



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 March 2020
EMA/PRAC/404462/2020
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of meeting on 10 – 13 February 2020

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 10-13 February 2020 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.

Following the withdrawal of the United Kingdom (UK) from the European Union on 01 February 2020, persons representing, appointed by, or nominated by the UK can no longer participate in EMA meetings. As a result, Julie Williams and Patrick Batty as the respective member and alternate for the UK did not participate in the current meeting. The Chairperson, Committee and EMA secretariat thanked them for their involvement in the Agency's scientific and regulatory activities and their valuable contributions to the PRAC.

See also under 12.20.3.

1.2. Agenda of the meeting on 10 - 13 February 2020

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 13 - 16 January 2020

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 13 - 16 January 2020 were published on the EMA website on 03 June 2020 ([EMA/PRAC/297855/2020](https://www.ema.europa.eu/en/PRAC/297855/2020)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

3.3.1. Cyproterone acetate (NAP) - EMEA/H/A-31/1488

Applicant(s): various

PRAC Rapporteur: Menno van der Elst; PRAC Co-rapporteur: Adam Przybylkowski

Scope: Review of the benefit-risk balance following notification by France 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 for the review of cyproterone acetate-containing medicine(s) and the risk of meningioma is about to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes July 2019](#) and [PRAC minutes November 2019](#)¹.

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs.

The PRAC reviewed the available data on risk of meningioma in association with cyproterone, in particular the epidemiological studies including the study conducted by the French Health Insurance² (CNAM), post-marketing case reports and data submitted by the MAHs.

¹ Held 28 – 31 October 2019

² Caisse nationale de l'Assurance Maladie

The PRAC concluded from the data that, while the absolute risk of meningioma in association with cyproterone use remains low, the risk increases with increasing cumulative doses of cyproterone. The PRAC noted that most cases occur after prolonged exposure to high doses of cyproterone, but cases of meningioma have also been identified after short-term exposure to high doses. Therefore, the PRAC recommended that in all indications except prostate carcinoma, treatment with cyproterone should be restricted to situations where alternative treatments are unavailable or considered inappropriate and that the lowest possible effective dose should be used.

The PRAC also noted that while the available data do not indicate an increased risk of meningioma in association with low dose combination products containing 2mg or less of cyproterone, these medicinal products are often used following treatment with higher dose cyproterone-containing products or concomitantly. Given that the risk increases with increasing cumulative doses of cyproterone, the Committee recommended that low dose combination products should also be contraindicated in patients with meningioma or history of meningioma.

Moreover, the PRAC recommended other updates to the product information of cyproterone-containing products to reflect current knowledge on the risk of meningioma.

Furthermore, the Committee recommended that MAHs conduct a joint observational cross-sectional survey to assess healthcare professionals' awareness and level of knowledge of this risk.

The PRAC concluded that the benefit-risk balance of cyproterone-containing products remains favourable subject to changes to the product information and additional pharmacovigilance activities as described above.

Summary of recommendation(s)/conclusions

- The PRAC adopted a recommendation to vary^{3 4} the terms of the marketing authorisations for cyproterone-containing products to be considered by CMDh for a position – see EMA Press Release ([EMA/70255/2020](#)) entitled 'Restrictions in use of cyproterone due to meningioma risk' published on 14 February 2020.
- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.

Post-meeting note 1: the press release entitled 'Restrictions in use of cyproterone due to meningioma risk' ([EMA/147755/2020](#)) representing the position adopted by the CMDh was published on the EMA website on 27 March 2020.

Post-meeting note 2: the PRAC assessment report ([EMA/134740/2020](#)) was published on 01 April 2020.

3.4. Re-examination procedures⁵

None

³ For medicinal products containing cyproterone only: update of SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1. The package leaflet is updated accordingly

⁴ For combination medicinal products containing cyproterone (cyproterone/ethinylestradiol; cyproterone/estradiol valerate): update of SmPC sections 4.3, 4.4 and 5.1. The package leaflet is updated accordingly

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

3.5. Others

None

4. Signals assessment and prioritisation⁶

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Macrogol 3350^{7 8} (NAP); macrogol 4000^{9 10} (NAP)

Applicant(s): various

PRAC Rapporteur: Ilaria Baldelli

Scope: Signal of colitis ischaemic

EPITT 19517 – New signal

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

Background

Macrogol is an osmotically acting laxative indicated for the treatment of chronic constipation and for bowel preparation before surgery or colonoscopy.

During routine signal detection activities, a signal of ischaemic colitis was identified by Italy, based on 61 cases retrieved from EudraVigilance. Italy as the lead Member State (LMS) confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and in the literature, and also taking into account the seriousness of the event, the PRAC agreed that the signal should be further assessed. The PRAC agreed to request a cumulative review of cases of ischaemic colitis from MAHs of macrogol-containing products.

The PRAC appointed Ilaria Baldelli as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs of macrogol 3350- and macrogol 4000-containing products¹¹ should submit to the EMA, within 60 days, a cumulative review of cases of ischaemic colitis from all sources including clinical trials and evaluate the biological plausibility for a possible association. Additionally, the MAHs for the originator macrogol-containing products (Helsinn, Ipsen, Norgine, Polifarma and Tillots Pharma AG) should provide an overview

⁶ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

⁷ With or without electrolytes

⁸ and combination(s)

⁹ With or without electrolytes

¹⁰ and combination(s)

¹¹ As mono-components and combinations

and analysis of relevant literature. The MAHs should discuss the need for amending the product information and/or the RMP and provide a proposal, as appropriate.

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

4.1.2. Lisdexamfetamine (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of QT prolongation and cardiac arrhythmia

EPITT 19533 – New signal

Lead Member State(s): SE

Background

Lisdexamfetamine is a centrally acting sympathomimetic substance indicated for the treatment of attention-deficit hyperactivity disorder (ADHD) in children, adolescents and adults.

The exposure for lisdexamfetamine-containing products is estimated to have been more than 10 million patient-years worldwide, in the period from first authorisation in 2007 to 2019.

During routine signal detection activities, a signal of QT prolongation and cardiac arrhythmia was identified by Sweden, based on 22 cases of cardiac arrhythmia and 15 cases of QT prolongation retrieved from EudraVigilance. Sweden as the lead Member State (LMS) confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the PRAC agreed that the signal should be further assessed. The PRAC agreed to request the MAH Shire Pharmaceuticals to provide a cumulative review of all cases of QT prolongation, cardiac arrhythmias and cases of sudden death reported with lisdexamfetamine.

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

Summary of recommendation(s)

- The MAH Shire Pharmaceuticals for lisdexamfetamine-containing product(s) should submit to the EMA, within 60 days, a cumulative review of all cases of QT prolongation, all type of cardiac arrhythmias and cases of sudden death. The analysis should include a review of published literature, data from spontaneous reports and reports from studies including epidemiological studies. The MAH should also discuss the possible mechanisms of action. In addition, the MAHs should discuss the need for amending the product information and/or the RMP and make proposal as appropriate. The MAH should also discuss the need to disseminate a direct healthcare professional communication (DHPC).
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Tramadol (NAP); tramadol, dextketoprofen (NAP); tramadol, paracetamol (NAP)

Applicant(s): various

PRAC Rapporteur: Ghania Chamouni

Scope: Signal of hiccups

EPITT 19529 – New signal

Lead Member State(s): ES, FR

Background

Tramadol is an opioid analgesic indicated, alone or in combinations with dextketoprofen or paracetamol for the treatment of acute and chronic pain.

The exposure for tramadol-containing products is estimated to have been more than 54.79 million patient-years worldwide, in the period from first authorisation in 1973 to 2017. The exposure for tramadol/dextketoprofen-containing products is estimated to have been more than 7 million therapeutic cycles worldwide, in the period from first authorisation in 2016 to 2019. The exposure for tramadol/paracetamol-containing products is estimated to have been more than 5.48 million patient-years worldwide, in the period from first authorisation to 2018.

During routine signal detection activities, a signal of hiccups was identified by Spain, based on 10 cases identified in the Spanish database (FEDRA) and 52 cases retrieved from EudraVigilance. France as the lead Member State (LMS) confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in the Spanish, French and EudraVigilance databases as well as the literature and taking into consideration previous PSUR assessments, the PRAC agreed to further assess this signal. The PRAC agreed to request the MAHs for tramadol-containing products to submit a cumulative review of all cases of hiccups reported with tramadol in the next PSUSA.

The PRAC appointed Ghania Chamouni as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for tramadol-containing products¹² should include in the next PSUR (data lock point (DLP): 22/05/2020) a cumulative review of cases of hiccups including a review of published literature, data from spontaneous reports and reports from studies. The MAH should also discuss potential mechanisms for development of hiccups in relation to tramadol. In addition, the MAHs should discuss the need for amending the product information and/or the RMP and make a proposal, as appropriate.

4.2. New signals detected from other sources

See also Annex I 14.2.

¹² Mono-component products part of PSUSA procedure (PSUSA/00003002/202005)

4.2.1. Azithromycin (NAP)

Applicant(s): various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of increased cancer risk among patients with bronchiolitis obliterans after hematopoietic cell transplantation

EPITT 19528 – New signal

Lead Member State(s): FI

Background

Azithromycin is a macrolide indicated for the treatment of various infections when caused by micro-organisms sensitive to azithromycin.

The exposure for azithromycin-containing products is estimated to have been more than 1.4 billion patients worldwide, in the period from first authorisation in 1991 to 2017.

Following the publication by *Cheng et al.*¹³, a signal of increased cancer risk among patients with bronchiolitis obliterans syndrome (BOS) after hematopoietic cell transplantation treated with azithromycin was identified by France. Finland as the lead Member State (LMS) confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information from the study on increased cancer risk among patients with BOS after hematopoietic cell transplantation treated with azithromycin and agreed that the signal required further analysis. The PRAC agreed to request the MAH for the originator azithromycin-containing product(s) to review long-term follow-up data for patients with long-term exposure to azithromycin from all sources including studies, in particular studies in prevention of myocardial infarction and other relevant literature.

