varied[10].

- In the next PSUR, the MAH should comment on whether there is any difference in the reporting rates and severity of injection site reactions (ISRs) in adults compared to children, and provide an analysis of serious cases, in particular those reporting anaphylaxis/anaphylactoid reaction. With reference to reduced efficacy associated with the development of anti-drug antibodies, the MAH should further discuss whether any specific treatment recommendations could be provided in the product information and make a proposal to update the latter as applicable. Finally, the MAH should discuss what measures could be taken to ensure that the antibody test becomes more widely available in the EU.

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. Azacitidine - VIDAZA (CAP) - PSUSA/00000274/201805

Applicant: Celgene Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Azacitidine is a pyrimidine analogue indicated, as Vidaza, for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS), with chronic myelomonocytic leukaemia (CMML) with 10-29 % marrow blasts without myeloproliferative disorder, with acute myeloid leukaemia (AML) with 20-30 % blasts and multi-lineage dysplasia, according to the World Health Organisation (WHO) classification, or with an AML with >30% marrow blasts according to the WHO classification.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vidaza, a centrally authorised medicine containing azacitidine 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 Vidaza (azacitidine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add pericarditis as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide a cumulative review of off-label cases and misuse cases in which Vidaza (azacitidine) was not reconstituted and stored according to

[10] 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
[11] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

the product information. In addition, the MAH should provide a cumulative review of cases of eosinophilic pneumonia together with a literature review, and a thorough discussion including a proposal to update the product information as warranted.

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

6.1.3. Dasatinib - SPRYCEL (CAP) - PSUSA/00000935/201806

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Dasatinib is a BCR[12]-ABL[13] tyrosine kinase inhibitor (TKI) indicated, as Sprycel, for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase; with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesylate; with Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy; with newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib. It is also indicated for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sprycel, a centrally authorised medicine containing dasatinib 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 Sprycel (dasatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add thrombotic microangiopathy (TMA) as an undesirable effect with a frequency 'not known' and as a warning to ensure that treatment with Sprycel (dasatinib) is discontinued in patients where laboratory or clinical findings are associated with TMA and a thorough evaluation for TMA, including ADAMTS13[14] activity and anti-ADAMTS13-antibody determination is completed. In addition, the existing undesirable effect on musculoskeletal pain is further detailed to reflect that it has been reported during or after discontinuing treatment with Sprycel (dasatinib). Therefore, the current terms of the marketing authorisation(s) should be varied[15].

[12] Breakpoint cluster region protein
[13] Abelson murine leukaemia viral oncogene homolog 1
[14] A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, also known as von Willebrand factor-cleaving protease (VWFCP)
[15] 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

- In the next PSUR, the MAH should present a detailed review of cases of posterior reversible encephalopathy syndrome (PRES) and other relevant types of encephalopathy, including a discussion on a plausible biological mechanism and a proposal to update the product information as warranted. In addition, the MAH should include TMA as part of the PSUR list of safety concerns and relevant new information and risk characterisation.

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.

Based on the evidence from the literature, the PRAC considered that TMA is a potential BCR-ABL TKI subclass effect. To address this potential effect, the MAHs for other BCR-ABL TKI-containing products[16] should submit a detailed review of cases of TMA as part of the next PSUR submissions. For imatinib, see under 6.2.2.

In addition, based on the confirmation of a causal relationship between discontinuation of dasatinib treatment and withdrawal syndrome (musculoskeletal symptoms), and given that this risk has been also identified with imatinib and nilotinib, the PRAC considered that withdrawal syndrome is a potential BCR-ABL TKI subclass effect. To address this potential effect, the MAHs for other BCR-ABL TKI-containing products[17] should submit a detailed review of cases reporting withdrawal syndrome as part of the next PSUR submissions. For imatinib, see under 6.2.2.

6.1.4. Ertugliflozin - STEGLATRO (CAP) - PSUSA/00010682/201806

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Ertugliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor indicated, as Steglatro, in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications, or in addition to other medicinal products for the treatment of diabetes.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Steglatro, a centrally authorised medicine containing ertugliflozin 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 Steglatro (ertugliflozin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on lower limb amputations to reflect further clinical study data and adding consideration on factors that may increase the risk for amputation before initiating treatment with

[16] I.e. nilotinib (data lock point (DLP): 31/01/2019), bosutinib (DLP: 03/03/2019) and ponatib (DLP: 13/12/2018)
[17] I.e. bosutinib (DLP: 03/03/2019) and ponatib (DLP: 13/12/2018)

ertugliflozin, including precautionary measures and when to stop treatment. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

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. Ertugliflozin, metformin - SEGLUROMET (CAP) - PSUSA/00010680/201806

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Ertugliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor and metformin a biguanide. In combination, ertugliflozin/metformin is indicated, as Segluromet, in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control in patients not adequately controlled on their maximally tolerated dose of metformin alone, in patients on their maximally tolerated doses of metformin in addition to other medicinal products for the treatment of diabetes, as well as in patients already being treated with the combination of ertugliflozin and metformin as separate tablets.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Segluromet, a centrally authorised medicine containing ertugliflozin/metformin 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 Segluromet (ertugliflozin/metformin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on lower limb amputations to reflect further clinical study data and adding consideration on factors that may increase the risk for amputation before initiating treatment with ertugliflozin, including precautionary measures and when to stop treatment. Therefore, the current terms of the marketing authorisation(s) should be varied[19].

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. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - PSUSA/00010681/201806

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[18] 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

[19] 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

Background

Ertugliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor and sitagliptin a dipeptidyl peptidase 4 (DPP-4) inhibitor. In combination, ertugliflozin/sitagliptin is indicated, as Steglujan, in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control when metformin and/or a sulphonylurea (SU) and one of the monocomponents of Steglujan do not provide adequate glycaemic control as well as in patients already being treated with the combination of ertugliflozin and sitagliptin as separate tablets.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Steglujan, a centrally authorised medicine containing ertugliflozin/sitagliptin 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 Steglujan (ertugliflozin/sitagliptin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on lower limb amputations to reflect further clinical study data and adding consideration on factors that may increase the risk for amputation before initiating treatment with ertugliflozin, including precautionary measures and when to stop treatment. Therefore, the current terms of the marketing authorisation(s) should be varied[20].

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. Mirabegron - BETMIGA (CAP) - PSUSA/00010031/201806

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Mirabegron is a selective beta 3-adrenoceptor agonist, indicated as Betmiga for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

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

[20] 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

- Nevertheless, the product information should be updated to include confusional state as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide a cumulative review with a discussion of the cases and a proposal for changes of the product information as warranted for the following topics: amnesia and memory loss, vertigo, muscle spasms and dysphagia.

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

6.1.8. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201807

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. It is indicated as Opdivo for the treatment of melanoma as monotherapy or in combination with ipilimumab and as monotherapy for the treatment of adults with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy, advanced renal cell carcinoma after prior therapy, relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, recurrent or metastatic squamous cell cancer of the head and neck progressing on or after platinum-based therapy and locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Opdivo (nivolumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include aseptic meningitis as a warning as well as an undesirable effect with a frequency 'not known'. Sarcoidosis should also be added as an undesirable effect with a frequency 'not known' and a footnote with clarifying information regarding anaemia should be added. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should discuss the strategies for routine monitoring of myocarditis including troponin measurement and data on the risk of immune-mediated

[21] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[22] 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

adverse events in patients with a history of thymoma. Additionally, the MAH should submit detailed reviews of immune-mediated cholangitis, eosinophilic fasciitis, lichen planus and lichenoid cutaneous reaction as well as a review of B-cell lymphoma.

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. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/201805

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Nusinersen is an antisense oligonucleotide (ASO) indicated as Spinraza for the treatment of 5q spinal muscular atrophy, a progressive neuromuscular disease resulting from mutations in chromosome 5q in the survival motor neuron 1 (SMN1) gene.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Spinraza, a centrally authorised medicine containing nusinersen 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 Spinraza (nusinersen) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include aseptic meningitis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide a review of neutrophilic eccrine hidradenitis and an evaluation of whether the current product information should be updated regarding the potential risk of renal toxicity based on follow-up/cumulative information. The MAH should also provide a summary on the maintenance of effect in nusinersen-treated patients with a ventriculo-peritoneal shunt and a summary on the reasons for nusinersen discontinuation in the post-marketing experience, in particular in the expanded access programme.

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. Pertuzumab - PERJETA (CAP) - PSUSA/00010125/201806

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

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

Scope: Evaluation of a PSUSA procedure

Background

Pertuzumab is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2). It is indicated as Perjeta (pertuzumab) for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence, adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence and in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Perjeta a centrally authorised medicine containing pertuzumab 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 Perjeta (pertuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the existing warnings and undesirable effects on infusion related reactions (IRR) and hypersensitivity/anaphylaxis reactions occuring during administration of pertuzumab to state that they may be associated with fatal outcome. Therefore, the current terms of the marketing authorisation(s) should be varied[24].

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. Rotavirus vaccine monovalent (live, oral) - ROTARIX (CAP) - PSUSA/00002665/201807

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

Background

Live attenuated human rotavirus vaccine is a monovalent rotavirus vaccine indicated as Rotarix for the active immunisation of infants aged 6 to 24 weeks for prevention of gastro-enteritis due to rotavirus infection in line with official recommendations.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rotarix, a centrally authorised medicine containing rotavirus vaccine monovalent (live, oral) and issued a recommendation on its marketing authorisation(s).

[24] 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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Rotarix (rotavirus vaccine monovalent (live, oral)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include further warnings on administration of Rotarix (rotavirus vaccine monovalent (live, oral)) to infants who have known or suspected immunodeficiency and to include urticaria as an undesirable effect with a frequency 'very rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should provide an updated and refined observed versus expected analysis for Kawasaki's disease, discuss the results from surveillance in Australia in 2016 and the final results of surveillance in 2017, and discuss the biological plausibility for rotavirus vaccines to play a role in the development of necrotising enterocolitis. The MAH should also consider all published data on the risk of intussusception in European settings in the discussion on public health impact of this safety concern. The MAH should further discuss cases of elevation/abnormalities of hepatic enzymes which co-reported events of gastroenteritis, rotavirus gastroenteritis or rotavirus infection, including an analysis of time-to-onset of hepatic events and gastrointestinal events.

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

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

See also Annex I 16.2.

6.2.1. Capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP); ECANSYA (CAP); XELODA (CAP); NAP - PSUSA/00000531/201804

Applicants: Accord Healthcare Limited (Capecitabine Accord), Krka, d.d., Novo mesto (Ecansya), Medac Gesellschaft fur klinische Spezialpraparate mbH (Capecitabine medac), Roche Registration GmbH (Xeloda), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU) indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, for the treatment of metastatic colorectal cancer, for first-line treatment of advanced gastric

[25] 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

cancer in combination with a platinum based regimen, and finally as monotherapy or in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer under certain conditions. The PRAC discussed the preliminary assessment of the PSUSA procedure in December 2018. For background information, see PRAC minutes December 2018.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Capecitabine Accord, Capecitabine Medac, Ecansya and Xeloda, centrally authorised medicines containing capecitabine, and nationally authorised medicines containing capecitabine 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 capecitabine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a contraindication and a warning regarding the recent or concomitant use of brivudine. Therefore, the current terms of the marketing authorisations should be varied[26].
- In the next PSUR, the MAHs should include a cumulative review of all cases of hepatic steatosis and steatohepatitis, as well as the issue of diminished efficacy due to drug-drug interaction with proton-pump inhibitors (PPI). MAHs should discuss whether in addition to brivudine/sorivudine other drug-drug interactions (DDI) between capecitabine and other antiviral thymidine analogues have been reported in the post-marketing settings and discuss the potential mechanism for DDI between antiviral thymidine analogues and fluoropyrimidines.
- The MAH Roche should submit to the EMA, within 60 days, a review of all cases of hyperammonaemia and hyperammonaemic encephalopathy.
- The MAH Roche should also further monitor the issue of dihydropyrimidine dehydrogenase (DPD) phenotyping and submit to the EMA a detailed review concerning DPD phenotyping within 60 days of the publication of the full manuscript of the results of study NCT02324452 on 'safety, feasibility and cost-effectiveness of genotype-directed individualised dosing of fluoropyrimidines'.

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.

Based on the available evidence and further evaluation, the PRAC considered that the potentially fatal interaction with brivudine is a class effect for fluoropyrimidine-containing products for systemic use. As patients treated with a fluoropyrimidine in oncological indications are at increased risk for herpes zoster infections, the MAHs for the following fluoropyrimidine-containing products indicated in oncological indications: 5-fluorouracil (intravenous (I.V.))- and tegafur-containing products should update their product information accordingly. Further consideration is to be given at the levels of the CMDh and CHMP.

[26] Update of SmPC sections 4.3, 4.4 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

In order to further address the potentially fatal interaction between brivudine and fluoropyrimidines, the MAHs of brivudine-containing products are requested with the next PSUR to provide a proposal for further risk minimisation measures (RMMs) including a proposal to amend the product information as warranted. Further consideration is to be given at the level of the CMDh.

6.2.2. Imatinib - GLIVEC (CAP); NAP - PSUSA/00001725/201805

Applicants: Novartis Europharm Limited, various

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Imatinib is a BCR[27]-ABL[28] tyrosine kinase inhibitor (TKI) is indicated in adult and paediatric patients with newly diagnosed Philadelphia chromosome (BCR-ABL) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment; in adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis; in adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy; in adult patients with relapsed or refractory Ph+ ALL as monotherapy; in adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements; in adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement. Imatinib is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive gastrointestinal stromal tumour (GIST) as well as for the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Glivec, a centrally authorised medicine(s) containing imatinib, and nationally authorised medicines containing imatinib 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 imatinib-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add thrombotic microangiopathy (TMA) as an undesirable effect with a frequency 'rare' and as a warning to ensure that treatment with imatinib is discontinued in patients where laboratory or clinical findings are associated with TMA and a thorough evaluation for TMA, including

[27] Breakpoint cluster region protein
[28] Abelson murine leukaemia viral oncogene homolog 1

ADAMTS13[29] activity and anti-ADAMTS13-antibody determination is completed. Therefore, the current terms of the marketing authorisations should be varied[30].

- In the next PSUR, the MAHs should include reversible encephalopathy syndrome (PRES) as an important potential risk in the PSUR list of safety concerns and closely monitor cases of PRES. In addition, MAHs should include a detailed review of cases of disseminated intravascular coagulation (DIC). Furthermore, the MAH Novartis/Sandoz should include a detailed review of cases of torsade de pointes/QT prolongation associated with imatinib and make a proposal for updating the product information as warranted. The MAH Novartis/Sandoz should also discuss whether paternal exposure to imatinib lead to similar important potential risks during pregnancy, as during maternal exposure. Finally, the MAH Novartis/Sandoz should perform a detailed review of cases of scleroderma and propose to amend the product information as warranted.

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

Based on the evidence from the literature, the PRAC considered that TMA is a potential BCR-ABL TKI subclass effect. To address this potential effect, the MAHs for other BCR-ABL TKI-containing products[31] should submit a detailed review of cases of TMA as part of the next PSUR submissions. For dasatinib, see under 6.1.3.

6.2.3. Lutetium (^{177}Lu) chloride - ENDOLUCINBETA (CAP); LUMARK (CAP); NAP - PSUSA/00010391/201806

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

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor indicated for radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of lutetium (^{177}Lu) chloride-containing medicinal products in the approved indications remains unchanged.

[29] A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, also known as von Willebrand factor-cleaving protease (VWFCP)
[30] 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
[31] I.e. nilotinib (data lock point (DLP): 31/01/2019), bosutinib (DLP: 03/03/2019) and ponatib (DLP: 13/12/2018)

- Nevertheless, the product information should be updated to include a warning regarding extravasation and to amend the warnings on myelodysplastic syndrome and acute myeloid leukaemia. Furthermore, myelodysplastic syndrome and acute myeloid leukaemia should be added as undesirable effects with a frequency 'common' and 'uncommon' respectively. Therefore, the current terms of the marketing authorisations should be varied[32].
- In the next PSUR, the MAHs should provide a cumulative review of cardiac disorders and propose an update of the product information as warranted. The MAHs should also provide a cumulative review of cases of pachymeningitis and its clinical manifestations (e.g. headaches, cranial nerve palsies, papilledema, visual impairment or blindness) and critically evaluate whether risk minimisation measures (RMMs) are warranted.

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

6.2.4. Measles, mumps, rubella vaccine (live, attenuated) - M-M-RVAXPRO (CAP); NAP - PSUSA/00001937/201805

Applicants: MSD Vaccins, various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Measles, mumps and rubella vaccines (live) are indicated for simultaneous vaccination against measles, mumps, and rubella in individuals from 12 months of age, in line with official recommendations.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of M-M-RVAXPRO, a centrally authorised medicine containing measles, mumps and rubella vaccine (live), and nationally authorised medicines containing measles, mumps and rubella vaccine (live) 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 measles, mumps and rubella vaccine (live)-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include crying as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisations should be varied[33].

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

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

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

See also Annex I 16.3.

6.3.1. Ceftriaxone (NAP) - PSUSA/00000613/201805

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Ceftriaxone is a beta-lactam antibacterial, a third-generation cephalosporin, indicated for the treatment of various infections in adults and children, including bacterial meningitis, community or hospital acquired pneumonia, acute otitis media, intra-abdominal infections, complicated urinary tract infections, bone and joint infections, and complicated skin and soft tissue infections.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ceftriaxone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on drug reaction with eosinophilia and systemic symptoms (DRESS) and Jarisch-Herxheimer reaction (JAR). DRESS and JAR are also added as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAH should provide a cumulative review of cases of encephalopathy and discuss the possible pathophysiological mechanism.

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.

[34] 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

6.3.2. Cefuroxime sodium[35] (NAP) - PSUSA/00010206/201805

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

Background

Cefuroxime sodium, for intracameral use, is a second-generation bactericidal cephalosporin indicated for the prophylaxis of postoperative endophthalmitis after cataract surgery.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of cefuroxime sodium-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the method of administration and to include macular oedema as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[36].

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. Ebastine (NAP) - PSUSA/00001191/201805

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Ebastine is an antagonist of histamine H1 receptors indicated for the symptomatic treatment of allergic rhinitis (seasonal and perennial) with or without allergic conjunctivitis, idiopathic chronic urticaria, allergic dermatitis, and to improve itching and to reduce new weal formation in urticarial of unclear origin.

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

[35] Intracameral use only
[36] Update of SmPC sections 4.2 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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ebastine-containing medicinal product(s) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include increased appetite and weight increased as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[37].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of hyperprolactinaemia and cases of micturition disorders. The MAH should also propose to update the product information as warranted.

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

6.3.4. Fentanyl[38] (NAP) - PSUSA/00001370/201804

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Fentanyl is an opioid analgesic. Fentanyl transdermal patches are indicated for the treatment of management of severe chronic pain under certain conditions. Fentanyl solution for injection is indicated in general or local anaesthesia.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of fentanyl-containing medicinal product(s) transdermal patches and solution for injection in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include delirium as an undesirable effect with a frequency 'not known'. Moreover, the product information for fentanyl transdermal patches should be updated to include androgen deficiency as an undesirable effect with a frequency 'not known'. The product information for fentanyl solution for injection should be updated to add a warning on drug dependence and potential for abuse, and withdrawal syndrome, and to include withdrawal syndrome as

[37] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[38] Transdermal patches and solution for injection only

an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[39].

- In the next PSUR, the brandleader MAHs should provide a cumulative review of cases of adrenal insufficiency, discuss the possible mechanisms underlying it and propose to update the product information as warranted. In addition, the MAHs should discuss the potential impact of patch cutting which might potentially reduce the efficacy of the adhesive and may increase the risk of accidental exposure.
- The PRAC considered that the risk of delirium is also relevant for inclusion in the product information of other medicinal products containing fentanyl including products for transmucosal route of administration and fixed dose combination products. Further consideration is to be given at the level of CMDh.

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

6.3.5. Loperamide (NAP); loperamide, simeticone (NAP) - PSUSA/00010665/201805

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Loperamide is a synthetic opioid and simeticone an anti-foaming agent. Loperamide is indicated for the treatment of symptomatic control of diarrhoea under certain conditions. In patients with an ileostomy, loperamide can be used to reduce the number and volume of stools and to harden their consistency. It is also indicated for the control and symptomatic relief of diarrhoea. Loperamide oxide is indicated for reducing the volume of stoma discharge and improving anorectal continence. In combination, loperamide/simethicone is indicated for the control of acute diarrhoea of any cause and commonly associated symptoms including abdominal discomfort, bloating, cramping, and flatulence.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of loperamide- and loperamide/simeticone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the existing warning on cardiac events QRS complex prolongation has been reported in association with

[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 CMDh for adoption of a position

overdose. Therefore, the current terms of the marketing authorisation(s) should be varied[40].

- In the next PSUR, the MAH should provide cumulative reviews of cases of pancreatitis, acute pancreatitis and sphincter of Oddi dysfunction.

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. Milnacipran (NAP) - PSUSA/00002063/201804

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Milnacipran is an inhibitor of serotonin and norepinephrine reuptake (SNRI) indicated for the treatment of major depressive episode (MDE).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of milnacipran-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include Takotsubo cardiomyopathy as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[41].
- In the next PSUR, the MAH(s) should provide a cumulative review of cases of toxidermia excluding Stevens-Johnson syndrome (SJS) and an exhaustive cumulative review of cases of neurodevelopmental disorders. The MAH(s) should closely monitor cases of reversible cerebral vasoconstriction syndrome (RCVS). In addition, the MAH(s) should explore the possibility to conduct a study assessing the causal association between clinical symptoms of QT prolongation and the use of milnacipran.

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.

[40] Update of SmPC sections 4.4 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[41] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.7. Misoprostol[42] (NAP) - PSUSA/00010353/201805

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Misoprostol is a synthetic prostaglandin E1 analogue indicated[43] for cervical maturation and induction of labour under certain conditions. Misoprostol is also indicated in one Member State for the expansion of non-pregnant uterine cervix before gynaecological procedures requiring access to the uterine cavity.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing misoprostol[44] and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of misoprostol-containing medicinal product(s) in the approved indication(s) [45] remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of teratogenicity if misoprostol is used during early pregnancy. Therefore, the current terms of the marketing authorisation(s) should be varied[46].

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. Nitrous oxide (NAP); nitrous oxide, oxygen (NAP) - PSUSA/00010572/201806

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

Background

Nitrous oxide (N_2O) is a colourless, sweet smelling gas and oxygen (O_2) is a colourless, odourless reactive gas. N_2O is indicated in anaesthesia, administered with varying concentrations of O_2, in combination with other inhalation anaesthetics or intravenous anaesthetics and in analgesia when pain relief/sedation of rapid onset and rapid offset are desirable.

[42] Gynaecological indication - labour induction only
[43] Gynaecological indication - labour induction only
[44] Gynaecological indication - labour induction only
[45] Gynaecological indication - labour induction only
[46] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of nitrous oxide-, nitrous oxide/oxygen-containing medicinal product(s) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include generalised seizures as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[47].

The frequency of PSUR submission should be revised from yearly to two-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.

6.3.9. Pelargonium sidoides DC and/or pelargonium reniforme Curt., radix (NAP) - PSUSA/00002329/201806

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Background

Pelargonium root (Pelargonii radix) is the dried, usually fragmented underground organs of *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt. It is indicated for acute upper respiratory tract infections under certain conditions. As a traditional plant-based medicinal product, it is indicated for the relief from common cold symptoms in adults, adolescents and children above the age of 6 years, based on the traditional use.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing Pelargonium sidoides DC and/or Pelargonium reniforme Curt., radix and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Pelargonium sidoides DC and/or Pelargonium reniforme Curt., radix -containing medicinal products in the approved indication(s) remains unchanged.
- The PRAC adopted, by majority, a recommendation to maintain the current terms of the marketing authorisation(s) to be considered by CMDh for a position.
- In the next PSUR, the MAH should closely monitor cases of hepatotoxicity.

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.

[47] 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

Twenty-seven members voted in favour of the recommendation whilst three members had divergent views[48]. The Norwegian PRAC member disagreed with the recommendation.

6.3.10. Pholcodine (NAP) - PSUSA/00002396/201805

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Pholcodine, a semi-synthetic alkaloid, is a cough suppressant indicated for the symptomatic treatment of non-productive (dry) cough.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of pholcodine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide a cumulative review of cases of severe cutaneous adverse reactions (SCARs) and propose an update of the product information as warranted.

The frequency of PSUR submission should be revised from three-yearly to yearly. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.11. Pholcodine, biclotymol, chlorphenamine maleate (NAP) - PSUSA/00010437/201804

Applicant(s): various

PRAC Lead: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

Background

Pholcodine, a semi-synthetic alkaloid, is a cough suppressant, chlorphenamine is a H1-antihistamine and biclotymol is a phenol derivative. In combination, pholcodine/biclotymol/chlorphenamine maleate is indicated for the the symptomatic treatment of troublesome non-productive cough, in particular night cough.

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

[48] Birgitta Grundmark, Kirsti Villikka, Maia Uusküla

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of pholcodine/biclotymol/chlorphenamine maleate-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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 also Annex I 16.4.

6.4.1. Dibotermin alfa - INDUCTOS (CAP) - EMEA/H/C/000408/LEG 074

Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Detailed evaluation of the effectiveness of the current educational materials as requested in the conclusions of PSUSA/00001034/201709 adopted in April 2018

Background

Dibotermin alfa is an osteoinductive protein indicated, as InductOs, a centrally authorised medicine, for single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition. It is also indicated for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on the evaluation of the effectiveness of the educational materials for InductOs (dibotermin alfa) (for background, see PRAC minutes April 2018). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the review of the MAH's assessment of the effectiveness of the additional risk minimisations (aRMMs), the PRAC agreed that no conclusions can be drawn on the effectiveness of the aRMMs for InductOs (dibotermin alfa). While acknowledging the challenges to conclude on the effectiveness of the aRMMs due to the relatively limited usage of the medicinal product in the EU and due to the nature of the risks addressed (i.e. heterotopic ossification is a consequence of medication/administration error), the PRAC advised to request the MAH to submit to the EMA, within 180 days, a protocol for an observational study to assess the effectiveness of the aRMM as well as an updated RMP accordingly.

6.4.2. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/LEG 037

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Review of the potential benefit of Gilenya (fingolimod) use in pregnant women and women of child-bearing potential (WCBP) not using effective contraception, as well as up-to-date information on reproductive toxicity, as requested in the conclusions of PSUSA/00001393/201802 adopted in September 2018

Action: For adoption of a list of questions (LoQ) for a Scientific Advisory Group on Neurology (SAG-N) meeting

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated, as Gilenya, a centrally authorised medicine, as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) in adult patients and paediatric patients aged 10 years and older with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT), or with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on the potential benefit of Gilenya (fingolimod) use in pregnant women and women of child-bearing potential (WCBP) not using effective contraception (for background, see PRAC minutes September 2018). Whilst the responses are being assessed by the Rapporteur for further PRAC advice due at the February 2019 PRAC meeting, the PRAC discussed the planned consultation of the Scientific Advisory Group on Neurology (SAG-N).

Summary of advice/conclusion(s)

- The PRAC adopted a list of questions (LoQ) to the SAG-N for a meeting organised on 4 February 2019.

6.4.3. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/LEG 066.1

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to LEG 066 [detailed study report of the retrospective analysis of extended interval dosing (EID) versus standard interval dosing (SID), a proposal for further investigation of efficacy and safety in terms of progressive multifocal leukoencephalopathy (PML) risk reduction with EID relative to SID, and updated pharmacokinetic/pharmacodynamic (PK/PD) modelling taking into account body weight and extended dosing intervals, as requested in the conclusions of PSUSA/00002127/201708 adopted by PRAC in March 2018] as per the request for supplementary information (RSI) adopted in September 2018

Background

Natalizumab is a humanised monoclonal antibody against the cell adhesion molecule α4-integrin indicated, as Tysabri, a centrally authorised medicine, as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit further data including the TOUCH[49] prescribing programme retrospective analysis of extended interval dosing (EID) versus standard interval dosing (SID) (for background, see PRAC minutes March 2018 and PRAC minutes September 2018). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- With regard to the TOUCH registry analyses, the PRAC considered that the MAH should submit to the EMA, within 60 days, responses to a second request for supplementary information (RSI) agreed by the PRAC. In particular, the MAH should provide a sensitivity analysis using propensity score methodology. In addition, the MAH should discuss the need for an update of the progressive multifocal leukoencephalopathy (PML) risk minimisation algorithm in the educational material. Furthermore, the MAH should refine its pharmacokinetic/pharmacodynamic (PK/PD) modelling sensitivity analysis.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[50]

See also Annex I 17.1.

7.1.1. Acitretin (NAP), alitretinoin (NAP), isotretinoin (NAP) - EMEA/H/N/PSP/J/0069

Applicant: F. Hoffmann-La Roche Ltd.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Protocol for a joint drug utilisation study (DUS) to describe the prescribing practices before and after the update of the pregnancy prevention programme (PPP) for the following oral retinoids: acitretin, alitretinoin and isotretinoin in order to assess the effectiveness of the updated risk minimisation measures (RMMs) in women of childbearing potential, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC for retinoids for oral use completed in 2018 (EMEA/H/A-31/1446)

[49] Tysabri Outreach: United Commitment to Health
[50] In accordance with Article 107n of Directive 2001/83/EC

Background

Acitretin, alitretinoin and isotretinoin belong to the class of retinoids. Acitretin is indicated for the treatment of severe extensive psoriasis which is resistant to other forms of therapy, palmo-plantar pustular psoriasis; severe congenital ichthyosis and severe Darier's disease (keratosis follicularis). Alitretinoin is indicated for the topical treatment of cutaneous lesions in patients with acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma (KS) when lesions are not ulcerated or lymphoedematous, and treatment of visceral KS is not required, and lesions are not responding to systemic antiretroviral therapy, and radiotherapy or chemotherapy are not appropriate. Isotretinoin is indicated for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

In line with the conclusions reached in 2018 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1446) conducted by the PRAC for retinoid-containing medicines, MAHs were required as a condition to the marketing authorisation(s) (Annex IV) to conduct a drug utilisation study (DUS) to assess the effectiveness of the updated risk minimisation measures in women of childbearing potential before and after the update of the pregnancy prevention programme (PPP) resulting from the referral procedure. For further background, see PRAC minutes February 2018.