The PRAC appointed Kimmo Jaakkola as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH Pfizer for the originator azithromycin-containing product(s) should include in the next PSUR (data lock point (DLP): 30/04/2020) a cumulative review of long-term follow-up data for patients with long-term exposure to azithromycin from all sources including studies, in particular studies in prevention of myocardial infarction (WIZARD¹⁴, ACES¹⁵, ACADEMIC¹⁶) and other relevant literature. The MAH should make a comment on the need for risk minimisation measures for the relevant patient groups and make a proposal for updating the product information and/or RMP, as appropriate.

¹³ Cheng GS et al. Azithromycin use and increased cancer risk among patients with bronchiolitis obliterans after hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2020;26(2):392-400

¹⁴ O'Connor CM et al. Azithromycin for the secondary prevention of coronary heart disease events: the WIZARD study: a randomized controlled trial. *JAMA.* 2003 Sep;290(11):1459-66

¹⁵ Grayston JT et al. Azithromycin for the secondary prevention of coronary events. *N Engl J Med.* 2005;352(16):1637-45

¹⁶ Muhlestein JB et al. Randomized secondary prevention trial of azithromycin in patients with coronary artery disease: primary clinical results of the ACADEMIC study. *Circulation.* 2000;102(15):1755-60

4.3. Signals follow-up and prioritisation

4.3.1. Bevacizumab – AVASTIN (CAP) - EMEA/H/C/000582/SDA/088; MVASI (CAP) - EMEA/H/C/004728/SDA/003; ZIRABEV (CAP) - EMEA/H/C/004697/SDA/003

Applicant(s): Amgen Europe B.V. (Mvasi), Pfizer Europe MA EEIG (Zirabev), Roche Registration GmbH (Avastin)

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of Guillain-Barré syndrome (GBS)

EPITT 19472 – Follow up to October 2019

Background

For background information, see [PRAC minutes October 2019](#)¹⁷.

The MAH for Avastin (bevacizumab) replied to the request for information on the signal of Guillain-Barré syndrome (GBS) and the responses were assessed by the Rapporteur.

Discussion

Based on the assessment of all the available data together with the responses from the MAH, the PRAC agreed that there is insufficient evidence to warrant regulatory actions at present. However, due to several cases with a possible causality relationship, the PRAC agreed to request MAHs to submit a further review on Guillain-Barré syndrome (GBS) in the next PSUR (data lock point (DLP): 25/02/2020).

Summary of recommendation(s)

- The MAHs for bevacizumab-containing products should submit to EMA, in the next PSUR, a cumulative review and detailed analysis of cases of GBS from all sources (i.e. spontaneous reports, literature and clinical trials).

4.3.2. Ifosfamide (NAP)

Applicant(s): various

PRAC Rapporteur: Annika Folin

Scope: Signal of increased risk of encephalopathy

EPITT 19433 – Follow up to December 2019

Background

For background information, see [PRAC minutes December 2019](#)¹⁸.

The PRAC Rapporteur assessed further information on the signal of increased risk of encephalopathy, including published studies and the results of a EudraVigilance search performed by the EMA.

Discussion

¹⁷ Held 30 September – 03 October 2019

¹⁸ Held 25-28 November 2019

Based on the review of the available data, the PRAC agreed that the evaluated epidemiological studies^{19 20} suggest an increased risk for ifosfamide-induced encephalopathy with ifosfamide solution for infusion compared with ifosfamide-containing powder. While it is acknowledged that uncertainties remain, the PRAC agreed that the data raise serious concerns that need to be further addressed.

Summary of recommendation(s)

- The PRAC concurred that a thorough evaluation at the EU level is warranted with involvement of all relevant expertise.

For the full PRAC recommendation, see [EMA/PRAC/64581/2020](#) published on 10/03/2020 on the EMA website.

Post-meeting note: On 28 February 2020, France initiated a referral procedure under Article 31 of Directive 2001/83/EC for the review of ifosfamide-containing solutions.

4.3.3. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/SDA/040

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of haemophagocytic lymphohistiocytosis

EPITT 19467 – Follow up to October 2019

Background

For background information, see [PRAC minutes October 2019](#)²¹.

The MAH for Opdivo (nivolumab) replied to the request for information on the signal of haemophagocytic lymphohistiocytosis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the cumulative review of all cases haemophagocytic lymphohistiocytosis together with data from the literature, clinical development and post marketing provided by the MAH, the PRAC agreed that there is sufficient evidence for establishing a causal relationship between nivolumab and the occurrence of haemophagocytic lymphohistiocytosis. Therefore, the PRAC agreed that the product information of Opdivo (nivolumab) should be updated accordingly.

Summary of recommendation(s)

- The MAH for Opdivo (nivolumab) should submit to EMA, within 60 days, a variation to update the product information²².

For the full PRAC recommendation, see [EMA/PRAC/64581/2020](#) published on 10/03/2020 on the EMA website.

¹⁹ Hillaire-Buys D, Mousset M, Allouchery M et al. Liquid formulation of ifosfamide increased risk of encephalopathy: A case-control study in a pediatric population. *Therapie*. 2019 Oct 28

²⁰ Chambord J, Henny F, Salleron J et al. Ifosfamide-induced encephalopathy: Brand-name (Holoxan) vs generic formulation (Ifosfamide EG). *J Clin Pharm Ther*. 2019;44:372-380

²¹ Held 30 September – 03 October 2019

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

4.3.4. Vismodegib – ERIVEDGE (CAP) - EMEA/H/C/002602/SDA/019

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Signal of pancreatitis

EPITT 19470 – Follow up to October 2019

Background

For background information, see [PRAC minutes October 2019](#)²³.

The MAH for Erivedge (vismodegib) 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 the cumulative review of all cases from clinical trials, post-marketing and literature provided by the MAH, the PRAC agreed that at present there is insufficient evidence to establish a causal relationship between treatment with vismodegib and the occurrence of pancreatitis. Therefore, the PRAC agreed that no further regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for Erivedge (vismodegib) should closely monitor cases of acute pancreatitis, lipase increased and amylase increased in future PSURs.

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. Bupivacaine, meloxicam - EMEA/H/C/005205

Scope: Reduction of postoperative pain

5.1.2. Cabazitaxel - EMEA/H/C/005178

Scope: Treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen

²³ Held 30 September – 03 October 2019

5.1.3. Ebola vaccine (rDNA²⁴, replication-incompetent) - EMEA/H/C/005343

Scope (accelerated assessment): Active immunisation for the prevention of disease caused by Ebola virus

5.1.4. Ebola vaccine (rDNA²⁵, replication-incompetent) - EMEA/H/C/005337

Scope (accelerated assessment): Active immunisation for the prevention of disease caused by Ebola virus (Zaire ebolavirus species)

5.1.5. Glasdegib - EMEA/H/C/004878, Orphan

Applicant: Pfizer Europe MA EEIG

Scope: Treatment of newly diagnosed de novo or secondary acute myeloid leukaemia

5.1.6. Imlifidase - EMEA/H/C/004849, Orphan

Applicant: Hansa Biopharma AB

Scope: Desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor

5.1.7. Ivosidenib - EMEA/H/C/005056, Orphan

Applicant: Agios Netherlands B.V.

Scope: Treatment of adult patients (≥ 18 years old) with relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation

5.1.8. Luspatercept - EMEA/H/C/004444, Orphan

Applicant: Celgene Europe BV

Scope: Treatment of adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anaemia and treatment of adult patients with beta-thalassaemia (β -thalassaemia)-associated anaemia who require red blood cell (RBC) transfusions

5.1.9. Sodium oxybate – HOPVEUS (CAP MAA) - EMEA/H/C/004962

Applicant: D&A Pharma

Scope (re-examination): Medium to long-term maintenance of alcohol abstinence and treatment of mild to moderate alcohol withdrawal syndrome

Previously, PRAC advice was provided in April 2019 and December 2019, see [PRAC minutes April 2019](#) and [PRAC minutes September 2019](#).

²⁴ Ribosomal deoxyribonucleic acid

²⁵ Ribosomal deoxyribonucleic acid

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

See also Annex I 15.2.

5.2.1. Daptomycin - CUBICIN (CAP) - EMEA/H/C/000637/II/0074

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Pernille Harg

Scope: Submission of an updated RMP (version 11.1) in order to delete all risks and additional risk minimisation measures in line with revision 2 of GVP module V on 'Risk management systems'. Annex II is updated accordingly. In addition, the MAH took the opportunity to align the product information with the quality review of documents (QRD) template (version 10.1) and update the list of local representatives

Background

Daptomycin is a cyclic lipopeptide natural agent active against Gram positive bacteria only. It is indicated, as Cubicin, for the treatment of adult and paediatric patients with complicated skin and soft-tissue infections (cSSTI), for the treatment of adult patients with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* as well as for the treatment of adult and paediatric patients with *Staphylococcus aureus* bacteraemia (SAB).

The PRAC is evaluating a type II variation procedure for Cubicin, a centrally authorised medicine containing daptomycin, to update the RMP in order to delete important safety concerns/missing information and to update the RMP and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' to retire the existing additional risk minimisation measures (aRMMs) consisting of a dosing guide for prescribers and an antimicrobial susceptibility testing guide for laboratories. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. For further background, see [PRAC minutes November 2019](#)²⁶.

Summary of advice

- The RMP (version 12.0) for Cubicin (daptomycin) in the context of the variation procedure under evaluation is considered acceptable. This includes the removal of 'bone marrow toxicity' as an important potential risk.
- The PRAC agreed that the existing aRMMs consisting of a dosing guide for prescribers and an antimicrobial susceptibility testing guide for laboratories are not warranted any longer. Regarding the dosing guide for prescribers, the PRAC agreed that in light of the knowledge gained by HCPs over time and taking into account the available product information, the dosing guide is no longer necessary. As for the laboratory guide, the PRAC noted that relevant expert scientific guidelines²⁷ are regularly published and these are those used by laboratories performing susceptibility testing of daptomycin. Therefore, the laboratory guide is not necessary any longer. Annex II-D is also updated accordingly.

²⁶ Held 28-31 October 2019

²⁷ European Committee on Antimicrobial Susceptibility Testing (EUCAST)

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

See Annex I 15.3.

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. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201907

Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Ingenol mebutate has shown *in vivo* and *in vitro* models a dual mechanism of action for the effects of induction of local lesion cell death and for promoting an inflammatory response characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. Ingenol mebutate was indicated²⁸, as Picato, for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Picato, a medicine containing ingenol mebutate.

In January 2020, the PRAC recommended, as a provisional measure, to suspend the use and the marketing authorisation(s) for Picato (ingenol mebutate), without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004. For further background, see [PRAC minutes January 2020](#). Following the submission and start of the PSUSA procedure, the PRAC was informed that the [marketing authorisation\(s\) for Picato had been withdrawn](#) throughout the European Union (EU) at the MAH's request as of 11 February 2020. In line with the 'Guidance on handling of PSUR procedures for suspended or withdrawn / non-renewed / revoked marketing authorisations' (EMA/576230/2015) (see [PRAC minutes January 2016](#)), the PRAC also reviewed the need for further/ad-hoc PSUR(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the PRAC discussed the PRAC Rapporteur's PSUSA assessment report for Picato (ingenol mebutate). The PRAC noted the European Commission (EC) decision dated 11 February 2020 withdrawing the marketing authorisation(s) for Picato (ingenol mebutate) at the MAH's request. The conclusions are without prejudice to the final recommendation of the ongoing referral procedure under Article 20 of Commission Regulation (EC) No 726/2004.

²⁸ European Commission (EC) decision on the MA withdrawal of Picato dated 11 February 2020

- The PRAC agreed that no further PSURs are necessary in light of the current context. Therefore, the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.2. Natalizumab - TYSABRI (CAP) - PSUSA/00002127/201908 (with RMP)

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Natalizumab is a humanised monoclonal antibody that binds to the $\alpha 4$ chain of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins. It is indicated, as Tysabri, as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) in patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) and 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.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tysabri (natalizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine an existing warning on the lack of statistically significant effect of plasma exchange/plasmapheresis (PLEX) on natalizumab-associated two-year survival post-progressive multifocal leukoencephalopathy (PML) outcome. In addition, the frequencies of the undesirable effects: urinary tract infection, nasopharyngitis, headache, dizziness, nausea, arthralgia and fatigue are changed from 'common' to 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.
- In the next PSUR, the MAH should provide detailed reviews of cases of lupus erythematosus as well as cases of immune thrombocytopenic purpura and thrombocytopenia.
- The MAH should submit to the EMA, within 60 days, additional analyses on cumulative data on pregnancy including foetal outcomes. Based on the analyses and on the recent systematic review by Peng *et al*³⁰, the MAH should propose an update of the product information as warranted.

²⁹ Update of SmPC sections 4.4, 4.8 and 5.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³⁰ Peng A *et al*. Natalizumab exposure during pregnancy in multiple sclerosis: a systematic review. *J Neurol Sci*. 2019;396:202-205

The next PSUR should be submitted and assess the need to update the product information 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. Pegaspargase³¹ - ONCASPAR (CAP) - PSUSA/00010457/201907

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Pegaspargase is a pegylated L-asparaginase indicated, as Oncaspar, as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric and adult patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Oncaspar, a centrally authorised medicine containing pegaspargase 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 Oncaspar (pegaspargase) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include anaphylactic shock as an undesirable effect with a frequency 'not known' and to reclassify toxic epidermal necrolysis under the system organ class (SOC) 'skin and subcutaneous tissue disorders'. Therefore, the current terms of the marketing authorisation(s) should be varied³².

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.

6.1.4. Perampanel - FYCOMPA (CAP) - PSUSA/00009255/201907

Applicant: Eisai GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Perampanel is a non-competitive antagonist of the glutamate receptor on post-synaptic neurons. It is indicated, as Fycompa, for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures or primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with epilepsy as well as for the adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy.

³¹ Centrally authorised product(s) only

³² 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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Fycompa, a centrally authorised medicine containing perampanel 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 Fycompa (perampanel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated in order to include a warning on hepatotoxicity and to amend the information regarding the use of contraceptives from oral contraceptive to hormonal contraceptive. In addition, Stevens-Johnson syndrome (SJS) is added to the existing warning on severe cutaneous adverse reactions (SCARs) and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³³.
- In the next PSUR, the MAH should provide an overview of all cases occurring in paediatric population assessed by age groups, an update on the specific monitoring of pregnancy and associated birth defects. The MAH should also provide a causality assessment for cases of aggression and provide reviews of cases of hepatic disorder and cases off-label use. In addition, cases of stupor, coma and decreased level of consciousness should be closely monitored as an important potential risk. Furthermore, the MAH should include a cumulative review and an assessment of cases where atypical absence appears after perampanel initiation, as well as the outcome of cases where patients with atypical absences were treated with perampanel. With these reviews, the MAH should discuss the need for updating the product information and make a proposal, as appropriate.

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. Sarilumab - KEVZARA (CAP) - PSUSA/00010609/201907

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Sarilumab is a human monoclonal antibody, namely immunoglobulin G1 (IgG1) subtype, that specifically binds to both soluble and membrane-bound interleukin-6 (IL-6) receptors (IL-6Ra). It is indicated, as Kevzara, alone or in combination with methotrexate (MTX) for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs).

³³ Update of SmPC sections 4.4, 4.5, 4.6 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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Kevzara, a centrally authorised medicine containing sarilumab 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 Kevzara (sarilumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pneumonia and cellulitis as undesirable effects with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAH should provide a detailed review of medication errors and provide a cumulative review of cases of gastrointestinal perforation.

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

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

6.2.1. Aripiprazole - ABILIFY (CAP); ABILIFY MAINTENA (CAP); ARIPIPRAZOLE SANDOZ (CAP); NAP - PSUSA/00000234/201907

Applicant(s): Otsuka Pharmaceutical Netherlands B.V. (Abilify, Abilify Maintena), Sandoz GmbH (Aripiprazole Sandoz), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Aripiprazole is an atypical antipsychotic indicated, as Abilify, Abilify Maintena and Aripiprazole Sandoz, for the treatment of schizophrenia in adults and in adolescents aged 15 years and older, for the treatment of moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode in adults and for the treatment of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 years and older. It is also indicated for the rapid control of agitation and disturbed behaviours in adult patients with schizophrenia or with manic episodes in bipolar I disorder and for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Abilify, Abilify Maintena and Aripiprazole Sandoz, centrally authorised medicines containing aripiprazole, and nationally authorised medicines containing aripiprazole and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

³⁴ 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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of aripiprazole-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include photophobia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisations should be varied³⁵.
- In the next PSUR, the MAHs should provide cumulative reviews of cases of off-label use in pediatric patients, cases of atrial fibrillation, cases of endocrine tumours and myopia, together with a proposal to update the product information, as appropriate.

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. Ibuprofen, pseudoephedrine (NAP) - PSUSA/00001711/201907

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a non-steroidal anti-inflammatory agent and pseudoephedrine a sympathomimetic agent. In combination, ibuprofen/pseudoephedrine is indicated for the symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with common cold and flu in adults and adolescents.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance nationally authorised medicine(s) containing ibuprofen/pseudoephedrine 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 ibuprofen/pseudoephedrine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on ischaemic optic neuropathy and to add ischaemic optic neuropathy as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.

³⁵ 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

³⁶ 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

- In the next PSUR, all MAHs should provide cumulative reviews of cases of ischaemic events and of cases of Kounis syndrome from post-marketing sources and the literature. MAHs should closely monitor cases of vanishing bile duct syndrome, pulmonary arterial hypertension, cardiovascular and neurovascular events.

Additionally, the PRAC considered that the risk of ischaemic optic neuropathy should also be included in the product information of medicinal products containing pseudoephedrine as a mono-component or in other fixed dose-combinations. Further consideration should 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.

6.3.2. Pitavastatin (NAP) - PSUSA/00010502/201907

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Pitavastatin is a 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor, commonly known as a statin. It is indicated in adults for the treatment of primary hypercholesterolaemia including heterozygous familial hypercholesterolaemia, and combined dyslipidaemia. It is also indicated in paediatric population for the treatment of primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia and combined (mixed) dyslipidaemia.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance nationally authorised medicine(s) containing pitavastatin 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 pitavastatin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include, as undesirable effects, angioedema and lupus-like syndrome with a frequency 'not known' and gynaecomastia with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁷.

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.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Levetiracetam - KEPRA (CAP) - EMEA/H/C/000277/LEG 087

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Cumulative review of cases of seizure worsening as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00001846/201811 adopted in July 2019

Background

Levetiracetam is a pyrrolidone derivative indicated, as Keppra, as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. As an adjunctive treatment, it is indicated for the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy; for the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy as well as for the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

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 cases of seizure worsening. For background, see [PRAC minutes July 2019](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC agreed that there is sufficient evidence supporting a probable causal relationship between levetiracetam and paradoxical reactions evidenced by seizures worsening.
- The MAH of Keppra (levetiracetam) should submit to the EMA, within 60 days, a variation to update the product information³⁸ to include worsening of seizures as a warning and 'seizures aggravated' as an undesirable effect with a frequency 'rare'.
- In the next PSUR, the important potential risk of 'seizure worsening' should be reclassified as an important identified risk, and a discussion on this risk should be provided.

6.4.2. Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/LEG 015

Applicant: Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Detailed reviews of cases of hyponatraemia and cases of serious hepatic reactions, including the adequacy of the current risk minimisation measures (RMM) of the product information as requested in the conclusions of periodic safety update single assessment

³⁸ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

procedure PSUSA/00002435/201902 adopted in September 2019

Background

Pirfenidone is an immunosuppressant indicated in adults, as Esbriet, for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on hyponatraemia and serious hepatic reactions. For background, see [PRAC minutes September 2019](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC agreed that the addition of drug induced liver injury (DILI) to the product information is warranted along with an advice for additional monitoring of patients in the presence of signs and symptoms of liver disease. The PRAC also agreed that communication of this update via a direct healthcare professional communication (DHPC) is necessary. In addition, the RMP should be updated accordingly.
- The PRAC also agreed that the product information should be updated with a warning on hyponatraemia.
- The MAH should submit to the EMA, within 60 days, variations to update the product information³⁹ of Esbriet (pirfenidone) together with a proposal for updating the RMP and a proposal for a DHPC.

7. Post-authorisation safety studies (PASS)

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

See also Annex I 7.1.