The MAH Roche submitted to EMA protocol version 1 of a joint DUS entitled: 'evaluation of the effectiveness of pregnancy prevention programme (PPP) for oral retinoids (acitretin, alitretinoin and isotretinoin): a European before-after drug utilisation study (DUS) using secondary data' for review by the PRAC.

Endorsement/Refusal of the protocol

- The PRAC considered that the study design and objectives are adequate. However, there are some issues that need improvement and/or clarification by the MAH, in particular the clarification of the research question, the alignment between defined objectives and the proposed data analysis, stratification by active substance and some possible weaknesses related to sampling from different databases.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.2. Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/J/0067

Applicant(s): Fresenius Kabi Deutschland GmbH, B. Braun Melsungen AG

PRAC Rapporteur: Adrien Inoubli

Scope: Protocol for a joint retrospective, multinational, drug utilisation study (DUS) to assess the non-adherence of physicians in hydroxyethyl starch (HES) accredited hospitals to the approved European product information regarding indication for use, contraindications and posology (dosage) for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures, as required in the outcome of the referral procedure under Article 107i of Directive 2001/83/EC for HES completed in 2018 (EMEA/H/A-107i/1457)

Background

Hydroxyethyl starch (HES) products derive from potato or corn with different molecular weights and substitution ratios (e.g. 200/0.5; 130/0.4). HES is approved for intravenous use for infusion and is indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

Further to the conclusions of the referral procedures under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1348) and Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) in 2013 for HES-containing medicines as well as a further referral procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1457) concluded in 2018, MAHs were required as a condition to the marketing authorisations (Annex IV) to implement additional risk minimisation measures. These measures include an additional direct healthcare professional communication (DHPC) including drug utilisation study (DUS) results, an additional box on the top of the product information, a training of healthcare professionals on appropriate use of HES-containing solutions and the implementation of a controlled access programme. These measures also include an obligation to perform a DUS to assess the effectiveness of the risk minimisation measures (RMMs) implemented as an outcome of the last referral procedure.

The MAHs Fresenius Kabi Deutschland GmbH and B. Braun Melsungen AG submitted to EMA a protocol version 1.0 for a joint study entitled: 'a retrospective, multinational, drug utilisation study (DUS) to investigate the routine use of HES-containing infusion solutions in HES-accredited European (EU) hospitals after implementation of a set of risk minimisation measures' for review by the PRAC.

Endorsement/Refusal of the protocol

- The PRAC considered that some clarifications and complementary information are needed before drawing final conclusions on the protocol. In addition, the MAHs should amend the protocol to provide further guarantees on the validity and reliability of the study. Furthermore, the MAHs should present detailed timelines of the study.
- The MAHs should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.1.3. Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/S/0068

Applicant: Serumwerk Bernburg AG

PRAC Rapporteur: Adrien Inoubli

Scope: Protocol for a retrospective, multinational, drug utilisation study (DUS) to assess the non-adherence of physicians in hydroxyethyl starch (HES) accredited hospitals to the approved European product information regarding indication for use, contraindications and posology (dosage) for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures, as required in the outcome of the referral procedure under Article 107i of Directive 2001/83/EC for HES completed in 2018 (EMEA/H/A-107i/1457)

Background

Hydroxyethyl starch (HES) products derive from potato or corn with different molecular weights and substitution ratios (e.g. 200/0.5; 130/0.4). They are approved for intravenous

use for infusion and are indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

Further to the conclusions of the referral procedures under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1348) and Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) in 2013 for HES-containing medicines as well as a further referral procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1457) concluded in 2018, MAHs were required as a condition to the marketing authorisations (Annex IV) to implement additional risk minimisation measures. These measures include an additional direct healthcare professional communication (DHPC) including drug utilisation study (DUS) results, an additional box on the top of the product information, a training of healthcare professionals on appropriate use of HES-containing solutions and the implementation of a controlled access programme. These measures also include an obligation to perform a DUS to assess the effectiveness of the risk minimisation measures (RMMs) implemented as an outcome of the last referral procedure.

The MAH Serumwerk Bernburg AG submitted to EMA protocol version 1.0 for a study entitled: 'a retrospective, multinational, drug utilisation study (DUS) to investigate the routine use of HES-containing infusion solutions in HES-accredited European (EU) hospitals after implementation of a set of risk minimisation measures' for review by the PRAC.

Endorsement/Refusal of the protocol

- The PRAC considered that some clarifications and complementary information are needed before drawing final conclusions on the protocol. In addition, the MAH should amend the protocol to provide further guarantees on the validity and reliability of the study. Furthermore, the MAH should present detailed timelines of the study.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[51]

See also Annex I 17.2.

7.2.1. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 002

Applicant: Akcea Therapeutics UK Ltd.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for a study to evaluate and further characterize the events of thrombocytopenia, glomerulonephritis and retinal toxicity/eye disease related to vitamin A deficiency when Tegsedi (inotersen) is prescribed in normal clinical practice (from opinion/MA)

Background

Inotersen is a 2'-O-2-methoxyethyl (2'-MOE) phosphorothioate antisense oligonucleotide (ASO) inhibitor indicated, as Tegsedi, a centrally authorised medicine, for the treatment of

[51] 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

stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

As part of the RMP for Tegsedi (inotersen), the MAH was required to conduct a PASS entitled 'a prospective, observational, registry study in order to further characterise for inotersen the area of missing information of extended long-term safety, the important identified risks of thrombocytopenia including a serious bleeding episode and glomerulonephritis, and the important potential risk of ocular toxicities due to vitamin A deficiency'.

The MAH submitted protocol version 001 for Tegsedi (inotersen) for the evaluation of the PASS which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC confirmed that the proposed study is non-interventional but does not meet its objectives at this stage. Therefore, the MAH should submit a revised protocol and satisfactory responses to the request for supplementary information (RSI) agreed by the PRAC. In particular, the MAH should provide further details on external unexposed cohort, a proposal for sample size that will enable the study to better meet its objectives, or an appropriate justification for the current sample size. The revised protocol should be also amended to aim to observe each patient for 10 years. In addition, the MAH is requested to submit a separate PASS protocol specific for German sites, in order to maintain the non-interventional nature of the study. The inclusion and exclusion criteria for the inotersen-exposed patients in Germany should be in accordance with the indication and contraindications specified in the product information.

7.2.2. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 024

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Protocol for study PGL18-002: a retrospective, multi-national, comparative, non-interventional cohort study to investigate the risk of liver injury possibly associated with Esmya (ulipristal acetate) use based on data from various national electronic health record based databases in Europe [final study report expected by Q4 2019] as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)

Background

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator indicated, as Esmya, a centrally authorised medicine, for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

Following a referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460), several additional pharmacovigilance activities were required to further characterise the identified risk of drug-induced liver injury (DILI) and effectiveness of risk minimisation measures.

As part of the RMP for Esmya (ulipristal acetate), the MAH was required to conduct a retrospective, multi-national, comparative, non-interventional cohort study in order to investigate the risk of DILI. The MAH submitted a protocol for a study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) for the evaluation of DILI which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The PRAC agreed that study PGL18-002: a retrospective, multi-national, comparative, non-interventional cohort study to investigate the risk of DILI possibly associated with ulipristal acetate use based on data from various national electronic health record based on databases in Europe is currently not feasible.
- The MAH should provide within this procedure a revised feasibility discussion also considering other German data sources. The critical discussion of the chosen databases as source of information and the choice of other databases covering larger patient populations need to be expanded. Apart from the IQVIA (formerly IMS Disease Analyzer) database, further databases with larger coverage of patients are available in Germany, such as the GePaRD database[52] and the WidO database[53]. Therefore, the MAH should also include the larger databases in the feasibility analysis.
- The MAH should provide annual reports from DILI registers and provide within those reports updated estimates of the precision of risk estimates.
- The exclusion of patients with significant hepatic conditions within 3 years prior to cohort entry requires further consideration. This time frame should be further justified.

7.2.3. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 028

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Protocol for study PGL18-001: a retrospective drug utilisation study (DUS) through a chart review across four major EU countries [final study report expected by Q2 2020], as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)

Background

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator indicated, as Esmya, a centrally authorised medicine, for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

Following a referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460), several additional pharmacovigilance activities were required to further characterise the identified risk of drug-induced liver injury (DILI) and effectiveness of risk minimisation measures.

[52] German Pharmacoepidemiological Research Database (GePaRD)
[53] Wissenschaftliches Institut der AOK (WIdO)

As part of the RMP for Esmya (ulipristal acetate), the MAH was required to conduct a retrospective chart review study focusing on liver monitoring in order to mitigate the risk of DILI. The MAH submitted a protocol for a study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) for the evaluation of DILI which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol V01 dated 8 October 2018 for study PGL18-001: Esmya drug utilisation in Europe: a retrospective chart review study focusing on liver monitoring could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) agreed by the PRAC are submitted to the EMA within 60 days before finalisation of the procedure.
- The MAH should state what is actually intended to be measured in order to reflect effectiveness of risk minimisation, consider implementing a control period with an index date well before the DILI signal was raised to facilitate the interpretation of the results and make sure that the results are representative of the entire target population. The MAH should further discuss the choice of countries and whether inclusion of further countries is warranted to ensure representativeness for the EU.
- The MAH should consider the sample size to obtain a sufficient number of observations from each country. The MAH is requested to provide a table with estimates of precision for a well justified interval of the key outcome variable with different sample sizes.
- The MAH should comment on the impact of requiring consent from patients before physicians can fill out the compliance questionnaire, particularly with regards to any patients experiencing severe liver events or death secondary to a severe liver event. The MAH is asked to discuss whether comorbidities strongly associated with hepatic adverse events should be collected.
- The MAH should subject the electronic case report form (eCRF) to pilot testing in a realistic setting. The MAH should verify that end of data collection is in February 2020 and final study report to be submitted in July 2020. The MAH should clarify whether the MAH plans for an approach in line with primary data collection or secondary data analysis.

7.3. Results of PASS imposed in the marketing authorisation(s)[54]

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

Applicant: Janssen Pharmaceutical Companies of Johnson & Johnson

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to PSR/S/0015 [results of a drug utilisation study (DUS) of domperidone in Europe using databases to investigate the effectiveness of risk minimisation measures and to describe the prescribing patterns before and after the changes to the domperidone label in routine clinical practice in selected European countries, as required in the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC

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

concluded in 2013] as per the request for supplementary information (RSI) adopted in September 2018

Background

Domperidone is a dopamine D_2 receptor antagonist indicated for the relief of the symptoms of nausea and vomiting under certain conditions.

In line with the conclusions reached in 2014 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1365) conducted by the PRAC for domperidone-containing medicines, MAHs were required as a condition to the marketing authorisations (Annex IV) to conduct a drug utilisation study (DUS) in several Member States to assess the effectiveness of the agreed risk minimisation measures (RMMs) and to monitor off-label use. The study protocol was to be submitted within 3 months after the European Commission decision. In October 2016, the PRAC endorsed the PASS (DUS) protocol version 2 submitted by the MAH Janssen Research and Development on behalf of a group of MAHs (the Domperidone Collaboration Study Group). For further background, see PRAC minutes November (24-27 October) 2016.

The final study report was submitted to the EMA by the MAH Janssen Research and Development on behalf of the Consortium (Domperidone Collaboration Study Group) and assessed in March 2018 first and in September 2018 following assessment of the responses of the Consortium to a first request for supplementary information (RSI). For further background, see PRAC minutes March 2018 and PRAC minutes September 2018. At the current meeting, the PRAC discussed the Consortium's responses to a further RSI.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'a drug utilisation study of domperidone in Europe using databases', as well as the Consortium's responses to the RSI, the PRAC considered that the benefit-risk balance of domperidone-containing product(s) concerned by the PASS final report remains unchanged. As a consequence, the PRAC recommended that the terms of the marketing authorisation(s) for domperidone-containing product(s) concerned by the PASS final report should be varied to remove the study as an obligation 'to perform a drug utilisation study to assess the effectiveness of the risk minimisation measures and to monitor off-label use' from the 'conditions or restrictions with regard to the safe and effective use of the medicinal product(s).
- The PRAC agreed key elements for the dissemination of a direct healthcare professional communication (DHPC) to remind healthcare professionals (HCPs) of the restricted indications of 'nausea and vomiting' and contraindications regarding the use of CYP3A4[55] inhibitors in case of hepatic impairment as well as the severe cardiac undesirable effects.

7.3.2. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/PSR/S/0020

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Results of an observational 5 year safety study to assess the identified and potential

[55] Cytochrome P450 3A4

risks of Bronchitol (mannitol) in cystic fibrosis (CF) through a comparison between Bronchitol-exposed patients and unexposed patients matched for key characteristics

Background

Mannitol is a mucolytic indicated, as Bronchitol a centrally authorised medicine, for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.

Bronchitol, a centrally authorised medicine containing mannitol, was authorised in 2012. As a condition to the marketing authorisation (Annex II-D), the MAH was required to set up a PASS[56] to assess the identified and potential risks of Bronchitol in CF through a comparison between Bronchitol-exposed patients and an unexposed patient group matched for key characteristics. The MAH shall provide the results of an epidemiological study addressing this issue, according to an agreed protocol.

The final study report was submitted to the EMA by the Pharmaxis Pharmaceuticals Limited on 5 November 2018. The PRAC discussed the final study results following assessment.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'observational safety 5 year safety study of Bronchitol (inhaled mannitol) in patients with cystic fibrosis using the UK Cystic Fibrosis Registry', the PRAC considered that a request for supplementary information (RSI) was necessary before a recommendation could be made on the benefit-risk balance of medicinal products containing mannitol concerned by the PASS final report. The MAH should discuss the higher incidence rate of any new fungal infection in the matched exposed group compared to the matched unexposed group, and present a statistical analysis of this difference. Finally, the MAH should consider and further discuss the inclusion of fungal infection, in particular of new Aspergillus infection, in the product information as warranted.
- The MAH should submit responses to the RSI within 60 days to the EMA. A 30 day-assessment timetable will be followed.

7.3.3. Piperaquine tetraphosphate, artenimol – EURARTESIM (CAP) - EMEA/H/C/PSR/S/0018

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Julie Williams

Scope: MAH's response to PSR/S/0018 [results of a safety registry study in the EU assessing the association between the QTc prolongation induced by Eurartesim (piperaquine tetraphosphate/artenimol) and various factors, co-morbidities and concomitant medications, as well as at monitoring patterns of drug utilisation] as per the request for supplementary information (RSI) adopted in September 2018

Background

Artenimol is an antimalarial and piperaquine a bisquinoline. In combination as Eurartesim, a centrally authorised medicine, artenimol/piperaquine tetraphosphate is indicated for the

[56] An observational safety 5 year safety study of Bronchitol (inhaled mannitol) in patients with cystic fibrosis using the UK Cystic Fibrosis Registry

treatment of uncomplicated *Plasmodium falciparum* malaria in adults, adolescents, children and infants 6 months and over and weighing 5 kg or more.