7.1.1. Buprenorphine - SIXMO (CAP) - EMEA/H/C/PSP/S/0086

Applicant: L. Molteni & C. dei Fratelli Alitti Societa di Esercizio S.p.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol for study MOLTeNI-2019-01: a prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in the routine clinical care

Background

Buprenorphine is an opioid partial agonist/antagonist which binds to the μ (μ) and κ (κ) receptors of the brain. It is indicated, as Sixmo a centrally authorised product, for substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine, within a framework of medical, social and psychological treatment.

³⁹ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

⁴⁰ In accordance with Article 107n of Directive 2001/83/EC

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product ([Annex II-D of the marketing authorisation\(s\)](#)), a prospective, observational safety cohort study should be conducted to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants in the routine clinical care. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted protocol version 1 for a study entitled 'a prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of Sixmo (buprenorphine implants) in routine clinical care (MOLTeNI-2019-01)'. The PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 1 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Sixmo (buprenorphine). The PRAC agreed that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage. In particular, the MAH should provide precise definition of the variables, information on how breakage of the first or the second implant in a single patient will be reported and describe strategies and data sources for determining exposures, outcomes and other variables, such as potential confounding variables and effect modifiers. The MAH should also explain the role of physicians and patient questionnaire in data collection. In addition, the MAH is requested to provide information on the countries where the study is planned to be performed and further information in patients older than 65 years old.
- 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)⁴¹

See also Annex 17.2.

7.2.1. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/MEA 004.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 004 [protocol for a prospective, observational safety study to characterise the risks of the use of apalutamide in non-metastatic castration-resistant prostate cancer (NM-CRPC) patients on androgen deprivation therapy (ADT) with clinically significant cardiovascular conditions [final report expected in 2023]] as per the request for supplementary information (RSI) adopted in June 2019

Background

Apalutamide is a selective androgen receptor inhibitor indicated, as Erleada a centrally authorised medicine, in adult men for the treatment of non-metastatic castration-resistant prostate cancer who are at high risk of developing metastatic disease. It is also indicated in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).

⁴¹ 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

As part of the RMP for Erleada (apalutamide), the MAH was required to conduct a prospective, observational safety study to characterise the risks of the use of apalutamide in non-metastatic castration-resistant prostate cancer (NM-CRPC) patients on androgen deprivation therapy (ADT) with clinically significant cardiovascular conditions in order to mitigate the risks of Erleada. The MAH submitted a feasibility study of a PASS to further investigate the use of apalutamide in patients with significant cardiovascular pathologies, notably major cardio-vascular events (MACE) (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the feasibility study submitted by the MAH. For further background, see [PRAC minutes June 2019](#).

Summary of advice

- The PRAC agreed that the evidence that emerged during the assessment of the current feasibility study from the SPARTAN⁴² and the TITAN⁴³ studies, which were representative of the target populations, is sufficient to better characterise the risk. Therefore, the PRAC advised that the study on apalutamide in patients with significant cardiovascular pathologies is not necessary any longer.
- The MAH should submit to the EMA, within 90 days, an updated RMP reflecting the deletion of the PASS.
- In future PSURs, the MAH should continue to monitor the safety in populations with significant cardiovascular disease as well as QT prolongation.

7.3. Results of PASS imposed in the marketing authorisation(s)⁴⁴

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

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to PSR/S/0020 [results of an observational 5 year safety study to assess the identified and potential risks of Bronchitol (mannitol) in cystic fibrosis (CF) through a comparison between Bronchitol-exposed patients and unexposed patients matched for key characteristics] as per the request for supplementary information (RSI) adopted in June 2019

Background

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

As a condition to the marketing authorisation(s) ([Annex II-D](#)), the MAH was required to conduct a PASS to assess the identified and potential risks of Bronchitol (mannitol) in CF through a comparison between Bronchitol-exposed patients and an unexposed patient group matched for key characteristics.

⁴² A multicentre, randomised, double-blind, placebo-controlled, phase 3 study of ARN-509 (apalutamide) in men with non-metastatic (M0) castration-resistant prostate cancer

⁴³ A phase 3 randomised, placebo-controlled, double-blind study of apalutamide plus ADT versus ADT in subjects with mHSPC

⁴⁴ In accordance with Article 107p-q of Directive 2001/83/EC

The final study report was submitted to EMA by the MAH Pharmaxis Pharmaceuticals Limited on 5 November 2018. The PRAC discussed the final study results in addition to the MAH's responses to two requests for supplementary information (RSI). The PRAC is responsible for evaluating the PASS final results. For further background, see [PRAC minutes January 2019](#) and [PRAC minutes June 2019](#).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'an 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 the benefit-risk balance of Bronchitol (mannitol) remains unchanged. As a consequence, the PRAC recommended that the terms of the marketing authorisation(s) for Bronchitol (mannitol) should be varied to remove the PASS as an obligation to perform the PASS in question from Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'.

7.3.2. Thiocolchicoside (NAP) - EMEA/H/N/PSR/J/0023

Applicant: Sanofi (on behalf of a consortium)

PRAC Rapporteur: Amelia Cupelli

Scope: Results for a joint drug utilisation study of thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records databases study

Background

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

In line with the conclusions of a referral procedure under Article 31 of Directive 2001/83/EC conducted in 2014 for thiocolchicoside-containing medicines ([EMA/H/A-1361](#)), MAHs were required as a condition to the marketing authorisations ([Annex IV](#)) to conduct a drug utilisation study (DUS) to assess the effectiveness of the risk minimisation measures, to further characterise prescribing patterns of use in representative groups of prescribers and to assess main reasons for prescription.

The final study report was submitted to EMA by the MAH Sanofi on behalf of a consortium on 3 December 2019. The PRAC discussed the final study results. The PRAC is responsible for evaluating the PASS results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the joint non-interventional PASS entitled a 'drug utilisation study of thiocolchicoside (TCC)-containing medicinal products for systemic use in France and Italy: an electronic medical records databases study', the PRAC recommended that the terms of the marketing authorisations for thiocolchicoside-containing products concerned by the PASS final report should be varied to remove the study as an obligation to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription from the conditions or restrictions with regard to the safe and

effective use of the medicinal product(s). The inclusion of thiocolchicoside-containing products in the list of medicinal products under additional monitoring is not warranted any longer.

- In the next PSUR (data lock point (DLP): 04/07/2021), the MAH(s) should provide feedback on the redistribution of the direct healthcare professional communication (DHPC) and the educational material (EM). For further background, see [PRAC minutes September 2018](#).
- The RMPs should be updated at the next regulatory opportunity.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁵

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

⁴⁵ 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

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

8.3.1. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/R/0074 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

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 programmed death-ligand 1 (PD-L1) and PD-L2. It is indicated as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Opdivo, a centrally authorised medicine containing nivolumab, was authorised in 2015.

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects. For further background, see [PRAC minutes December 2019](#)⁴⁶.

Summary of advice

- Based on the review of the available pharmacovigilance data for Opdivo (nivolumab) and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal of the marketing authorisation(s) could be granted with unlimited validity.
- The PRAC agreed to remove the 'physician educational material' as an additional risk minimisation measure (aRMM) in light of the knowledge gained by healthcare professionals (HCPs) over time and their awareness of the management of the risks of Opdivo (nivolumab). The PRAC advised to maintain the patient alert card but to remove the following safety concerns: severe infusion reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT) following nivolumab therapy as well as the risk of graft versus host disease (GvHD) with nivolumab after allogeneic HSCT. Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is to be updated accordingly.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

⁴⁶ Held 25-28 November 2019

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

10.3.1. Nitrosamine impurities in medicinal products for human use containing chemically synthesised active pharmaceutical ingredients (API) - EMEA/H/A-5(3)/1490

Applicant(s): various

PRAC Lead: Martin Huber, Ulla Wändel Liminga

Scope: PRAC consultation on a CHMP review under Article 5(3) of Regulation (EC) No 726/2004 on nitrosamine impurities in human medicinal products containing chemically synthesised API

Background

Nitrosamines are chemical compounds classified as probable human carcinogens on the basis of animal studies. In September 2019, a review under Article 5(3) of Regulation (EC) No 726/2004 was initiated at CHMP in order to provide guidance to MAHs on how to avoid the presence of nitrosamine impurities in medicines for human use. As part of the review ([EMA/189634/2019](#)), the CHMP requested MAHs of medicines containing chemically synthesised active substances to review their medicinal products for the possible presence of nitrosamines and test all products at risk. The PRAC was requested to provide advice on existing epidemiological data and the need for further studies to better evaluate a potential relationship between exposure to nitrosamines in medicinal products and the risk of cancer in humans.

Summary of advice

- Based on the available data, the PRAC agreed that while further studies are desirable to quantify the risk of cancer after exposure to potentially contaminated medicinal products, the conduct of such studies is challenging, due to several issues. The

committee considered that, in principle, a study may in some specific settings be feasible, however, a general conclusion on feasibility could not be reached. Furthermore, a number of critical challenges were identified leading to the conclusion that it is unlikely to be possible to design a study which can achieve meaningful results. These include the difficulty of reliably determining the exposure (preferably available at product name level), selection bias, the availability of a suitable comparison group, the requirement for a large sample size, accurate information about the exposure and the cumulative dose, information on potential confounders, long follow-up time and a suitable endpoint, which may need to be a composite of several individual cancers. Finally, the PRAC advised to consider the previous feasibility analysis regarding sartan contamination published in the EU PAS Register ([EUPAS31895](#)).

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

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

Following the call for nominating PRAC member(s) as a joint PRAC-SAWP representative to the CHMP Scientific advice working party ([SAWP](#)), the PRAC nominated Brigitte Keller-Stanislowski as the PRAC representative to the SAWP. For further background, see [PRAC](#)

[minutes December 2019](#)⁴⁷.

12.4. Cooperation within the EU regulatory network

12.4.1. EMA Regulatory science strategy to 2025

The PRAC was invited by the EMA secretariat to comment on the draft [EMA Regulatory science strategy](#) to 2025, which aims to enhance the available regulatory tools to continue supporting the European medicines regulatory network and fulfil its ongoing mission in light of upcoming scientific challenges, by 21 February 2020.

12.5. Cooperation with International Regulators

12.5.1. Health Canada (HC) - overview of structure and processes

The PRAC was informed of the structure and processes for supervision of medicines at [Health Canada](#), the Canadian body for regulating drugs and health products.

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q4 2019 and predictions

The EMA Secretariat presented to the PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see [PRAC minutes November 2019](#).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

⁴⁷ Held 25-28 November 2019

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

None

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 February 2020, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of February 2020, the updated EURD list was adopted by the CHMP and CMDh at their February 2020 meetings and published on the EMA website on 04/03/2020, 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

None

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 the EMA website on 26/02/2020, 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

12.13.2. EudraVigilance operational plan – milestones 2020 to 2022

The EMA secretariat consulted the PRAC on the EudraVigilance operational plan and its milestones between 2020 and 2022. The operation plan was set up to ensure sustainability of EudraVigilance in support of the EU pharmacovigilance activities and the protection of public health, to outline technical and operational activities as well as how stakeholders that interact with EudraVigilance will be affected.

Post-meeting note: On 23 March 2020, the EudraVigilance operational plan – milestones 2020 to 2022 ([EMA/509378/2019](#)) was published on the EMA website.

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. Medical Dictionary for Regulatory Activities (MedDRA) points to consider group – call for EU expert nomination

The EMA Secretariat presented to PRAC a call for EU expert nomination to join the Medical Dictionary for Regulatory Activities (MedDRA) points to consider group. The group is responsible for developing and maintaining guidance on coding and analysing data using MedDRA. Follow-up discussion will be scheduled in March 2020.

12.20.2. Strategy on measuring the impact of pharmacovigilance - PRAC interest group (IG) Impact – impact guidance

PRAC Lead: Antoine Pariente

The EMA secretariat together with the PRAC lead presented to the PRAC a revised draft guidance on pharmacovigilance impact research developed by the PRAC interest group (IG), which includes product, population or healthcare setting targeted by the regulatory action and also includes the potential unintended consequences of regulatory actions following implementation of the comments received. The PRAC discussed the next steps regarding the finalisation of the guidance vis-à-vis the existing GVP modules. PRAC members were invited to send written comments by 9 June 2020. Further discussion will be scheduled in

July 2020. For further background, see [PRAC minutes December 2019](#)⁴⁸.

12.20.3. UK withdrawal from the EU – update

The EMA secretariat updated the PRAC on practical aspects of the [UK's withdrawal from the EU](#). The withdrawal agreement (WA) was ratified and the UK is considered as a 'third country' from 1 February 2020. The WA foresees a transition period until 31 December 2020. During the transition period, the UK still needs to comply with the EU pharmaceutical 'acquis communautaire' and is to be treated as if it was a Member State of the EU, with exception of aspects related to nomination/appointment/election of members of EU entities, participation in decision making and governance, and attendance in EMA meetings.

See also under 1.1.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁴⁹

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables⁵⁰.

14.1.1. Adalimumab - AMGEVITA (CAP); HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP); HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP)

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Humira), Amgen Europe B.V. (Amgevita), Fresenius Kabi Deutschland GmbH (Idacio), Mylan S.A.S (Hulio), Samsung Bioepis NL B.V. (Imraldi), Sandoz GmbH (Halimatoz, Hefiya, Hyrimoz)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of abnormal weight gain

EPITT 19520 – New signal

Lead Member State(s): SE

14.1.2. Teriparatide - FORSTEO (CAP), MOVYMIA (CAP); TERROSA (CAP); NAP

Applicant(s): Eli Lilly Nederland B.V. (Forsteo), Gedeon Richter Plc. (Terrosa), Stada Arzneimittel AG (Movymia), various

⁴⁸ Held 25-28 November 2019

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

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

PRAC Rapporteur: Adrien Inoubli

Scope: Signal of myeloma

EPITT 19511 – New signal

Lead Member State(s): FR

14.1.3. Sevoflurane (NAP)

Applicant(s): various

PRAC Rapporteur: Ronan Grimes

Scope: Signal of diabetes insipidus

EPITT 19531 – New signal

Lead Member State(s): IE

14.2. New signals detected from other sources

14.2.1. Lorlatinib – LORVIQUA (CAP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of nephrotic syndrome

EPITT 19518 – New signal

Lead Member State(s): HR

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. Fingolimod - EMEA/H/C/005191

Scope: Treatment of multiple sclerosis

15.1.2. Fingolimod - EMEA/H/C/005282

Scope: Treatment of multiple sclerosis

15.1.3. Insulin aspart - EMEA/H/C/005033

Scope: Treatment of diabetes mellitus

15.1.4. Teriparatide - EMEA/H/C/005087

Scope: Treatment of osteoporosis

15.1.5. Teriparatide - EMEA/H/C/005388

Scope: Treatment of osteoporosis

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. 5-aminolevulinic acid - AMELUZ (CAP) - EMEA/H/C/002204/II/0040

Applicant: Biofrontera Bioscience GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 11.1) brought in line with revision 2 of GVP module V on 'Risk management systems', including also the implementation of changes as requested by PRAC in the conclusions of the periodic safety update report single assessment (PSUSA) procedure PSUSA/00010006/201806 adopted in February 2019

15.2.2. Alogliptin, pioglitazone - INCRESYNC (CAP) - EMEA/H/C/002178/II/0029

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 10.0) in order to remove additional risk minimisation measures (aRMMs) as requested in the outcome of periodic safety update report single assessment (PSUSA) procedure PSUSA/00002417/201807 for pioglitazone, glimepiride/pioglitazone and metformin/pioglitazone adopted in March 2019 and consequently the removal of the drug utilisation study (DUS) on the utilisation of pioglitazone-alogliptin containing medicinal product(s) in clinical practice with regard to diabetic treatment regimen and comorbidities as well as the removal of relevant commitments as per the conclusions of LEG 008 adopted in September 2015. In addition, the RMP is brought in line with revision 2 of the guidance on the format of RMP in the EU (template) reflecting changes in the categorisation of safety concerns. Furthermore, the targeted adverse event (AE) follow-up questionnaires related to AEs of severe hypersensitivity skin reactions, hepatic events, pancreatitis, bladder cancer, malignancies (including pancreatic cancer), bone fractures, and macular oedema are removed. Finally, the RMP is updated to reflect the removal of the additional monitoring inverted black triangle as per the conclusion of the renewal procedure R/0023 finalised in March 2018. Annex II is updated accordingly. The MAH took the opportunity to update the product information to amend the details of the local representative for Poland

15.2.3. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/II/0038, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 4.3) to revise the summary of safety concerns as requested by PRAC/CHMP in the conclusions of the renewal procedure of the conditional marketing authorisation R/0035 adopted in November 2019. As requested by the PRAC/CHMP, data on co-administration of bedaquiline and human immunodeficiency virus (HIV)-protease inhibitors are also summarised

15.2.4. Bortezomib - VELCADE (CAP) - EMEA/H/C/000539/II/0093

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 30.1) in order to revise the list of safety concerns as requested in the conclusions of periodic single assessment procedure (PSUSA) PSUSA/00000424/201804 adopted in December 2018. As a consequence, Annex II is updated to reflect the removal of the additional risk minimisation activities. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is being brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.2.5. Epoetin zeta - RETACRIT (CAP) - EMEA/H/C/000872/II/0094

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 11.1) in order to align the safety concerns of Retacrit (epoetin zeta – biosimilar) to the medicinal product of reference containing epoetin alfa (Eprex). The RMP (version 15.0) is updated accordingly

15.2.6. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1747/0231; LIFMIOR (CAP) - EMEA/H/C/004167/WS1747/0025

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 7.0) to revise the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to implement the outcomes of variation WS/1270 adopted in January 2019 and periodic single assessment procedure (PSUSA) PSUSA/001295/201902 adopted in September 2019 as requested by PRAC/CHMP in order to remove or consolidate several risks. Finally, the MAH removed the addendum to RMP (version 6.3), introduced some clinical and post-marketing data updates and reflected the completion of post-authorisation studies

15.2.7. Interferon beta-1a - REBIF (CAP) - EMEA/H/C/000136/II/0144

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 11) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to ensure the appropriate time needed for the effective review and analysis of all RMP sections

15.2.8. Tegafur, gimeracil, oteracil - TEYSUNO (CAP) - EMEA/H/C/001242/II/0042

Applicant: Nordic Group B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 9.0) in order to revise the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' as requested in the conclusions of the periodic safety update report single assessment (PSUSA) procedure PSUSA/00002875/201801 adopted in September 2018

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. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0029

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy. 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 12.0) are updated accordingly

15.3.2. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0013

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Update of section 5.1 of the SmPC in order to update efficacy information following results from study EMR100070-003 Part B (listed as a specific obligation in Annex II): a phase 2, open-label, multicentre trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma. The MAH took the opportunity to update Annex II proposing the deletion of the specific obligation and proposing the switch from conditional to full marketing authorisation. The package leaflet and the RMP (version 2.1) are updated accordingly

15.3.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0076

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information based on the final results from study BEL115467 (listed as an imposed PASS in

Annex II): a Randomized, double-blind, placebo-controlled 52-week study to assess adverse events of special interest in adults with active, autoantibody-positive systemic lupus erythematosus receiving belimumab. The package leaflet is updated accordingly. The RMP (version 36) is updated in accordance and includes minor updates. In addition, the MAH took the opportunity to introduce minor editorial changes to Annex II and the labelling

15.3.4. [Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY \(CAP\) - EMEA/H/C/004449/II/0027](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.8 and 5.1 of the SmPC to reflect pooled efficacy and safety data from the final clinical study reports of two antiretroviral therapy-naïve adult studies (listed as category 3 studies in the RMP) through 144 weeks of treatment, namely study GS-US-380-1489: a phase 3, randomized, double-blind study to evaluate the safety and efficacy of GS-9883 (bictegravir)/emtricitabine/tenofovir alafenamide versus abacavir [ABC]/dolutegravir [DTG]/lamivudine [3TC] in human immunodeficiency virus-1 (HIV-1) infected, antiretroviral treatment-naïve adults) and study GS-US-380-1490: a phase 3, randomized, double-blinded study to evaluate the safety and efficacy of GS-9883/emtricitabine/tenofovir alafenamide versus dolutegravir + emtricitabine/tenofovir alafenamide in HIV-1 infected, antiretroviral treatment-naïve adults (in fulfilment of MEA 001 and MEA 002). The RMP (version 2.1) is updated accordingly. In addition, the MAH took the opportunity to make some minor editorial changes to the product information and update Annex II with regards to PSUR requirements