Eurartesim, a centrally authorised medicine containing piperaquine tetraphosphate/dihydroartemisinin, was authorised in 2011. As a condition to the marketing authorisation (Annex II-D), the MAH was required to set up a PASS[57] to further substantiate the cardiac safety of Eurartesim use in patients with signs and symptoms of uncomplicated malaria, including the effect of Eurartesim administration on QTc intervals. The MAH should provide the results of an epidemiological study addressing this issue, according to an agreed protocol.

The final study report was submitted to EMA by MAH Alfasigma S.p.A and was initially assessed in September 2018. For further background, see PRAC minutes September 2018. At the current meeting, the PRAC discussed the final study results together with the MAH's response to a request for supplementary information (RSI).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'safety registry for Eurartesim: an observational, non-comparative, non-interventional, longitudinal, multi-centre safety registry for malaria patients treated with Eurartesim' as well as the MAH's responses to the RSI, the PRAC considered that the benefit-risk balance of Eurartesim (piperaquine tetraphosphate/artenimol) remains unchanged. As a consequence, the PRAC recommended that the terms of the marketing authorisation(s) for Eurartesim (piperaquine tetraphosphate/artenimol) should be varied to remove the PASS as an obligation 'to perform an epidemiological study to further substantiate the cardiac safety of Eurartesim use in patients with signs and symptoms of uncomplicated malaria, including the effect of Eurartesim administration on QTc intervals' from the 'conditions or restrictions with regard to the safe and effective use of the medicinal product'.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[58]

See also Annex I 17.4.

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

Applicant: Pfizer Europe MA EEIG

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 (i.e. without etanercept or other biologics during pregnancy), using merged data from Sweden, Denmark and Finland

[57] EUPAS6942. Safety registry for Eurartesim: an observational, non-comparative, non-interventional, longitudinal, multi-centre safety registry for malaria patients treated with Eurartesim

[58] 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

Background

Etanercept is a tumour necrosis factor alfa (TNF-α) inhibitor indicated, as Enbrel and Lifmior, centrally authorised products, for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis, plaque psoriasis as well as peadiatric plaque psoriasis, under certain conditions.

As stated in the RMP of Enbrel and Lifmior (etanercept), the MAH conducted a non-imposed non-interventional PASS (study B1801396) 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 treated with non-biologic systemic drugs. The Rapporteur assessed the MAH's final study report in addition to the MAH's responses to requests for supplementary information (RSI). The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation. For further background, see PRAC minutes May 2018 and PRAC minutes September 2018.

Summary of advice

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report could go for a positive opinion.
- The PRAC supported the conclusions that no increased risk of birth defects, infections in the first year of life, preterm birth, low birth weight, small gestational age or stillbirth with etanercept during pregnancy was detected in the study. The PRAC noted possible increased risks of low birth weight with treatment in the first trimester and small gestational age with treatment in the second and third trimesters. However, the strength of these analyses is limited by the small numbers, multiple testing and possible residual confounding. The PRAC supported updating the existing information about pregnancy in the product information[59] to include a summary of the results of study B1801396, and to state that etanercept should only be used during pregnancy if clearly needed and that women of childbearing potential should consider the use of appropriate contraception. This wording is aligned with the product information of other TNF-α antagonists.

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

See Annex I 17.5.

7.6. Others

See also Annex I 17.6.

7.6.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/LEG 031

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Karen Pernille Harg

[59] Update of SmPC section 4.6. The package leaflet is updated accordingly

Scope: Comprehensive review of the results of study CLE-20098-096 (listed as a category 3 study in the RMP): agomelatine drug utilisation study (DUS) in selected European countries: a multinational, observational study to assess effectiveness of risk-minimisation measures, together with a review of post-marketing observational studies and available pharmacovigilance data in relation to hepatotoxicity and consideration on the need for continuing and improving the current additional risk minimisation measures (RMMs) including a discussion on whether liver function testing prior to and during treatment with agomelatine is regarded as a standard of care in the EU Member States, as requested in the conclusions of variation II/38 adopted in September 2018

Background

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT^{60}_{2C} antagonist, indicated as Thymanax, a centrally authorised medicine, in adults for the treatment of major depressive episodes.

Since the initial marketing authorisation of Thymanax (agomelatine) in 2009, risk minimisation measures (routine and additional measures) have been implemented mainly in order to prevent or reduce the hepatic risk of agomelatine, by ensuring the respect of contra-indications and liver function monitoring according to product information recommendations. The MAH was asked to perform a critical and comprehensive review of the results of the CLE-20098-096 PASS study. Based on this review, and on post-marketing observational studies and available pharmacovigilance data in relation to hepatotoxicity, the MAH was requested to discuss if additional risk minimisation measures (RMMs) should be continued.

Summary of advice

- The PRAC, having considered the data submitted by the MAH supported by the PRAC Rapporteur's assessment, agreed that the MAH should continue to distribute the educational materials (physician guide and patient booklet) at this stage with distribution frequency changed from biannually to annually and plan and implement measures aiming at assessing the effectiveness of the RMMs.
- The MAH should include in the next PSUR (with a data lock point (DLP): 19/02/2021) a detailed analysis on the usefulness and effectiveness of the RMMs, focusing on distribution modalities and targeted audience (detailing the tailored process confirming whether healthcare professionals (HCPs)/patients have effectively and timely received these materials, have understood and found them useful). Further to this evaluation, the MAH should also discuss whether the distribution of the educational materials should be continued.

7.6.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/LEG 031

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Karen Pernille Harg

Scope: Comprehensive review of the results of study CLE-20098-096 (listed as a category 3 study in the RMP): agomelatine drug utilisation study (DUS) in selected European countries: a multinational, observational study to assess effectiveness of risk-minimisation measures,

[60] 5-hydroxytryptamine

together with a review of post-marketing observational studies and available pharmacovigilance data in relation to hepatotoxicity and consideration on the need for continuing and improving the current additional risk minimisation measures (RMM) including a discussion on whether liver function testing prior to and during treatment with agomelatine is regarded as a standard of care in the EU Member States, as requested in the conclusions of variation II/39 adopted in September 2018

Background

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT^{61}_{2C} antagonist, indicated as Valdoxan, a centrally authorised medicine, in adults for the treatment of major depressive episodes.

Since the initial marketing authorisation of Valdoxan (agomelatine) in 2009, risk minimisation measures (routine and additional measures) have been implemented mainly in order to prevent or reduce the hepatic risk of agomelatine, by ensuring the respect of contra-indications and liver function monitoring according to product information recommendations. The MAH was asked to perform a critical and comprehensive review of the results of the CLE-20098-096 PASS study. Based on this review, and on post-marketing observational studies and available pharmacovigilance data in relation to hepatotoxicity, the MAH was requested to discuss if additional risk minimisation measures (RMMs) should be continued.

Summary of advice

- The PRAC, having considered the data submitted by the MAH supported by the PRAC rapporteur's assessment, agreed that the MAH should continue to distribute the educational materials (physician guide and patient booklet) at this stage with distribution frequency changed from biannually to annually and plan and implement measures aiming at assessing the effectiveness of the RMMs.
- The MAH should include in the next PSUR with a data lock point (DLP): 19/02/2021) a detailed analysis on the usefulness and effectiveness of the RMMs, focusing on distribution modalities and targeted audience (detailing the tailored process confirming whether healthcare professionals (HCPs)/patients have effectively and timely received these materials, have understood and found them useful). Further to this evaluation, the MAH should also discuss whether the distribution of the educational materials should be continued.

7.6.3. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/REC 001.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: MAH's response to REC 001 [protocol for study R668-AD-1225: a non-imposed, interventional PASS: an open-label study of dupilumab in patients with atopic dermatitis who participated in previous dupilumab clinical trials, five year open label extension study] as per the request for supplementary information (RSI) adopted at the November 2017 PRAC meeting

[61] 5-hydroxytryptamine

Background

Dupilumab is a recombinant human immunoglobulin (Ig) G4 monoclonal antibody indicated, as Dupixent a centrally authorised medicine, for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy.

As part of the RMP for Dupixent (dupilumab), long-term safety including malignancy is included as missing information. The MAH was requested to conduct a non-interventional PASS to investigate long-term adverse events including the risk of malignancy. The MAH proposed a PASS based on existing AD registries in Europe, using a network of registries called Treatment of Atopic Eczema Registry Taskforce (TREAT) to examine the risk of malignancies in the real world setting. The PRAC endorsed this proposal and requested the submission of a non-interventional PASS protocol. For further background, see PRAC minutes November 2017 (23-26 October 2017). In this submission the MAH investigated alternative study designs and data sources.

Summary of advice

- The MAH should evaluate and discuss the feasibility and value of using a prevalent new-user cohort design (*Suissa et al.*[62]) or other designs that have been used to compare associations with second or third line treatments. The MAH should discuss whether such designs could address the weaknesses anticipated in the registry study.

7.6.4. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 023

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Feasibility assessment for study 3083-S03-000: a physiologically based pharmacokinetic (PBPK) modelling of ulipristal acetate under conditions of impaired bile secretion, as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)

Background

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator indicated, as Esmya, a centrally authorised medicine, for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

Following a referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460), several additional pharmacovigilance activities were required to further characterise the identified risk of DILI and effectiveness of risk minimisation measures. The aim of this procedure was to perform feasibility assessment of pharmacokinetic (PBPK) modelling of ulipristal acetate (UPA) in bile secretion impaired conditions. Moreover, if feasible, the specific aim was to estimate the concentrations of UPA and its metabolite PGL4002 in human blood and liver in a PBPK model in which bile secretion is impaired.

[62] Suissa et al. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiology and Drug safety 2017 Apr; 26(4): 459-468

Summary of advice

- The PRAC agreed that the post-authorisation commitments regarding the feasibility assessment for PBPK modelling under conditions of impaired bile flow (study 3083-S03-000) are not fulfilled at the current stage.
- Therefore, the MAH is requested to provide details about the previously developed PBPK model for the parent compound (UPA), consider the inclusion of enterohepatic circulation as an integral part of the PBPK model and perform alternative modelling strategies in order to overcome lack of informative data for the individual metabolites.

7.6.5. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 025

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Feasibility report for a retrospective case control study utilising medical records of transplantation centres in at least five EU Member States as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)

Background

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator indicated, as Esmya a centrally authorised medicine, for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

Following a referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460), several additional pharmacovigilance activities were required to further characterise the identified risk of drug-induced liver injury (DILI) and effectiveness of risk minimisation measures. The aim of this procedure was a feasibility report for a retrospective case control study utilising medical records of transplantation centres in at least five EU Member States.

Summary of advice

- The PRAC agreed that the use of case data from transplantation centres may be of value to further characterise the risk of DILI following ulipristal acetate exposure, and provide some estimation of absolute risk. Nevertheless, the Committee agreed that the MAH should address a request for supplementary information (RSI) before concluding on this feasibility report.
- The MAH should discuss the impact of cases of acute liver injury not leading to being placed on the transplant list/not being registered in the transplant registry, on the overall feasibility, reliability and precision of the proposed study.
- The MAH should for the feasibility exercise further clarify whether it is possible to define a meaningful population denominator for a situation with non-complete participation of transplantation centres in the data source. The MAH should comment on the number of anticipated cases with Esmya (ulipristal acetate) as the feasibility of this study depends on the sufficient number of cases of transplantation in which Esmya is used.

- The MAH should discuss the inclusion of additional European countries that have an adequate Esmya exposure and an adequate rate of liver transplantations. This discussion could be presented within the final feasibility assessment after receiving the feedback from further transplant centres.

7.6.6. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 026

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Feasibility report for an observational study using EU registries with biomarker data, as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)

Background

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator indicated, as Esmya a centrally authorised medicine, for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

Following a referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460), several additional pharmacovigilance activities were required to further characterise the identified risk of risk of drug-induced liver injury (DILI) and effectiveness of risk minimisation measures. The aim of this procedure was a feasibility report for an observational study using EU registries with biomarker data e.g. The Health Improvement Network (THIN, United Kingdom), German Pharmacoepidemiological Research Database (GePaRD, Germany), Pro-EURO drug-induced liver injury (DILI) registry, Spanish registry and International DILI consortium (iDILIC) registry.

Summary of advice

- The PRAC agreed that two of the DILI registers reviewed may also be of value for in-depth characterisation of cases but their coverage (i.e. their ability to capture available cases) remains uncertain.
- The MAH should further clarify the catchment areas of participating centres in the Pro-Euro DILI registry and the Spanish registry, along with an estimate of exposure to Esmya (ulipristal acetate) in those populations. This would allow a better view on how plausible it is that Esmya-exposed DILI cases will be captured by these data sources.

7.6.7. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 027

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Feasibility report for a genetic analysis (human leukocyte antigen (HLA)) study using data from EU registries with biomarker data in patients with severe drug-induced liver injury (DILI), as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)

Background

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator indicated, as Esmya a centrally authorised medicine, for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

Following a referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460), several additional pharmacovigilance activities were required to further characterise the identified risk of drug-induced liver injury (DILI) and effectiveness of risk minimisation measures. The aim of this procedure was a feasibility report for a genetic analysis (HLA) study using data from EU registries with biomarker data in patients with severe DILI in registries such as, the International drug-induced liver injury (DILI) Consortium (iDILIC), Spanish registry and the Pro-EURO DILI registry.

Summary of advice

- The PRAC agreed that two of the DILI registers reviewed may also be of value for in-depth characterisation of cases but their coverage (i.e. their ability to capture available cases) remains uncertain.
- The MAH should further clarify the catchment areas of participating centres in the Pro-Euro DILI registry and the Spanish registry, along with an estimate of Esmya exposure in those populations. This would allow a better view on how plausible it is that Esmya-exposed DILI cases will be captured by these data sources.

7.6.8. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 029

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Feasibility report for a study using EU registries and the drug-induced liver injury (DILI) registry databases to measure the effectiveness of the risk minimisation measures to mitigate the risk of DILI, as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460)

Background

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator indicated, as Esmya a centrally authorised medicine, for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

Following a referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460), several additional pharmacovigilance activities were required to further characterise the identified risk of drug-induced liver injury (DILI) and effectiveness of risk minimisation measures. The aim of this procedure was a feasibility report for a study to measure the effectiveness of the risk minimisation measures to mitigate the risk of DILI, using EU registries and the DILI registry databases.

Summary of advice

- The PRAC agreed that the use of available EU registries would provide limited value to measure effectiveness of RMM due to lack of necessary data collection and agreed not to pursue this study. The PRAC also agreed that using targeted follow-up questionnaires on DILI cases is unlikely to allow a meaningful evaluation of effectiveness of RMMs.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/II/0032

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Consultation on a type II variation to update section 4.4 of the SmPC following a cumulative review of acute kidney injury (AKI) events requested by PRAC in May 2018 (EPITT 19204) in order to add information on the potential for dulaglutide to contribute to volume depletion events which could indirectly contribute to the occurrence of AKI. The package leaflet is updated accordingly

Background

Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist indicated as Trulicity in adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control under certain conditions.