15.3.5. [Brigatinib, brigatinib - ALUNBRIG \(CAP\) - EMEA/H/C/004248/II/0003](#)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor for Alunbrig (brigatinib). The addition of a new indication is supported by data from study AP26113-13-301 (ALTA 1L): a phase 3, randomized, open label, comparative, multicentre, international phase 3 study of brigatinib versus crizotinib in patients With ALK-positive advanced lung cancer. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet, labelling and the RMP (version (version 5.1) are updated accordingly. The MAH took the opportunity to introduce minor editorial corrections in the product information

15.3.6. [Buprenorphine, naloxone - SUBOXONE \(CAP\) - EMEA/H/C/000697/X/0042](#)

Applicant: Indivior Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Extension application to introduce a new pharmaceutical form (sublingual film) associated with four new strengths (2/0.5 mg, 4/1 mg, 8/2 mg and 16/4 mg) and a new route of administration (either sublingual or buccal administration). The RMP (version 14.0) is updated accordingly

15.3.7. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0046

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to add the treatment of stage 2 or 3 chronic kidney disease (CKD) and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus (T2DM), based on new clinical efficacy and safety data from study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre phase 3 study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy. 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 8.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.8. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0051

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to add the treatment of stage 2 or 3 chronic kidney disease (CKD) and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus (T2DM), based on new clinical efficacy and safety data from study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre phase 3 study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy. 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 8.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.9. Carmustine - CARMUSTINE OBVIUS (CAP) - EMEA/H/C/004326/II/0002

Applicant: Obvius Investment B.V

PRAC Rapporteur: Jan Neuhauser

Scope: Extension of indication to add carmustine with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases. As a consequence, sections 4.1, 4.2 and 6.3 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.10. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/X/0122/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped applications consisting of: 1) extension application to add two new pharmaceutical forms coated granules (20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg) and powder and solvent for oral solution (6.25 mg/mL)); 2) extension of indication to include treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE

in paediatric patients from birth to less than 18 years of age for Pradaxa (dabigatran etexilate) 75 mg, 110 mg, 150 mg capsules based on paediatric trials, namely study 1160.106: an open-label, randomized, parallel-group, active-controlled, multi-centre non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age, and study 1160.108: an open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and labelling are updated in accordance. The RMP (version 37.0) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.11. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1737/0034; FORXIGA (CAP) - EMEA/H/C/002322/WS1737/0053

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to add a new indication for the treatment of symptomatic heart failure with reduced ejection fraction in adults. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and labelling are updated in accordance. The RMP (version 18) is updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1). Finally, the MAH took the opportunity to introduce an editorial change in the product information

15.3.12. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/II/0040, Orphan

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include adolescents and children above 6 years with a body weight of at least 30 kg. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.2) are updated accordingly. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.13. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0014/G

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Grouped variations consisting of: 1) extension of indication to include the use of Imfinzi (durvalumab) in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). The proposed indication is supported by study D419QC00001 (CASPIAN): an ongoing phase 3 randomised, multicentre, open-label, comparative study designed to determine the efficacy and safety of durvalumab, or durvalumab and tremelimumab, in combination with etoposide and platinum-based chemotherapy (EP) for the first-line treatment of patients with ES-SCLC; 2) update of sections 4.4 and 4.8 of the SmPC to update the safety information

based on the durvalumab pan-tumour pool: a safety dataset comprising of 9 clinical studies building on the existing safety database and summarising the safety information for durvalumab monotherapy characterised across tumour types in the durvalumab clinical programme to date, The package leaflet and the RMP (version 2) are updated in accordance

15.3.14. Emtricitabine, tenofovir alafenamide - DESCovy (CAP) - EMEA/H/C/004094/II/0044

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study GS-US-311-1717 (listed as a category 3 in the RMP): a phase 3b, randomized, double-blind, switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in human immunodeficiency virus type 1 (HIV-1) infected subjects who are virologically suppressed on regimens containing abacavir/lamivudine (ABC/3TC). The RMP (version 4.1) is updated accordingly

15.3.15. Entecavir - BARACLUDE (CAP) - EMEA/H/C/000623/II/0064

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to reflect the completion of the two paediatric studies, namely: study AI463028: evaluation of the pharmacokinetics, safety, tolerability and efficacy of entecavir (ETV) in paediatric subjects with chronic hepatitis B virus (HBV) infection who are hepatitis B e-antigen (HBeAg)-positive; and study AI463189: a comparative study of the antiviral efficacy and safety of ETV versus placebo in paediatric subjects with chronic HBV infection who are HBeAg-positive. In addition, section 5.3 of the SmPC is updated to reflect the outcome of study AI463080 (REALM Study): a randomized, observational study of entecavir to assess long-term outcomes associated with nucleoside/nucleotide monotherapy for patients with chronic HBV infection. Section 5.2 of the SmPC is also updated to remove information on the pharmacokinetics of entecavir in lamivudine-experienced paediatric patients, at the request of the CHMP. The RMP (version 15) is updated accordingly and in line with revision 2.0 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1) and to introduce minor editorial changes to the product information

15.3.16. Insulin degludec, liraglutide - XULTOPHY (CAP) - EMEA/H/C/002647/II/0034

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.2 of the SmPC in order to change the wording 'transfer from basal insulin' to 'transfer from any insulin regimen', based on data from study NN9068-4184 (DUAL II Japan): a double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects with type 2 diabetes mellitus (T2DM) inadequately controlled with basal or pre-mix/combination insulin therapy and oral anti-diabetic drugs, together with data from the post-marketing setting. In addition, the MAH took the opportunity to make a minor correction in section 5.1 of the SmPC and to implement changes in Annexes in line with

the latest quality review of documents (QRD) template (version 10.1). The RMP (version 9.0) is updated accordingly

15.3.17. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/X/0081/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength (45/200 mg film-coated tablets) and a new pharmaceutical form (oral granules) associated with new strengths (33.75/150 mg and 45/200 mg). The new presentations are indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in patients aged 3 to <12 years; 2) inclusion of paediatric use in patients aged 3 to < 12 years who weigh greater than or equal to 35 kg to the existing presentations of 90/400 mg film-coated tablets. The RMP (version 8.3) is updated accordingly. In addition, the MAH took the opportunity to implement minor linguistic corrections throughout the product information

15.3.18. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0026, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include a new indication for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to introduce minor linguistic corrections to the Annexes in French and Swedish

15.3.19. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0036, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.8 and 5.1 of the SmPC based on data from the final clinical study report (CSR) of pivotal study GA04753g/GO01297 (GADOLIN) (listed as category 3 study in the RMP): an open-label, multicentre, randomized, phase 3 Study to investigate the efficacy and safety of bendamustine compared with bendamustine+ obinutuzumab (RO5072759 (GA101)) in patients with rituximab-refractory, indolent non-Hodgkin's lymphoma. The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.20. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0038, Orphan

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Submission of final clinical study report (CSR) for study MO28543/GREEN: a multicentre, open-label, single-arm, phase 3b, international study evaluating the safety of obinutuzumab alone or in combination with chemotherapy in patients with previously

untreated or relapsed/refractory chronic lymphocytic leukaemia (in fulfilment of the post authorisation commitment MEA 005). The RMP (version 6.1) is updated accordingly

15.3.21. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/II/0101

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include treatment of nasal polyps in adult patients with inadequate response to intranasal corticosteroids. 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 16.0) are updated in accordance. In addition, the MAH took the opportunity to introduce minor editorial changes in section 4.2 of the SmPC and in the package leaflet and to update the details of the Dutch local representative. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.22. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0142

Applicant: Roche Registration GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC following completion of paediatric studies NV25719 and NV20234 and downstream population pharmacokinetic (PK) and PK/pharmacodynamic (PD) analysis in order to include a dose recommendation for the treatment of paediatric immunocompromised (IC) patients. Study NV25719 was a prospective, open-label, randomized study which investigated PK and PD of two weight adjusted oseltamivir doses for the treatment of influenza-infected immunocompromised (IC) children less than 13 years of age. Study NV20234 was a prospective, double-blind, randomized trial which investigated safety and viral resistance to oseltamivir treatment in influenza-infected IC adults, adolescents and children. The package leaflet, labelling and the RMP (version 19.0) are updated accordingly

15.3.23. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0057

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include first line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) tumours expressing programmed death-ligand 1 (PD-L1) with a $\geq 1\%$ tumour proportion score (TPS), based on data from study KEYNOTE-042: an international, randomized, open-label phase 3 study investigating Keytruda (pembrolizumab) monotherapy compared to standard of care platinum-based chemotherapy in patients with locally advanced or metastatic PD-L1 positive (TPS $\geq 1\%$) NSCLC, and on supportive data from the final planned analysis of KEYNOTE-024: a phase 3 randomized open-label study of Keytruda (pembrolizumab) monotherapy compared to platinum-based chemotherapy in metastatic NSCLC with PD-L1 TPS $\geq 50\%$. As a result, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The RMP (version 18.1) is updated accordingly

15.3.24. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0021

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to add a warning on interstitial lung disease (ILD)/pneumonitis and related dose modification recommendations. The package leaflet and the RMP (version 4.0) are updated accordingly

15.3.25. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0057

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy for Cosentyx (secukinumab). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. Section 6.6 of the SmPC for the solution for injection is also updated. The package leaflet and the RMP (version 6.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, Annex II is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.26. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/X/0059/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength (200 mg film-coated tablets) and a new pharmaceutical form (oral granules) associated with new strengths (150 and 200 mg). The new presentations are indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in patients aged 3 to <12 years; 2) inclusion of paediatric use in patients aged 3 to <12 years who weigh greater than or equal to 35 kg to the existing presentations of 400 mg film-coated tablets. The RMP (version 8.3) is updated in accordance. In addition, the MAH took the opportunity to implement minor linguistic corrections throughout the product information

15.3.27. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/X/0043/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength (200/50 mg film-coated tablets). The new formulation is indicated for the treatment of chronic hepatitis C (CHC) in patients aged 6 years and older; 2) inclusion of paediatric use in patients aged 6 to <18 years who weigh greater than or equal to 35 kg to the existing presentation (400/100 mg film-coated tablets). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 5.1) are updated in accordance

15.3.28. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0035

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include adolescent population from 12 years old and older to the existing indication of treatment of acute bacterial skin and skin-structure infections (ABSSSI) in adult. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 5.1) are updated in accordance. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.29. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/II/0016, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the information based on final results from study VX14-661-110 (listed as a category 3 study in the RMP): a phase 3, multicentre, open label, rollover study for studies 103, 106, 107, 108, 109, 111, 112 and 114 designed to evaluate the long-term safety and tolerability of tezacaftor/ivacaftor (TEZ/IVA) treatment for 96 weeks in cystic fibrosis (CF) subjects 12 years and older, homozygous or heterozygous for the phenylalanine in position 508 of the cystic fibrosis transmembrane conductance regulator (F508del CFTR) mutation. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1). The RMP (version 2.2) is updated accordingly

15.3.30. Tisagenlecleucel - KYMRIAHA (CAP) - EMEA/H/C/004090/II/0013/G, Orphan

Applicant: Novartis Europharm Limited, ATMP⁵¹

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC to implement 24 month follow-up results from study CCTL019C2201: a phase 2, single arm, multicentre trial to determine the efficacy and safety of CTL019 (tisagenlecleucel) in adult patients with relapsed or refractory diffuse large b-cell lymphoma (DLBCL); 2) update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC based on interim results from study CCTL019B2202: a phase 2, single arm, multicentre trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory b-cell acute lymphoblastic leukaemia; 3) update of section 5.2 of the SmPC based on interim results from study CCTL019B2205J: a phase 2, single arm, multicentre trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory b-cell acute lymphoblastic leukaemia. Annex II, the package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to clarify the wording of the indication in order to reflect that patients of 25 years of age are being included and to introduce some minor editorial corrections throughout the SmPC and the package leaflet

⁵¹ Advanced therapy medicinal product

15.3.31. Trastuzumab - HERCEPTIN (CAP) - EMEA/H/C/000278/II/0158

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study BO29159 (MetaPHER) (listed as a category 3 study in the RMP): a phase 3b study to evaluate the safety and tolerability of Herceptin (trastuzumab) subcutaneous (SC) with Perjeta (pertuzumab) and docetaxel in patients with HER2-positive Advanced Breast Cancer in order to generate and evaluate additional safety and tolerability data for the approved triplet regimen in the advanced breast cancer setting. In addition, bioanalytical supportive studies are presented. The RMP (version 21) is updated accordingly

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

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

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

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

16.1.1. Acridinium bromide - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP) - PSUSA/00009005/201907

Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.2. Aflibercept⁵² - ZALTRAP (CAP) - PSUSA/00010019/201908

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.3. Alirocumab - PRALUENT (CAP) - PSUSA/00010423/201907

Applicant: Sanofi-aventis groupe

⁵² In oncological indication(s) only

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.4. Apalutamide - ERLEADA (CAP) - PSUSA/00010745/201907

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.5. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/201907

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.6. Beclometasone, formoterol, glycopyrronium bromide - RIARIFY (CAP); TRIMBOW (CAP); TRYDONIS (CAP) - PSUSA/00010617/201907

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.7. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - PSUSA/00010695/201908

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.8. Birch bark extract⁵³ - EPISALVAN (CAP) - PSUSA/00010446/201907

Applicant: Amryt AG

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.9. Brodalumab - KYNTHEUM (CAP) - PSUSA/00010616/201907

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

⁵³ Centrally authorised product(s) only

[16.1.10. Catridecacog - NOVOTHIRTEEN \(CAP\) - PSUSA/00010034/201907](#)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

[16.1.11. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL \(CAP\) - PSUSA/00010701/201908](#)

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

[16.1.12. Dolutegravir – TIVICAY \(CAP\); dolutegravir, lamivudine - DOVATO \(CAP\); dolutegravir, abacavir, lamivudine - TRIUMEQ \(CAP\) - PSUSA/00010075/201907](#)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

[16.1.13. Evolocumab - REPATHA \(CAP\) - PSUSA/00010405/201907](#)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

[16.1.14. Glecaprevir, pibrentasvir - MAVIRET \(CAP\) - PSUSA/00010620/201907](#)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

[16.1.15. Guselkumab - TREMFYA \(CAP\) - PSUSA/00010652/201907](#)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[16.1.16. Idursulfase - ELAPRASE \(CAP\) - PSUSA/00001722/201907](#)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.17. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/201907

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.18. Metreleptin - MYALEPTA (CAP) - PSUSA/00010700/201907

Applicant: Aegerion Pharmaceuticals B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Neratinib - NERLYNX (CAP) - PSUSA/00010712/201907

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.20. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/201908

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.21. Peginterferon beta-1A - PLEGRIDY (CAP) - PSUSA/00010275/201907

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.22. Rotavirus vaccine monovalent (live, oral) - ROTARIX (CAP) - PSUSA/00002665/201907

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.23. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/201907

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.24. Saxagliptin, dapagliflozin - QTERN (CAP) - PSUSA/00010520/201907

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

16.1.25. Smallpox vaccine (live modified vaccinia Ankara virus) - IMVANEX (CAP) - PSUSA/00010119/201907 (with RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.26. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - PSUSA/00010619/201907

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.27. Tocoferolan - VEDROP (CAP) - PSUSA/00002981/201907

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.1.28. Voretigene neparvovec - LUXTURNA (CAP) - PSUSA/00010742/201907

Applicant: Novartis Europharm Limited, ATMP⁵⁴

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.29. Zanamivir⁵⁵ - DECTOVA (CAP) - PSUSA/00010763/201907

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

None

⁵⁴ Advanced therapy medicinal product

⁵⁵ Centrally authorised product(s) only

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

16.3.1. Clebopride (NAP) - PSUSA/00000789/201906

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.2. Dienogest, estradiol⁵⁶ (NAP) - PSUSA/00010443/201906

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.3. Ganciclovir (NAP) - PSUSA/00001516/201906

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.4. Human plasma proteins⁵⁷ (NAP) - PSUSA/00010605/201907

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.5. Itopride (NAP) - PSUSA/00010606/201906

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.6. Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide (NAP) – PSUSA/00010390/201907

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

⁵⁶ Hormone replacement therapy (HRT) indication(s) only

⁵⁷ With not less than 95% albumin

16.3.7. Misoprostol⁵⁸ (NAP) - PSUSA/00010291/201906

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.8. Mitoxantrone (NAP) - PSUSA/00002076/201906

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.9. Octenidine (NAP) - PSUSA/00010748/201907

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/LEG 035.1

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 035 [cumulative review of cases of metabolic/toxic encephalopathy as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00001816/201808 adopted in April 2019] as per the request for supplementary information (RSI) adopted in September 2019

16.4.2. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/LEG 088

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Laurence de Fays

Scope: Cumulative review of cases of cardiac arrhythmia and cases of torsades de pointes/QT prolongation as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00001846/201811 adopted in July 2019

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.

⁵⁸ Gastrointestinal indication(s) only

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁵⁹

17.1.1. Aprotinin (NAP) - EMEA/H/N/PSA/J/0046

Applicant: Nordic Group BV

PRAC Rapporteur: Laurence de Fays

Scope: Substantial amendment to a previously agreed protocol (N/PSP/0004.1) in March 2015 for a joint non-interventional study: Nordic aprotinin patient registry to record utilisation information on patients at cardiac surgery centres

17.1.2. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSP/S/0071.2

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: MAH's response to PSP/S/0071.1 [protocol for study 20180130: an observational PASS to describe the long-term safety profile of first-relapse B-precursor acute lymphoblastic leukaemia (ALL) paediatric patients who have been treated with blinatumomab or chemotherapy prior to undergoing haematopoietic stem cell transplant] as per the request for supplementary information (RSI) adopted in October 2019

17.1.3. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/PSA/S/0047

Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment to a previously agreed protocol (PSP/S/0065) in July 2018: a registry of patients with high-risk neuroblastoma being treated with Qarziba (dinutuximab beta) to assess: 1) pain severity and use of analgesics during treatment; 2) incidence of neurotoxicity, visual impairment, capillary leak syndrome, cardiovascular events and hypersensitivity reactions; 3) long term safety

17.1.4. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/PSA/S/0041.2

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0041.1 [substantial amendment to a protocol previously endorsed in June 2018 (PSP/S/0059) for a non-interventional PASS in male patients with haemophilia B receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate safety of N9-GP during long-term routine use] as per the request for supplementary information (RSI) adopted in November 2019

17.1.5. Sotagliflozin - ZYNQUISTA (CAP) - EMEA/H/C/PSP/S/0084.1

Applicant: Sanofi-aventis groupe

⁵⁹ In accordance with Article 107n of Directive 2001/83/EC

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0084 [protocol for an observational retrospective cohort study using existing data sources on the incidence of diabetic ketoacidosis (DKA) in adult patients with type 1 diabetes mellitus (T1DM) treated with sotagliflozin as an adjunct to insulin versus insulin alone, as required in the outcome of the initial opinion/marketing authorisation (EMA/H/C/004889) finalised in February 2019] as per the request for supplementary information (RSI) adopted in September 2019

17.1.6. Valproate (NAP) - EMA/H/N/PSP/J/0072.3

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0072.2 [protocol for a joint retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in December 2019

17.1.7. Valproate (NAP) - EMA/H/N/PSP/J/0073.3

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0073.2 [protocol for a joint survey among healthcare professionals (HCP) to assess the knowledge of HCP and behaviour with regard to the pregnancy prevention programme (PPP), the receipt/use of direct healthcare professional communication (DHPC) and educational materials as well as for a survey among patients to assess the knowledge of patients with regards to PPP and receipt/use of educational materials, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in December 2019

17.1.8. Valproate (NAP) - EMA/H/N/PSP/J/0075.3

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0075.2 [protocol for a joint drug utilisation study (DUS) to assess the effectiveness of the new risk minimisation measures (RMMs) and to further characterise the prescribing patterns for valproate as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in December 2019