A type II variation proposing to update the product information of Trulicity (dulaglutide) on acute kidney injury (AKI) events is under evaluation at the CHMP. This procedure was initiated following a recommendation for a signal evaluated by the PRAC. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information and the CHMP Rapporteur's assessment, the PRAC agreed on the revision of the existing warning to advise that cases of dehydration leading to deterioration of renal function in association with dulaglutide can also occur independently from episodes of gastrointestinal (GI) effects such as vomiting and diarrhoea. In addition, the PRAC supported adding 'dehydration' as an undesirable effect. Moreover, the Committee advised to add to the product information details around the timing of events of dehydration and that these have tended to be reported at the initiation of treatment.

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Methylphenidate hydrochloride (NAP) - DE/H/XXXX/WS/547

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

PRAC Lead: Martin Huber

Scope: PRAC consultation on a national worksharing variation on RMP safety concerns for methylphenidate-containing products considering the additional risk minimisation measures (aRMM) currently in place and the outcome of the referral procedure for methylphenidate-containing products under Article 31 of Directive 2001/83/EC (EMEA/658285/2008) completed in 2009, in light of revision 2 of GVP module V on 'Risk management systems', on request of Germany

Background

Methylphenidate is a central nervous system (CNS) stimulant drug, indicated for the treatment of attention deficient hyperactivity disorder (ADHD) under certain conditions.

Most RMPs of methylphenidate-containing products contain the elements of the core safety specification and certain risk minimisation activities following the referral procedure for methylphenidate-containing products under Article 31 of Directive 2001/83/EC (EMEA/658285/2008) concluded in 2009. Taking into consideration that some differences remain, partly due to differences in indications and considering the recent revisions of GVP module V on 'Risk management systems' and GVP module VII on 'Periodic safety update report', Germany, as lead Member State (LMS), requested PRAC advice on its assessment in the context of the evaluation of a worksharing variation procedure.

Summary of advice

- Based on the review of the available information, the PRAC agreed with the LMS and the proposal to revise the core safety specification for methylphenidate-containing products for RMPs and for PSURs. In future PSURs detailed information should be requested for the risks of arrhythmias, ischaemic cardiac events, cardiomyopathy, QT prolongation and sudden death belonging to the important identified risk of 'serious cardiovascular events' and the risk of diversion belonging to the important identified risk of 'drug abuse/drug dependence'.

11.1.2. Valproate (NAP) - NL/H/xxxx/WS/0312

Applicant(s): Sanofi (Depakine)

PRAC Lead: Liana Gross-Martirosyan

Scope: PRAC consultation on a national worksharing variation on the RMP for Depakine

(valproate) relating to scientific aspects relevant to the condition requesting 'MAHs to conduct a PASS preferably based on existing registries to further characterise the foetal anticonvulsant syndrome in children with valproate in utero exposure as compared to other anti-epileptic drugs' imposed in the outcome of the referral procedure for valproate-containing products under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) completed in 2018, on request of the Netherlands

Background

Sodium valproate is indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

A worksharing variation procedure (NL/H/xxxx/WS/0312) including a RMP is currently assessed for Depakine (valproate) and refers to one of the conditions imposed in the outcome of the recent referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1454) conducted by the PRAC for valproate-containing medicines (Annex IV) and finalised in 2018. The condition refers to the obligation to conduct a PASS, preferably based on existing registries, to further characterise the foetal anticonvulsant syndrome in children with valproate in utero exposure as compared to other anti-epileptic drugs (AEDs). The MAH (on behalf of a consortium of MAHs) provided an update on the collaboration with existing registries. In the context of the evaluation of the worksharing variation procedure, Netherlands as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC agreed with the LMS regarding the feasibility issues presented by the MAH and the need to investigate alternative data sources. The PRAC supported the LMS to request the MAH (on behalf of the consortium of MAHs) to provide a thorough review and analysis of the recent publication in Lancet Neur[63] based on data from the 'European Registry of Antiepileptic Drugs in Pregnancy' (EURAP) and any other relevant publications regarding foetal anticonvulsant syndrome (FACS) in children exposed to valproate in utero that have become available since the finalisation of the referral procedure. The MAH should evaluate whether the data provides new information on FACS in children exposed to valproate in utero compared to other AEDs, and discuss the limitations of this data in addressing current gaps in knowledge. In addition, the MAH should assess the feasibility and value of using alternative data sources in EU and outside of EU (e.g. North America, Australia) in order to characterise FACS in children exposed to valproate in utero as compared with other AEDs. For data sources in EU, the MAH should consider the data sources as described in the published inventory of data sources in 28 Member States. Furthermore, the MAH should take into account the methodological considerations as described in the generic protocols 'exposure to antiepileptic medicines in-utero and neurodevelopmental disorders in the off-spring' (EUPAS21171).

[63] T Tomson et al, 2018. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurology,Volume 17, Issue 6, 2018, Pages 530-538

11.2. Other requests

11.2.1. Phenylephrine hydrochloride, tropicamide (NAP) - DK/H/PSUFU/00010430/201711

Applicant(s): Thea Laboratoires (Mydriasert), Visufarma SpA (Visumidriatic Fenilefrina)

PRAC Lead: Anette Kirstine Stark

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on a cumulative review and characterisation of the risk of 'systemic adverse reactions' associated with ophthalmic use of medicinal products containing phenylephrine/tropicamide in the paediatric population, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on phenylephrine/tropicamide (PSUSA/00010430/201711) concluded in July 2018, on request of Denmark

Background

Phenylephrine is an alfa sympathomimetic and tropicamide an anticholinergic. In combination, phenylephrine/tropicamide is indicated to obtain pre-operative mydriasis or mydriasis for diagnostic purposes. As an ophthalmic solution, it is also indicated for therapeutic use in the context of iritis, iridocyclitis, and uveitis.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for phenylephrine/tropicamide (PSUSA/00010430/201711) concluded in July 2018, the PRAC considered that 'systemic adverse reactions' associated with ophthalmic use of medicinal products containing phenylephrine in the paediatric population needed to be further assessed (for further background, see PRAC minutes July 2018). The originator MAH(s) for phenylephrine/tropicamide-containing product(s) were requested by CMDh to submit a thorough cumulative review and characterisation of the risk of systemic adverse reactions associated with use in children, as a worksharing PSUR follow-up (PSU FU) procedure. In the context of the evaluation of the worksharing PSU FU procedure, Denmark as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and taking into account the potential mechanisms explaining higher sensitivity to serious systemic adverse reactions in children aged below 12 years, the PRAC supported the conclusions of the LMS that there is sufficient available evidence at this stage to contraindicate the use of phenylephrine/tropicamide fixed drug combination (FDC) products for ophthalmic use containing 10% phenylephrine in children under 12 years of age as well as to include a warning against use of phenylephrine/tropicamide FDC products for ophthalmic use containing 10% phenylephrine in adolescents (12-18 years), as clinical experience is missing in this age group.
- The PRAC supported the LMS conclusions that MAHs of phenylephrine-mono component containing products for ophthalmic use[64] should be requested to submit with the next PSUR (data lock point (DLP): 01/01/2020) a cumulative review and risk characterisation of systemic adverse reactions associated with use in paediatric patients.

[64] As per the requirements set out in the list of Union reference dates and frequency of submission of PSURs (EURD list), procedure: PSUSA/00010402/202001

11.2.2. Rosuvastatin (NAP) - NL/H/PSUFU/00002664/201711

Applicant: AstraZeneca (Crestor, Provisacor)

PRAC Lead: Menno van der Elst

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on the safety concern of 'systemic lupus erythematosus/lupus erythematosus/lupus-like syndrome' and 'muscle rupture/ torn muscle' and causal association with rosuvastatin as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on rosuvastatin (PSUSA/00002664/201711) concluded in July 2018, on request of the Netherlands

Background

Rosuvastatin is a selective, potent and competitive inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase, and is indicated for the treatment of hypercholesterolaemia and prevention of cardiovascular events.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for rosuvastatin (PSUSA/00002664/201711) concluded in July 2018, the PRAC considered that the safety concern of 'systemic lupus erythematosus/lupus erythematosus/lupus-like syndrome' and 'muscle rupture/ torn muscle' needed to be further assessed (for further background, see PRAC minutes July 2018). The originator MAH for rosuvastatin-containing product(s) was requested by CMDh to submit safety reviews of cases of 'systemic lupus erythematosus/lupus erythematosus/lupus-like syndrome' and 'muscle rupture/ torn muscle' from post-marketing exposure and from the literature, together with a thorough discussion of the possible patho-mechanisms and a proposal for updating the product information as warranted, as part of a worksharing PSUR follow-up (PSU FU) procedure. In the context of the evaluation of the worksharing PSU FU procedure, the Netherlands as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions from the LMS and concurred that there was sufficient available evidence at this stage to support a possible causal relationship between 'lupus-related events' and 'muscle rupture' with rosuvastatin. As a consequence, the PRAC supported the conclusion of the LMS to update the product information in order to include 'lupus-like syndrome' and 'muscle rupture' as undesirable effects with a frequency 'rare'.
- The PRAC agreed with the LMS that MAHs of rosuvastatin-fixed dose combination (FDC) medicinal products should be requested to add to their product information 'lupus-like syndrome' and 'muscle rupture' as undesirable effects.

11.2.3. Ulipristal acetate - AT/H/0862/001/DC, AT/H/0863/001/DC

PRAC Lead: Jan Neuhauser

Scope: PRAC consultation on the evaluation of initial marketing authorisation application(s) under the decentralised procedure for generic ulipristal-containing medicinal products on request of Austria

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

12.3.1. Working Party with Patients' and Consumers' Organisations (PCWP) – revised mandate and composition

The EMA Secretariat presented to the PRAC the revised mandate and composition of the Working Party with Patients' and Consumers' Organisations (PCWP). The revision is based on experience gained over the years and feedback received from the working party members. As a consequence, the mandate and composition of the PCWP are refined. The PRAC agreed with this revision.

12.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP) - revised mandate and composition

The EMA Secretariat presented to the PRAC the revised mandate and composition of the Working Party with Healthcare Professionals' Organisations (HCPWP). The revision is based on experience gained over the years and feedback received from the working party members. As a consequence, the mandate and composition of the HCPWP are refined. The PRAC agreed with this revision.

12.3.3. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP) - revised rules of procedure

The EMA Secretariat presented to the PRAC the revised rules of procedure of the Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP). The revision is based on experience gained over the years and feedback received from the working party members. As a consequence, the rules of procedure of both PCWP and HCPWP are merged, as well as future work plans. The PRAC adopted the joint rules of procedure, due also for adoption at the other EMA Committees and CMDh.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2019

PRAC lead: Sabine Straus, Martin Huber

As a follow-up to previous discussions on the PRAC work plan 2019 (for further background, see PRAC minutes November 2018 (29-31 October 2018) and PRAC minutes December 2018 (26-29 November 2018), the PRAC further consolidated the draft final document and adopted the work plan 2019.

Post-meeting note: On 25/03/2019, the PRAC work plan 2019 (EMA/PRAC/190876/2019) was published on the EMA website.

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q4 2018 and predictions

At the organisational matters teleconference held on 31 January 2019, 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 November 2018 (29-31 October 2018).

12.8.2. Marketing authorisation applications (MAA) forecast for 2019 – planning update dated Q4 2018

At the organisational matters teleconference held on 31 January 2019, the EMA Secretariat presented for information to PRAC a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline'). For previous update, see PRAC minutes October 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.

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 January 2019, 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 in January 2019, the updated EURD list was adopted by the CHMP and CMDh at their January 2019 meetings and published on the EMA website on 06/02/2019, 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: Menno van der Elst

The January 2019 SMART meeting was cancelled.

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 30/01/2019 on the EMA website (see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>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. Drug induced hepatotoxicity – PRAC review status update

PRAC lead: Amelia Cupelli, Liana Gross-Martirosyan, Jolanta Gulbinovic, Martin Huber, Zane Neikena, Sabine Straus, Menno van der Elst, Stefan Weiler

In line with the PRAC work plan 2018 and PRAC work plan 2019, the PRAC agreed on a draft proposal for the review of drug induced hepatotoxicity. The aim of this review is to collate the available guidance for detecting and assessing drug induced hepatotoxicity, building on the existing expertise of individual PRAC members, in order to improve its management. A proposal from the working group will be presented to the PRAC in Q2 2019.

12.20.2. Strategy on measuring the impact of pharmacovigilance - PRAC interest group (IG) Impact work plan 2019

As a follow-up to the last discussion (for background: see PRAC minutes November 2018 (29-31 October 2018), the PRAC adopted the Interest Group (IG) Impact work plan 2019-2020 which includes several deliverables on measuring the impact of pharmacovigilance activities. Measuring the impact of the tools and interventions used in pharmacovigilance is one of the key aspects of the work of the PRAC.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[65]

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[66].

[65] [65] 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

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

14.1.1. Atezolizumab – TECENTRIQ (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Signal of anaphylactic reaction

EPITT 19335 – New signal

Lead Member State(s): PT

14.2. New signals detected from other sources

14.2.1. Dabigatran – PRADAXA (CAP)

Applicant(s): Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of alopecia

EPITT 19337 – New signal

Lead Member State(s): DK

14.2.2. Dimethyl fumarate – TECFIDERA (CAP), SKILARENCE (CAP), NAP

Applicant(s): Almirall S.A (Skilarence), Biogen Netherlands B.V. (Tecfidera), various

PRAC Rapporteur: Martin Huber

Scope: Signal of arthritis and arthralgia

EPITT 19338 – New signal

Lead Member State(s): DE

14.2.3. Pantoprazole – CONTROLOC CONTROL (CAP), PANTOLOC CONTROL (CAP), PANTOZOL CONTROL (CAP), SOMAC CONTROL (CAP), NAP

Applicant(s): Takeda GmbH (Controloc Control, Pantoloc Control, Pantozol Control, Somac Control), various

PRAC Rapporteur: Patrick Batty

Scope: Signal of colitis microscopic

EPITT 19342 – New signal

Lead Member State(s): UK

14.2.4. Pregabalin – LYRICA (CAP), PREGABALIN ACCORD (CAP), PREGABALIN MYLAN (CAP), PREGABALIN MYLAN PHARMA (CAP), PREGABALIN PFIZER (CAP), PREGABALIN SANDOZ (CAP), PREGABALIN SANDOZ GMBH (CAP), PREGABALIN ZENTIVA (CAP), PREGABALIN ZENTIVA K.S. (CAP); NAP

Applicant(s): Accord Healthcare Limited (Pregabalin Accord), Mylan S.A.S. (Pregabalin Mylan, Pregabalin Mylan Pharma), Pfizer Europe MA EEIG (Lyrica, Pregabalin Pfizer),

Sandoz GmbH (Pregabalin Sandoz, Pregabalin Sandoz GmbH), Zentiva k.s. (Pregabalin Zentiva, Pregabalin Zentiva k.s.), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of respiratory depression with and without concomitant opioid use

EPITT 19339 – New signal

Lead Member State(s): NL

14.2.5. Sertraline (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of maculopathy

EPITT 19341 – New signal

Lead Member State(s): NL

14.2.6. Temozolomide – TEMODAL (CAP)

Applicant(s): Merck Sharp & Dohme B.V.

PRAC Rapporteur: Martin Huber

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

EPITT 19332 – New signal

Lead Member State(s): DE

14.2.7. Topiramate (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of uveitis

EPITT 19345 – New signal

Lead Member State(s): SE

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. Ambrisentan - EMEA/H/C/004955

Scope: Treatment of pulmonary arterial hypertension (PAH)

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

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. Adefovir dipivoxil - HEPSERA (CAP) - EMEA/H/C/000485/II/0081

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Adrien Inoubli

Scope: Update of the RMP (version 2.1) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.2. Aztreonam - CAYSTON (CAP) - EMEA/H/C/000996/II/0075, Orphan

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of the RMP (version 7.1) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.2.3. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0072

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 14.1) in order to remove the prescriber guide to the list of educational materials and to revise the RMP in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template), including the update of the important identified risks, important potential risks and missing information. The PASS protocol for study UP0038 designed to assess the effectiveness of the educational material is updated to add dermatologists to the healthcare professional study population, to remove Italy and Spain from the study participation and to make additional administrative changes. In addition, the MAH took the opportunity to introduce some administrative changes in the RMP.

15.2.4. Corifollitropin alfa - ELONVA (CAP) - EMEA/H/C/001106/II/0043

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 8.1) in order to implement changes in line with revision 2 of the guidance on the format of RMP in the EU (template), to include data following the

completion of study P017: a phase 3 follow-up trial to collect outcome and safety of frozen-thawed embryo transfer (FTET) cycles performed with the embryos cryopreserved in studies P016 (a phase 3, randomized, double-blind, active-controlled, non-inferiority trial to investigate the efficacy and safety of a single injection of corifollitropin alfa to induce multifollicular development for controlled ovarian stimulation (COS) using daily recombinant FSH (recFSH) as a reference in women aged 35 to 42 years) and P031 (a phase 3, multicentre, open label trial to evaluate the efficacy and safety of corifollitropin alfa in combination with human chorionic gonadotropi n (hCG) in inducing testicular development and spermatogenesis in adult azoospermic men with hypogonadotropic hypogonadism), as requested in the conclusion of PSUSA/00000875/201407 adopted in February 2015, and to delete the important potential risks of 'hypersensitivity' and 'lack of effect due to immunogenicity' from the list of safety concerns as requested in the conclusion of PSUSA/00000875/201707 adopted in March 2018. In addition, the MAH took the opportunity to include some data from ongoing study P043: a multicentre, open label, single-group trial to investigate the efficacy and safety of corifollitropin alfa in combination with hCG for initiation or restoration of puberty assessed by increased testicular volume in adolescent males 14 to <18 years old with hypogonadotropic hypogonadism (HH)

15.2.5. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0078/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of an update of the RMP (version 25) in order to: 1) bring it in line with revision 2 of GVP module V on 'Risk management systems'; 2) add study 20170534 (listed as category 3 study in the RMP): an open-label extension of the currently ongoing study 20130173 involving paediatric subjects with osteogenesis imperfecta, based on the MAH's commitment arising from Prolia (denosumab) approved paediatric investigation plan (PIP: EMEA-000145-PIP02-12): open-label, prospective, extension study; 3) add a study (listed as category 3 study in the RMP) to further characterize potential increased risk of cerebrovascular events (stroke) and other serious cardiovascular events in subjects with osteoporosis, as per the conclusion of procedure PSUSA/00000954/201709 adopted in April 2018

15.2.6. Emtricitabine, rilpivirine, tenofovir disoproxil - EVIPLERA (CAP) - EMEA/H/C/002312/II/0098

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 13.1) in order: to 1) implement revision 2 of the guidance on the format of RMP in the EU (template); 2) reflect changes in the categorisation of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' based on exposure data from clinical studies and post-marketing use; 3) change the MAH name from Gilead Sciences International Ltd., Cambridge, UK (GSIL) to Gilead Sciences Ireland UC, Cork, Ireland (GSIUC)

15.2.7. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0026

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 12.0) following the completion of study D6030C00001 (BLOOM study): a phase 1, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of osimertinib (AZD9291) in patients with epidermal growth factor receptor (EGFR) mutation positive advanced stage non-small cell lung cancer (NSCLC) in order to remove 'use in patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥2' and 'use in patients with symptomatic brain metastases' as missing information

15.2.8. Paclitaxel - ABRAXANE (CAP) - EMEA/H/C/000778/II/0092

Applicant: Celgene Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 17.0) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'

15.2.9. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/II/0073

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 17.0) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

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. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/X/0117/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped applications consisting of: 1) extension application to add two new strengths of 50 mg and 87.5 mg for solution for injection in a pre-filled syringe with needle guard for subcutaneous administration; 2) variation to include paediatric use in polyarticular juvenile idiopathic arthritis (pJIA) (2 years and above) for the solution for injection (50 mg, 87.5 mg and 125 mg) and to update the pJIA indication transitioning Orencia treatment of pJIA patients from third line (after tumour necrosis factor (TNF) inhibitors) to second line (after first line treatment, e.g. methotrexate) and also use as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate for the subcutaneous formulation and intravenous formulation. The RMP (version 25.2) is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the product information and to update the list of local representatives in the package leaflet

15.3.2. Adalimumab - CYLTEZO (CAP) - EMEA/H/C/004319/II/0006

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study 1297.12 (listed as a category 3 study in the RMP): efficacy, safety and immunogenicity of Cyltezo (BI 695501, adalimumab) versus Humira (adalimumab) in patients with moderate to severe chronic plaque psoriasis: a randomized, double-blind, parallel-arm, multiple-dose, active comparator trial. The RMP (version 3.0) is updated accordingly

15.3.3. Adalimumab - HULIO (CAP) - EMEA/H/C/004429/II/0004

Applicant: Mylan S.A.S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study FKB327-003 (listed as a category 3 study in the RMP): an open-label extension study to compare the long term efficacy, safety, immunogenicity and pharmacokinetics of Hulio (adalimumab) and Humira (adalimumab) in patients with rheumatoid arthritis on concomitant methotrexate (ARABESC-OLE). The RMP (version 2.0) is updated accordingly. In addition, the MAH took the opportunity to remove the product information text from Annex 6 of the RMP and proposed to only keep the text for patient alert card in the RMP as an additional risk minimisation measure

15.3.4. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0042

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease based on the final study report of study EFC11570: a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an acute coronary syndrome. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.5. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0018

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include Tecentriq (atezolizumab), in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated accordingly

15.3.6. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0019

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include Tecentriq (atezolizumab), in combination with nab-paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) who do not have epidermal growth factor receptor (EGFR) mutant or ALK-positive NSCLC. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 9.0) are updated accordingly

15.3.7. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/X/0017

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension application to add a new strength of 840 mg (60 mg/mL) for Tecentriq (atezolizumab) concentrate for solution for infusion in a vial and to add a new indication for the treatment of metastatic triple-negative breast cancer (TNBC). The new indication applies only to the 840 mg strength. The RMP (version 7.0) is updated accordingly

15.3.8. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/II/0033/G, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include patients 12 years of age and older based on week 24 analysis of cohort 1 (adolescent subjects aged ≥12 to <18 years) for study TMC207-TIDP59-C211: a phase 2, open-label, multicentre, single-arm study to evaluate the pharmacokinetics, safety, tolerability and anti-mycobacterial activity of bedaquiline (TMC207) in combination with a background regimen (BR) of multidrug resistant tuberculosis (MDR-TB) medications for the treatment of children and adolescents 0 months to <18 years of age who have confirmed or probable pulmonary MDR-TB. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.2) are updated accordingly; 2) update of section 4.9 of the SmPC to remove reference to the use of activated charcoal as an aid to remove unabsorbed bedaquiline in case of overdose

15.3.9. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0106/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of: 1) update of section 5.1 of the SmPC to reflect final overall survival data from the long-term follow-up study JO25567 (erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer (NSCLC) harbouring epidermal growth factor receptor (EGFR) mutations: an open-label, randomised, multicentre, phase 2 study) in order to fulfil ANX 085 for study JO29424 (survival follow up of JO25567); 2) change in the deadline for the fulfilment of ANX 086 (discussion on any further outcome data on the combination of bevacizumab and erlotinib in the first-line treatment of patients with non-squamous NSCLC harbouring EGFR activating mutations) from Q4 2018 to Q2 2019. Annex II-D on 'conditions or restrictions

with regard to the safe and effective use of the medicinal product' and the RMP (version 29.0) are updated accordingly. The RMP is submitted in line with revision 2 of the guidance on the format of RMP in the EU (template) and consolidates the approved versions (versions 27.1 and 28.1)

15.3.10. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/X/0025

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Extension application to introduce a new pharmaceutical form (film-coated tablets). The RMP (version 12) is updated accordingly

15.3.11. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0026

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.5 of the SmPC in order to update the safety information based on the final results from study CLDK378A2103 (listed as a category 3 study in the RMP, MEA 002): a phase 1, multicentre, open label, drug-drug interaction study to assess the effect of ceritinib on the pharmacokinetics of warfarin and midazolam administered as a two-drug cocktail in patients with anaplastic lymphoma kinase (ALK)-positive advanced tumours including non-small cell lung cancer (NSCLC). The package leaflet and the RMP (version 14) are updated accordingly

15.3.12. Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/II/0031

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of section 5.1 of the SmPC in order to add information on long-term efficacy and drug resistance based on final results from study AI444046 (listed as a category 3 study in the RMP): a phase 3 non-randomized, open-label, long-term follow-up and observational study of durability of efficacy, resistance and characterization of progression of liver disease in subjects with chronic hepatitis C previously treated with daclatasvir and/or asunaprevir. In addition, the MAH took the opportunity to postpone the due date of safety study AI444427: a post-authorisation safety study of early recurrence of hepatocellular carcinoma in hepatitis C virus (HCV)-infected patients after direct-acting antiviral therapy (DAA PASS) evaluating recurrence of hepatocellular carcinoma from Q2 2021 to Q2 2023. Annex II and the RMP (version 6.0) are updated accordingly

15.3.13. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0020, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of study report of study SMM2001: a randomised phase 2 trial to evaluate 3 daratumumab dose schedules in smouldering multiple myeloma. As a consequence, the RMP is updated (version 4.1) in order to remove QTc prolongation as an

important potential risk

15.3.14. Deferiprone - FERRIPROX (CAP) - EMEA/H/C/000236/II/0126/G

Applicant: Apotex Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped variations consisting of an update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update safety information on the use of Ferriprox (deferiprone) in patients with renal or hepatic impairment, based on the final results of two clinical studies (listed as category 3 studies in the RMP): 1) study LA39-0412: an open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox (deferiprone) in subjects with impaired renal function and healthy volunteers; 2) study LA40-0412: an open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox in subjects with impaired hepatic function and healthy volunteers. The package leaflet and labelling are updated accordingly. The RMP (version 13.1) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to introduce minor editorial changes in the product information

15.3.15. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/X/0004/G

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 200 mg solution for injection in pre-filled syringe with safety system (PFS-S) and pre-filled pen (PFP); 2) extensions of indication to add as indications: 'add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, who are inadequately controlled with medium-to-high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment, including those with or without an eosinophilic phenotype', 'maintenance therapy to improve lung function' and 'maintenance therapy to reduce oral steroid use and improve lung function in steroid-dependent asthma patients' based on pivotal studies, namely study DRI12544: a randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma; study LIBERTY ASTHMA QUEST: a randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma; and study VENTURE: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma. As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH proposed to merge the SmPCs for the 200 mg and 300 mg strengths

15.3.16. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/II/0012

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to extend the adult atopic dermatitis indication to the paediatric, 12 years to 17 years (adolescent) patients under Article 8 of Regulation (EC) No

1901/2006 on medicinal products for paediatric use. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.17. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/II/0012

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to extend the Maviret (glecaprevir/pibrentasvir) indication to adolescents from 12 to 18 years of age with chronic hepatitis C infection, based on new clinical data from study M16-123: an open-label, multicentre study to evaluate the pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in paediatric subjects with genotypes 1-6 chronic hepatitis C virus infection (DORA), using the adult co-formulated tablets in adolescents. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated accordingly. In addition, the RMP (version 4.0) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.18. Insulin glargine - TOUJEO (CAP) - EMEA/H/C/000309/II/0105/G

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations to introduce a new 3 mL pre-filled pen. Introduction of four new pack sizes: packs of 1, 3, 6 (multipack) and 9 pens (multipack). As a consequence, Annex A, I, IIA and IIIB are amended. In addition, the RMP (version 5.0) in line with revision 2 of the guidance on the format of RMP in the EU (template) is updated accordingly

15.3.19. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0063

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 4.8 of the SmPC and of Annex II in order to add safety information regarding graft versus host disease (GvHD) in allogeneic haematopoietic stem cell transplant (HSCT) recipients after treatment with ipilimumab. The update is based on a review of post-marketing data. The package leaflet and the RMP (version 25.0) are updated accordingly. In addition, the MAH took the opportunity to introduce some editorial changes in the product information and to reflect changes to the RMP as requested in the conclusions of previous procedures

15.3.20. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/X/0018

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension application to introduce a new pharmaceutical form, solution for injection (in pre-filled syringe or in pre-filled pen). The RMP (version 4.0) is updated accordingly

15.3.21. Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/II/0035

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information and to add urticaria as an adverse reaction following the final results from study POX-MVA-037 (listed as a category 3 study in the RMP (post-authorisation measure MEA 007)): a phase 2, randomized, open-label, multicentre trial designed to evaluate the safety and immunogenicity of Imvanex (modified vaccinia Ankara-Bavarian Nordic (MVA-BN) live virus smallpox vaccine) when increasing the dose or the number of injections compared with the standard 2-dose regimen in a population of adult, vaccinia naive, immunocompromised subjects with human immunodeficiency virus (HIV) infection. The RMP (version 7.1) is updated accordingly. Furthermore, the product information is brought in line with the latest the quality review of documents (QRD) template (version 10)

15.3.22. Pemetrexed - PEMETREXED FRESENIUS KABI (CAP) - EMEA/H/C/003895/X/0009

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application to introduce a new pharmaceutical form (concentrate for solution for infusion) associated with new strength 25 mg/mL. The RMP (version 2.0) is updated accordingly

15.3.23. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0074/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include a new indication for the vial presentation 'treatment of retinopathy of prematurity (ROP) in preterm infants'. As a consequence, sections 2, 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet, labelling and the RMP (version 18.0) are updated accordingly; 2) introduction of a low volume high accuracy syringe, as a stand-alone medical device for the administration of the Lucentis (ranibizumab) 0.2 mg paediatric dose (corresponding to 0.02 mL of the Lucentis 10 mg/mL solution for injection in vial presentation)

15.3.24. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0003/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of: 1) update of section 5.2 of the SmPC in order to reflect results from study CLEE011A2109: a phase 1, open label, multicentre, parallel cohort, single dose study to evaluate the pharmacokinetics (PK) of ribociclib (LEE011) in healthy subjects with normal hepatic function and subjects with impaired hepatic function; 2) update of sections 4.2 and 5.2 of the SmPC in order to reflect results from study CLEE011A2116-Part I: a phase 1, open label, multicentre, parallel-group, single dose two-

staged study to evaluate the pharmacokinetics and safety of a single 400 mg oral dose of ribociclib (LEE011) in subjects with varying degrees of impaired renal function compared to matched healthy volunteers with normal renal function. The RMP (version 2.0) is updated accordingly

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

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

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

15.3.26. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0157

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' resulting from the obligation fulfilment for the rituximab subcutaneous (SC) formulation at a dose of 1,400 mg by the submission of the final clinical study report for study BO22334 (SABRINA, listed as a category 1 study) including reports on long-term safety in relation to body surface area (BSA) (as a measure for exposure variation) and to gender. SABRINA is a two-stage phase 3, international, multicentre, randomized, controlled, open-label study investigating the pharmacokinetics (PK), efficacy and safety of rituximab SC in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy or cyclophosphamide, vincristine, prednisolone (CVP) chemotherapy versus rituximab intravenous (IV) in combination with CHOP or CVP chemotherapy followed by maintenance treatment with either rituximab SC or rituximab IV. The RMP (version 19.0) is updated accordingly. In addition, the MAH took the opportunity to include other changes to the RMP including the fulfilment of the previous information on concluded commitments such as the prolonged B-cell depletion and immunogenicity associated with the subcutaneous formulation

15.3.27. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0158

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product', resulting from the obligation fulfilment for the rituximab subcutaneous formulation at a dose of 1,400 mg by the submission of the final clinical study report for study BO25341 (SAWYER, listed as a category 1 study) including reports on long-term safety in relation to body surface area (BSA) (as a measure for exposure variation) and to gender. SAWYER is a phase Ib adaptive, comparative, randomized, parallel-group, multicentre study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated chronic lymphocytic leukaemia (CLL). The RMP (version 19.0) is updated accordingly. In addition, the MAH took the

opportunity to include the changes on the concluded commitment such as the prolonged B-cell depletion and immunogenicity associated with the subcutaneous formulation

15.3.28. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0012

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension application to introduce a new pharmaceutical form (prolonged-release tablet) associated with a new strength (11 mg), and presented in pack sizes of 28, 30, 90 and 91 tablets. The extension of indication includes a change in pharmacokinetics. The RMP (version 4.0) is updated accordingly

15.3.29. Trifluridine, tipiracil - LONSURF (CAP) - EMEA/H/C/003897/II/0012

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, platinum-, and either a taxane- or irinotecan-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. The RMP (version 6.1) is also updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.30. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/II/0045/G

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of final study reports from five mechanistic in vitro studies, namely, 3083-N03-050: inhibition of multidrug resistance-associated protein 2 (MRP2) in vitro in membrane vesicles (PAM MEA 020), 3083-N04-050: cell viability in 3D spheroid micro-tissues (PAM MEA 021), 3083-N05-050: cell viability in 'sandwich' (PAM MEA 022), 3083-N01-050: effects of ulipristal acetate (UPA) and its main metabolite PGL4002 on mitochondrial function and cell health markers in vitro in HepG267 cells (PAM REC) and 3083-N02-050: in vitro interaction studies of UPA and PGL4002 test articles with human bile salt export pump (BSEP), MRP3 (multidrug resistance-associated protein 3) and multidrug resistance-associated protein 4 (MRP4) efflux (ABC) transporters and with the human sodium/taurocholate co-transporting polypeptide (NTCP) uptake transporter (PAM REC), as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460). The RMP (version 16.1) is updated accordingly

[67] Human liver cancer cell line

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

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

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

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

16.1.1. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201806

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.2. Alectinib - ALECENSA (CAP) - PSUSA/00010581/201807

Applicant: Roche Registration GmbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.3. Atazanavir - REYATAZ (CAP) - PSUSA/00000258/201806

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.4. Autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence - STRIMVELIS (CAP) - PSUSA/00010505/201805

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[68]

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[68] Advanced therapy medicinal product

16.1.5. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201806

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.6. Brinzolamide, brimonidine tartrate - SIMBRINZA (CAP) - PSUSA/00010273/201806

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.7. Budesonide[69] - JORVEZA (CAP) - PSUSA/00010664/201807

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.8. Cabazitaxel - JEVTANA (CAP) - PSUSA/00000476/201806

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.9. Canakinumab - ILARIS (CAP) - PSUSA/00000526/201806

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.10. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/201807

Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.11. Chlorhexidine - UMBIPRO (Art 58[70]) - EMEA/H/W/003799/PSUV/0004

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Jolanta Gulbinovic

[69] Centrally authorised product(s) only

[70] 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)

Scope: Evaluation of a PSUR procedure

16.1.12. Cladribine[71] - MAVENCLAD (CAP) - PSUSA/00010634/201807

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.13. Daclatasvir - DAKLINZA (CAP) - PSUSA/00010295/201807

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

16.1.14. Dimethyl fumarate[72] - SKILARENCE (CAP) - PSUSA/00010647/201806

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.15. Edotreotide - SOMAKIT TOC (CAP) - PSUSA/00010552/201806

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.1.16. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/201806

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.17. Elotuzumab - EMPLICITI (CAP) - PSUSA/00010500/201805

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.18. Fluciclovine (^{18}F) - AXUMIN (CAP) - PSUSA/00010594/201805

Applicant: Blue Earth Diagnostics Ltd

PRAC Rapporteur: Patrick Batty

[71] Indicated in the treatment of multiple sclerosis (MS)
[72] Indicated in the treatment of psoriasis

Scope: Evaluation of a PSUSA procedure

16.1.19. Follitropin delta - REKOVELLE (CAP) - PSUSA/00010554/201805

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.20. Galsulfase - NAGLAZYME (CAP) - PSUSA/00001515/201805

Applicant: BioMarin International Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.21. Human fibrinogen, human thrombin - EVICEL (CAP); TACHOSIL (CAP); VERASEAL (CAP) - PSUSA/00010297/201806

Applicants: Instituto Grifols, S.A. (VeraSeal), Omrix Biopharmaceuticals N. V. (Evicel), Takeda Austria GmbH (TachoSil)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.22. Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201806

Applicant: MSD Vaccins

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.23. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP); SILGARD (CAP) - PSUSA/00001634/201805

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.24. Hydroxycarbamide[73] - SIKLOS (CAP) - PSUSA/00001692/201806 (with RMP)

Applicant: Addmedica S.A.S.

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

[73] Centrally authorised product(s) only

16.1.25. Icatibant - FIRAZYR (CAP) - PSUSA/00001714/201807

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.26. Imiglucerase - CEREZYME (CAP) - PSUSA/00001727/201805

Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.27. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/201806

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.28. Levofloxacin[74] - QUINSAIR (CAP) - PSUSA/00010429/201805

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.29. Lonoctocog alfa - AFSTYLA (CAP) - PSUSA/00010559/201807

Applicant: CSL Behring GmbH

PRAC Rapporteur: Daniela Philadelphy

Scope: Evaluation of a PSUSA procedure

16.1.30. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/201806

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.31. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/201805

Applicant: Amicus Therapeutics UK Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

[74] Centrally authorised product(s) only

16.1.32. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches - VELPHORO (CAP) - PSUSA/00010296/201805

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.33. Nevirapine - VIRAMUNE (CAP) - PSUSA/00002147/201805

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.34. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/201806

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.35. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201806

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.36. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/201805

Applicant: Intercept Pharma Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.37. Opicapone - ONGENTYS (CAP) - PSUSA/00010516/201806

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.38. Pentosan polysulfate sodium[75] - ELMIRON (CAP) - PSUSA/00010614/201806

Applicant: bene-Arzneimittel GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

[75] Centrally authorised product(s) only

16.1.39. Peramivir - ALPIVAB (CAP) - PSUSA/00010687/201806

Applicant: Biocryst UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.40. Rilpivirine - EDURANT (CAP) - PSUSA/00009282/201805 (with RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.41. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201806

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.42. Semaglutide - OZEMPIC (CAP) - PSUSA/00010671/201805

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.43. Sildenafil[76] - REVATIO (CAP) - PSUSA/00002700/201805

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.44. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/201806

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.45. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201806

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

[76] Indicated for the treatment of pulmonary arterial hypertension (PAH)

16.1.46. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/201807

Applicant: CO.DON AG, ATMP[77]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.47. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201807

Applicant: Vanda Pharmaceuticals Ltd.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.48. Tedizolid phosphate - SIVEXTRO (CAP) - PSUSA/00010369/201806

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.49. Trametinib - MEKINIST (CAP) - PSUSA/00010262/201805

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.50. Venetoclax - VENCLYXTO (CAP) - PSUSA/00010556/201806

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Naloxone[78] - NYXOID (CAP); NAP - PSUSA/00010657/201805

Applicants: Mundipharma Corporation (Ireland) Limited (Nyxoid), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

[77] Advanced therapy medicinal product
[78] For use in non-medical settings only

16.2.2. Olopatadine - OPATANOL (CAP); NAP - PSUSA/00002211/201804

Applicants: Novartis Europharm Limited (Opatanol), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

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

16.3.1. 5 fluorouracil, salicylic acid - PSUSA/00000008/201805

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.3.2. Acemetacin - PSUSA/00000026/201805

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.3. Acipimox (NAP) - PSUSA/00000050/201805

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.4. Bismuth subcitrate potassium, metronidazole, tetracycline (NAP) - PSUSA/00010199/201805

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.5. Carmustine[79] (NAP) - PSUSA/00010349/201804

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.6. Chlorphenoxamine hydrochloride (NAP) - PSUSA/00010361/201805

Applicant(s): various

[79] Powder and solvent for solution for infusion only

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.7. Cidofovir (NAP) - PSUSA/00010558/201806

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.8. Clevidipine (NAP) - PSUSA/00010288/201805

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.9. Flunarizine (NAP) - PSUSA/00001416/201805

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.10. Human hemin (NAP) - PSUSA/00001629/201805

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.11. Iodine (^{131}I) iobenguane (NAP) - PSUSA/00001764/201805

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.12. Methoxyflurane (NAP) - PSUSA/00010484/201805

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.13. Nalbuphine (NAP) - PSUSA/00002110/201805

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.14. Olodaterol, tiotropium (NAP) - PSUSA/00010489/201805

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.15. Ozenoxacin (NAP) - PSUSA/00010651/201805

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.16. Pamidronate (NAP) - PSUSA/00002269/201805

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.17. Patent blue V sodium (NAP) - PSUSA/00002320/201804

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.18. Praziquantel (NAP) - PSUSA/00002503/201804

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.19. Ranitidine (NAP) - PSUSA/00002610/201805

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.20. Tafluprost (NAP) - PSUSA/00002843/201804

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.21. Terlipressin (NAP) - PSUSA/00002905/201804

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.22. Thiamphenicol (NAP) - PSUSA/00002925/201805

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.23. Treprostinil (NAP) - PSUSA/00003013/201805

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/LEG 018

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Detailed review of the signal of hepatic failure in patients with Child-Pugh A (compensated) as requested in the conclusions of PSUSA/00010363/201801 adopted in September 2018

16.4.2. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/MEA 027

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Feasibility assessment report for a study (listed as category 3 study in the RMP) designed to further understand the effect of ibrutinib on various component functions of the innate and adaptive immune systems as requested in the conclusions of procedure PSUSA/00010301/201611 adopted in June 2017

16.4.3. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/LEG 020

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Detailed review of the signal of hepatic failure in patients with Child-Pugh A (compensated) as requested in the conclusions of PSUSA/00010367/201801 adopted in September 2018

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)[80]

17.1.1. Dexketoprofen, tramadol (NAP) - EMEA/H/N/PSP/S/0062.1

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

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to PSP/S/0062 [PASS protocol for a drug utilisation study (DUS) on dexketoprofen-tramadol (DKP-TRAM) fixed combination to evaluate the pattern of prescriptions of DKP-TRAM and assess the risk of adverse events (AE) (e.g. nausea, vomiting, diarrhoea, vertigo) in DKP-TRAM *vs.* tramadol monotherapy (including tramadol-paracetamol combinations) users, with a special focus on patients 75 years old and over] as per the request for supplementary information (RSI) adopted in June 2018

17.1.2. Lesinurad – ZURAMPIC (CAP) - EMEA/H/C/PSA/S/0036

Applicant: Grünenthal GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a previously agreed protocol in June 2017 (PSP/S/0050.2) for a study to further characterise the cardiovascular safety of lesinurad in combination with a xanthine oxidase inhibitor (XOI) (lesinurad + XOI cohort) in patients aged 18 years and older who have a diagnosis of gout compared with similar patients who are continuing treatment with XOI monotherapy (XOI mono cohort)

17.1.3. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064.1

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

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0064 [protocol for a multicentre, observational, prospective PASS 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] as per the request for supplementary information (RSI) adopted in July 2018

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

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[81]

17.2.1. Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/MEA 019.3

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 019.2 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.2. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 007.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 007.2 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.3. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/MEA 003.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: MAH's response to MEA 003 [protocol for study R668-AD-1639 pregnancy registry: a safety study to monitor pregnancy and infant outcomes following administration of dupilumab during planned or unexpected pregnancy in North America] as per the request for supplementary information (RSI) adopted in April 2018

17.2.4. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/MEA 004.3

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 004.2 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A)

[81] 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

without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.5. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for study BO40853: a PASS based on healthcare professional (HCP) and patient/carer survey to evaluate the awareness, knowledge and compliance of HCPs and patients/carers to the additional risk minimisation measures (guide for HCPs, patient/carer guide, patient alert card), in relation to the safety concerns of thromboembolic events, thrombotic microangiopathy as well as life-threatening bleeding due to misinterpretation of the standard coagulation tests [final study report due date: 30/04/2021] (from initial opinion/MA)

17.2.6. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/MEA 006.2

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 006.1 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.7. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001

Applicant: Akcea Therapeutics UK Ltd.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for a retrospective chart review for evaluating adherence to and effectiveness of the proposed platelet monitoring schedule, proposed cut-off points, dose adaptation, and initiation of corticosteroids on thrombocyte recovery (from opinion/MA)

17.2.8. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 002.3

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 002.2 [protocol for a study/survey (listed as a category 3 study in the RMP): a cross-sectional multinational, multichannel survey conducted among

healthcare professionals and patients to measure the effectiveness of Suliqua (insulin glargine/lixisenatide) educational materials set up to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide] as per the request for supplementary information (RSI) adopted in September 2018

17.2.9. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 017.3

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 017.2 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.10. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/MEA 014

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Annika Folin

Scope: Protocol for an observational study to characterise hepatic related toxicity and overall safety profile in real-life conditions in the EU (Western population) in hepatocellular carcinoma (HCC) patients, including patients with Child-Pugh B

17.2.11. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/MEA 003.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 003 [protocol for study B1971060: a phase 4, open-label, single-arm trial, to describe the safety, tolerability and immunogenicity of Trumenba (bivalent rLP2086 vaccine) when administered in immunocompromised subjects $\geqslant$ 10 years of age] as per the request for supplementary information (RSI) adopted in July 2018

17.2.12. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/MEA 004.1

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 004 [protocol for study BA39730 (listed as a category 3 study in the RMP): a long term surveillance study to assess and characterize the long-term safety data from the use of ocrelizumab in treated patients with multiple sclerosis (MS) [final report due date expected in 12/2028] as per the request for supplementary information (RSI) adopted in September 2018

17.2.13. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 007.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 007.2 including a revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.14. Sirolimus - RAPAMUNE (CAP) - EMEA/H/C/000273/MEA 054

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study B1741224: a non-interventional observational PASS to present additional long-term safety and effectiveness data on patients with sporadically lymphangioleiomyomatosis (S-LAM) treated with sirolimus, as requested in the conclusion of variation II/164 finalised in June 2018

17.2.15. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/MEA 024.3

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 024.2 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.16. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/MEA 008.3

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 008.2 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in

December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.17. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/MEA 002.2

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 002.1 including revised protocol version 2 [retrospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in July 2018

17.2.18. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/MEA 021.3

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to 021.3 [amendment to the previously agreed protocol in July 2016 for study CLDE225A2404: a non-interventional, multi-national, multicentre PASS to assess the long-term safety and tolerability of Odomzo (sonidegib) administered in patients with locally advanced basal cell carcinoma (laBCC), in order to execute and update the milestones, sample size and execution methods] as per the request for supplementary information (RSI) adopted in October 2018

17.2.19. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 007.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 007.1 [protocol for a non-interventional PASS study A3921298 (listed as a category 3 study in the RMP) evaluating the effectiveness of additional risk minimisation measures (aRMM) for Xeljanz (tofacitinib) in the European Union via a survey of healthcare professionals (HCPs) considered as an additional pharmacovigilance activity in the RMP] as per the request for supplementary information (RSI) adopted in September 2018

17.2.20. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/MEA 001

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study VON (BAX0111) VWF-500 COL (listed as category 3 study in the RMP): a real world safety and effectiveness study of factor replacement for clinically severe von Willebrand disease (VWD) [interim report due date: 30/06/2019; final report due date:

30/06/2022] (as requested in initial opinion/MA)

17.3. Results of PASS imposed in the marketing authorisation(s)[82]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[83]

17.4.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0185

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from the Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) registry (listed as a category 3 study in the RMP): an ongoing long-term observational cohort study initiated in Germany in 2001 by the German Society of Rheumatology to investigate the long-term safety, effectiveness, and costs of biologic therapies for rheumatoid arthritis

17.4.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0040

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for study RRA-21651: a retrospective, observational, new-user cohort study using 4 administrative claims databases in the US, undertaken to investigate the incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with sodium-glucose cotransporter 2 (SGLT2) inhibitors or other antihyperglycemic agents

17.4.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0041

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report (CSR) for study RRA-21651: a retrospective, observational, new-user cohort study using 4 administrative claims databases in the US, undertaken to investigate the incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus (T2DM) treated with sodium-glucose cotransporter 2 (SGLT2) inhibitors or other antihyperglycemic agents

17.4.4. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0074/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report from study

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

RA0021 (Anti-Rheumatic Therapies in Sweden (ARTIS) registry) (listed as a category 3 studies in the RMP): registry to gather short- and long-term safety data from the use of certolizumab pegol (CZP) in Sweden for rheumatoid arthritis (RA) patients; 2) submission of the final report from study RA005 (NBD registry) (listed as a category 3 studies in the RMP): registry to gather safety and outcome data in RA patients receiving CZP and other RA treatments. In addition, the MAH submitted interim results for two ongoing registries studies, namely: study RA0020/Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT): a German long-term observation of biologics/disease-modifying antirheumatic drugs (DMARD) in RA; and study RA0022/British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR): a longitudinal observational study of patients with RA treated with biologic agents, and prospective surveillance study for adverse events

17.4.5. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0054

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of the final study report, as requested by PRAC in the conclusions of MEA 11.5 adopted at the October 2016 meeting, from study H80-MC-B015 extension/D5550R00003: 'incidence of pancreatic malignancy and thyroid neoplasm in type 2 diabetes mellitus (T2DM) patients who initiate exenatide compared to other antihyperglycemic drugs' as well as the feasibility study on 'incidence of pancreatic cancer and thyroid neoplasm among T2DM who initiated Bydureon (exenatide) as compared with those who initiated other glucose lowering drugs'. The RMP (version 32) is updated accordingly

17.4.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0085

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study CNTO148ART4002 (listed as a category 3 study in the RMP): an observational phase 4 study using the Optum Research Database (ORD) to estimate the long-term safety profile in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) who are initiating Simponi (golimumab) treatment and/or other types of biologic and non-biologic treatments. The RMP (version 19.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems' in order to reflect changes in the categorisation of safety concerns

17.4.7. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0218

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final study report from the Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) cohort 2 portion of the registry: a German rheumatoid arthritis (RA) registry established as a prospective observational cohort study on the long-term safety and effectiveness of biologic disease-modifying anti-rheumatic drugs (DMARDs) in patients with RA. The RMP (version 19) is updated accordingly. The MAH also revised the

RMP list of safety concerns as requested in the conclusions of procedure LEG 156 adopted in October 2017

17.4.8. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/II/0030

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report for study 178-PV-002: a drug utilisation study (DUS) of mirabegron using real-word healthcare databases from Finland, the Netherlands (NL) and the United Kingdom (UK) (in fulfilment of post-approval commitment MEA 009.2)

17.4.9. Ocriplasmin - JETREA (CAP) - EMEA/H/C/002381/II/0042/G

Applicant: Oxurion NV

PRAC Rapporteur: Julie Williams

Scope: Grouped variations consisting of: 1) submission of the final report from study (TG-MV-018) 'ocriplasmin research to better inform treatment (ORBIT)': a multicentre, prospective, observational study which assesses clinical outcomes and safety of Jetrea (ocriplasmin) administered in a real-world setting for the treatment of symptomatic vitreomacular adhesion (VMA); 2) submission of the final report from a prospective drug utilisation study TG-MV-017 (listed as a category 3 study in the RMP): a European, multicentre, observational study exploring the utilisation patterns of intravitreal Jetrea (ocriplasmin) in real-life clinical practice. The study includes two parts, a drug utilisation study (DUS) and the patient educational material evaluation survey (PEMES); 3) submission of the final report from study INJECT (investigation of Jetrea (ocriplasmin) in patients with confirmed vitreomacular traction): a non-interventional, multicentre, worldwide study in patients treated with Jetrea (ocriplasmin) in order to evaluate safety, clinical effectiveness, and health-related quality of life (HRQoL) outcomes in a real world setting among a large population of patients exposed to ocriplasmin across different countries according to country's approved indications. The RMP (version 7.2) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

17.4.10. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/II/0041

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report from the pregnancy registry H4621g study (MotHER) (listed as a category 3 study in the RMP): an observational study of pregnancy and pregnancy outcome in women with breast cancer treated with trastuzumab, pertuzumab in combination with trastuzumab, or ado-trastuzumab emtansine during pregnancy or within 7 months prior to conception. The RMP (version 11) is updated accordingly

17.4.11. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0082

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final study report (listed as a category 3 study in the RMP): 'safety report on hypersensitivity in patients who switched between tocilizumab intravenous and subcutaneous routes of administration' based on safety data from the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR), study WA22479: a prospective observational cohort study for safety data collection (BSRBR) and study ML22928: a prospective, non-interventional multicentre observational study to evaluate the long-term effectiveness and safety of tocilizumab in patients with active rheumatoid arthritis in daily practice

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

17.5.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 046.8

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Ninth annual interim report for study P10-262, a registry study in juvenile idiopathic arthritis (JIA) patients: a long term, multicentre, longitudinal post-marketing, observational study to assess long term safety and effectiveness of Humira (adalimumab) in children with moderately to severely active polyarticular or polyarticular-course JIA – STRIVE [final study report due date: 31 December 2024]

17.5.2. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.7

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 007.6 [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)] as per the request for supplementary information (RSI) adopted in September 2018

17.5.3. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 006.4

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Interim results for year 3 for the UK clinical practice research datalink (CPRD) database data analysis for psoriatic arthritis (PsA) and psoriasis [due date: CPRD data analysis at years 1, 3 and 5 starting from the date of first commercial availability in the UK. Final study report due for submission within 6 months after the 5 year-data analysis cut-off date]

17.5.4. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/MEA 024.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Third interim report for study A8081062 (listed as category 3 study in the RMP): a PASS descriptive study evaluating the frequency of risk factors for and sequelae of potential sight threatening event and severe visual loss among patients following exposure to Xalkori (crizotinib) and measuring the effectiveness of the crizotinib therapeutic management guide in communicating risks, and recommended actions to minimize risks, among physicians prescribing crizotinib in Europe

17.5.5. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/MEA 010.4

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth interim report for study TMC207TBC4002 (listed as a category 3 study in the RMP): a multi-country prospective multidrug resistant tuberculosis (MDRTB) patient registry to monitor bedaquiline safety, utilisation, and emergence of resistance

17.5.6. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 008.1

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 008 [annual progress report (version 2.0) for study 109MS402: Biogen multiple sclerosis pregnancy exposure registry [final clinical study report (CSR) expected due date: Q4 2021] as per the request for supplementary information (RSI) adopted in September 2018

17.5.7. Human rotavirus, live attenuated - ROTARIX (CAP) - EMEA/H/C/000639/MEA 094

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual report for study EPI-ROTA-052 BOD EU SUPP (201433) (EuroRotaNet): observational community-based strain surveillance study

17.5.8. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 114.10

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim results for 2017 for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): a multicentre, open study of patients with plaque psoriasis who are candidates for systemic therapy including biologics [final clinical study report (CSR) for PSOLAR expected in June 2023]

17.5.9. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/ANX 002.5

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Interim results for a prospective, multi-country, observational registry study to

collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole using the existing European registry on Cushing's syndrome (ERCUSYN) to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

17.5.10. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/ANX 001.6

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

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

17.5.11. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/ANX 001.1

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Interim results for study P15-11: a multicentre, observational PASS to document the drug utilisation of Wakix (pitolisant) and to collect information on the safety of Wakix when used in routine medical practice [final results planned in 2023] (from opinion/MA)

17.5.12. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/MEA 003.6

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

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

17.5.13. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.15

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 022.14 [annual report for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics] as per the request for supplementary information (RSI) adopted in September 2018

17.5.14. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Patrick Batty

Scope: Interim analysis for study P16-562: a prospective observational study to assess the long term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients [final clinical study report (CSR) planned in December 2025]

17.6. Others

17.6.1. Desloratadine - AERIUS (CAP) - EMEA/H/C/000313/MEA 065.4

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 065.3 [status update and study milestones for a Nordic register-based study exploring the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter] as per the request for supplementary information (RSI) adopted in July 2018

17.6.2. Desloratadine - AZOMYR (CAP) - EMEA/H/C/000310/MEA 065.4

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 065.3 [status update and study milestones for a Nordic register-based study exploring the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter] as per the request for supplementary information (RSI) adopted in July 2018

17.6.3. Desloratadine - NEOCLARITYN (CAP) - EMEA/H/C/000314/MEA 065.4

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 065.3 [status update and study milestones for a Nordic register-based study exploring the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter] as per the request for supplementary information (RSI) adopted in July 2018

17.6.4. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 047.6

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 047.45 on sensitivity analysis [revised statistical analysis plan (SAP) amendment 5 for the HUBIN registry: 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] as per the request

for supplementary information (RSI) adopted in May 2018

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. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0012 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.2. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0032 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/R/0029 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0033 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

18.2.3. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - EMEA/H/C/003963/R/0019 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Daniela Philadelphy

Scope: Conditional renewal of the marketing authorisation

18.2.4. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0016 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

18.2.5. Pixantrone - PIXUVRI (CAP) - EMEA/H/C/002055/R/0046 (with RMP)

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Conditional renewal of the marketing authorisation

18.2.6. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/R/0008 (without RMP)

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Budesonide, formoterol - BIRESP SPIROMAX (CAP) - EMEA/H/C/003890/R/0027 (without RMP)

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.2. Budesonide, formoterol - DUORESP SPIROMAX (CAP) - EMEA/H/C/002348/R/0027 (without RMP)

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.3. Capsaicin - QUTENZA (CAP) - EMEA/H/C/000909/R/0047 (with RMP)

Applicant: Grunenthal GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.4. Everolimus - AFINITOR (CAP) - EMEA/H/C/001038/R/0060 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.5. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/R/0049 (with RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ghania Chamouni

Scope: 5-year renewal of the marketing authorisation

18.3.6. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - EMEA/H/C/002705/R/0018 (without RMP)

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.7. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/R/0031 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.8. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/R/0051 (without RMP)

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.9. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/R/0027 (without RMP)

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.10. Siltuximab - SYLVANT (CAP) - EMEA/H/C/003708/R/0029 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.11. Tacrolimus - ENVARSUS (CAP) - EMEA/H/C/002655/R/0014 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 14-17 January 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Daniela Philadelphy	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	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
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
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	16.1.28. Levofloxacin - QUINSAIR (CAP) - PSUSA/00010429/201805 (MAH: Chiesi Farmaceutici S.p.A.)
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrímsdóttir	Alternate	Iceland	No interests declared	Full involvement
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Ruta Kerpauskiene	Alternate	Lithuania	No interests declared	Full involvement
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	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
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	4.2.1. acetylsalicylic acid (NAP) 4.3.2. Biotin (NAP) 6.2.4. Measles, mumps, rubella vaccine (live, attenuated) - M-M-RVAXPRO (CAP); NAP - PSUSA/00001937/201805
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Jasmina Klopcic	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	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
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No participation in final deliberations and voting on:	16.1.36. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/201805 6.3.10. Pholcodine

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP) - PSUSA/00002396/201805 6.3.11. Pholcodine, biclotymol, chlorphenamine maleate (NAP) - PSUSA/00010437/201804
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Francoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Josiane Uwera	Expert - in person*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Katrin Keerma	Expert - in person*	Estonia	No interests declared	Full involvement
Nathalie Dumarcet	Expert - via telephone*	France	No interests declared	Full involvement
Bilal Majed	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Jelena Katic	Expert - via telephone*	Germany	No interests declared	Full involvement
Anne Kleinau	Expert - via telephone*	Germany	No interests declared	Full involvement
Nils Lilienthal	Expert - via telephone*	Germany	No interests declared	Full involvement
Kerstin Loeschcke	Expert - via telephone*	Germany	No interests declared	Full involvement
Valerie Strassmann	Expert - in person*	Germany	No interests declared	Full involvement
Zsuzsanna Birone Sandor	Expert - in person*	Hungary	No interests declared	Full involvement
Emma Lawless	Expert - via telephone*	Ireland	No interests declared	Full involvement
Gunta Pauksena	Expert - in person*	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Expert - in person*	Lithuania	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	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
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Natalie Bandoo	Expert - in person*	United Kingdom	No interests declared	Full involvement
Marta Busana	Expert - in person*	United Kingdom	No interests declared	Full involvement
Victoria O'Keefe	Expert - in person*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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