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁰

17.2.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/MEA 003.2

Applicant: Kite Pharma EU B.V., ATMP⁶¹

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 003.1 [protocol for study KT-EU-471-0116: a prescriber survey to assess the prescribers' understanding of serious neurologic adverse reactions and cytokine release syndrome (CRS)] as per the request for supplementary information (RSI) adopted in October 2019

17.2.2. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 053.2

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Amendment to a previously agreed protocol for study M07-001: a prospective registry for an observational, multicentre, multinational study of patients with paroxysmal nocturnal haemoglobinuria (PNH)

17.2.3. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/MEA 005.3

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Amendment to a previously agreed protocol (version 2.0) for study EVM-19596-00-001 (listed as a category 3 study in the RMP): a drug utilisation study (DUS) using relevant healthcare databases at two different time periods in order to define the compliance to contraindications over time and the number of subjects diagnosed with pancreatitis after eluxadoline treatment

17.2.4. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/MEA 003.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to MEA 003 [protocol for study I5Q-MC-B002 (listed as a category 3 study in the RMP): galcanezumab European drug utilisation and safety outcomes study to describe, in real-world clinical practice the utilisation of galcanezumab in Europe, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including serious cardio-vascular events, and malignancies [final clinical study report (CSR) expected in Q4 2026]] as per the request for supplementary information (RSI) adopted in September 2019

⁶⁰ 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

⁶¹ Advanced therapy medicinal product

17.2.5. L-lysine hydrochloride, L-arginine hydrochloride - Lysakare (CAP) - EMEA/H/C/004541/MEA 001

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylowski

Scope: Protocol for study CAAA001A12401 (listed as a category 3 study in the RMP): an international PASS to assess the effect of Lysakare (L-lysine hydrochloride/L-arginine hydrochloride) administration on potassium blood levels concentration up to 24hr compared to baseline (from MAA initial/opinion)

17.2.6. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/MEA 010.1

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 010 [protocol for study 151(A)PO19107 (lurasidone PASS programme): an evaluation of the safety profile of lurasidone: a PASS using United States administrative claims databases] as adopted in October 2019

17.2.7. Mexiletine - NAMUSCLA (CAP) - EMEA/H/C/004584/MEA 001.2

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: MAH's response to MEA 001.1 [protocol for a registry study to determine the long-term safety and tolerability of Namuscla (mexiletine) for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorder] as per the request for supplementary information (RSI) adopted in October 2019

17.2.8. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.2

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylowski

Scope: MAH's response to MEA 003.1 [MAH's response to MEA 003 [protocol for study M-14745-40: European psoriasis registry to collect long-term safety data for tildrakizumab and to further characterise the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical practice (from initial MAA/opinion)]] as per the request for supplementary information (RSI) adopted in September 2019

17.3. Results of PASS imposed in the marketing authorisation(s)⁶²

None

⁶² In accordance with Article 107p-q of Directive 2001/83/EC

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁶³

17.4.1. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0086

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study UP0038 (listed as a category 3 study in the RMP): a non-interventional PASS with the aim to evaluate the effectiveness of Cimzia (certolizumab pegol) risk minimisation educational materials for healthcare professionals and patients

17.4.2. Colistimethate sodium - COLOBREATHE (CAP) - EMEA/H/C/001225/II/0044/G

Applicant: Teva B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of the submission of the final report for study CLB-MD-05 (listed as a category 3 study in the RMP): an observational safety study of Colobreathe (colistimethate sodium dry powder for inhalation) compared with other inhaled anti-pseudomonal antibiotics in cystic fibrosis patients using cystic fibrosis registries. The RMP (version 9.0) is updated accordingly, together with the results from study CLB-MD-08: (listed as a category 3 study in the RMP): a non-interventional PASS cross-sectional survey study to evaluate the effectiveness of Colobreathe (colistimethate sodium) risk minimisation educational programme among healthcare professionals and patients, as per the outcome of variation II/39 adopted in February 2019

17.4.3. Degarelix - FIRMAGON (CAP) - EMEA/H/C/000986/II/0035

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Revised PASS report for study FE 200486 CS39: a prospective observational safety study in patients with advanced prostate cancer treated with Firmagon (degarelix) or a gonadotropin-releasing hormone (GnRH) agonist

17.4.4. Fampridine - FAMPYRA (CAP) - EMEA/H/C/002097/II/0046

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC in order to update the existing contraindication for renal impaired patients, update the frequency of seizure to 'uncommon' and reflect safety information based on the final results from study 218MS401 (LIBERATE) (listed as category 3 study in the RMP): a phase 4 prospective, non-interventional, multicentre, observational study in multiple sclerosis (MS) patients who began Fampyra (fampridine) treatment in the post-marketing setting. The package leaflet is

⁶³ 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

updated accordingly. The RMP (version 13.1) is also updated accordingly and in line with revision 2.0 of the guidance on the format of RMP in the EU (template)

17.4.5. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/II/0043

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study 'linaclotide utilisation study in selected European populations' (listed as a category 3 study in the RMP): a drug utilisation study (DUS) addressing the potential for off-label use and abuse/excessive use, the extent of use in pregnancy and lactation, and male patients as well as assessing the extent of off-label use and the extent of use in males and in pregnant females

17.4.6. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/II/0025

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study NN8022-4241 (listed as a category 3 study in the RMP): a retrospective drug utilisation study (DUS) to investigate patterns of use of Saxenda and Victoza (liraglutide) in routine clinical practice in order to assess the use of Saxenda (liraglutide) according to the approved indication (adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial body mass index (BMI) of ≥ 30 kg/m² (obese), or ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity) and the use of Victoza (liraglutide) for the treatment of weight management while the approved indication is for the treatment of adults with type 2 diabetes mellitus (T2DM). The RMP (version 31) is updated accordingly

17.4.7. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/II/0033

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final study report for study 178-CL-114: an evaluation of cardiovascular events in users of mirabegron and other treatments for overactive bladder

17.4.8. Rasagiline - AZILECT (CAP) - EMEA/H/C/000574/WS1749/0084; RASAGILINE RATIOPHARM (CAP) - EMEA/H/C/003957/WS1749/0016

Applicant: Teva B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study TV1030-CNS-50024 (listed as a category 3 study in the RMP): a non-interventional retrospective cohort study which was conducted using the United States Medicare research database to assess the potential risk of melanoma associated with the use of rasagiline mesylate in patients with Parkinson's disease

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

17.5.1. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/MEA 166.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Third biennial interim analysis report for study B1801023: an open-label extension study to assess the long-term safety and clinical benefit of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1-3338-WW (B1801014)

17.5.2. Etanercept - LIFMIOR (CAP) - EMEA/H/C/004167/MEA 002.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Third biennial interim analysis report for study B1801023: an open-label extension study to assess the long-term safety and clinical benefit of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1-3338-WW (B1801014)

17.5.3. Filgrastim - NIVESTIM (CAP) - EMEA/H/C/001142/MEA 015.4

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Third annual report for study ZOB-NIV-1513 (C1121008): a multinational, multicentre, prospective, non-interventional PASS in healthy donors (HDs) exposed to Nivestim (biosimilar filgrastim) for haematopoietic stem cell (HSC) mobilisation (NEST) [final clinical study report (CSR) due date: March 2023]

17.5.4. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 027.7

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth annual progress report of the ENEIDA registry (study MK-8259-042): a long-term, non-interventional observational study of patients with inflammatory bowel disease (IBD) in Spain to evaluate whether the use of golimumab is associated with a risk of colectomy for intractable disease, advanced neoplasia (colorectal cancer or high grade dysplasia), and hepatosplenic T-cell lymphoma (HSTCL) in patients with ulcerative colitis (UC) as compared with alternative therapies for similar severity of disease [final clinical study report (CSR) expected: March 2023]

17.5.5. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/ANX 003.4

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual report for study VX14 809 108: an observational study to evaluate the utilisation patterns and long-term effects of lumacaftor/ivacaftor therapy in patients with cystic fibrosis (CF) [final report expected: December 2021]

17.5.6. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 002.5

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Annual progress report for PASS D3820R00006: a post-marketing observational drug utilisation study (DUS) of Moventig (naloxegol) conducted in selected European populations in order to describe demographic, clinical, and treatment characteristics in the baseline of patients treated with naloxegol as well as to describe treatment pattern characteristics of naloxegol utilisation at initiation and follow-up

17.5.7. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.8

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Annual progress report for study D3820R00009: an observational PASS of Moventig (naloxegol) among patients aged 18 years and older treated with opioids chronically

17.5.8. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁶⁴) - EMEA/H/W/002300/MEA 002.2

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Interim result for study EPI-MAL-002: a prospective study to estimate the incidence of diseases specified as adverse events of special interest (AESI) leading to hospitalisation or death, and of meningitis in infants and young children in sub-Saharan Africa prior to implementation of Mosquirix (RTS, S/AS01E) [final clinical study report due in December 2022]

17.5.9. Radium-223 - XOFIGO (CAP) - EMEA/H/C/002653/MEA 004.2

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Second interim result for study 16913 (REASSURE): an observational PASS to assess the long term safety profile and risks of developing second primary malignancies and

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

their potential relationship to radium-223 in the routine clinical practice setting

17.5.10. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 005.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Annual progress reports for: 1) pregnancy registry OBS12751 (international): an international pregnancy exposure registry of women with multiple sclerosis (MS) exposed to Aubagio (teriflunomide) and; 2) pregnancy registry OBS13499 (US/CA): teriflunomide pregnancy outcome exposure registry: a 'teratology information specialists (OTIS)' autoimmune diseases in pregnancy project

17.5.11. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/MEA 006.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Annual progress report 2019 for study OBS12753: a prospective cohort study of long-term safety of Aubagio (teriflunomide) in multiple sclerosis (MS) patients in Europe

17.6. Others

17.6.1. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.6

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's request to close study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation, in light of available data

17.6.2. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.6

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's request to close study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation, in light of available data

17.6.3. Somatropin - OMNITROPE (CAP) - EMEA/H/C/000607/MEA 012.4

Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's request to close post-marketing surveillance study EP00-501 [PATRO Children]: a multicentre, non-interventional study to monitor the long-term safety and

efficacy of Omnitrope (somatropin) in paediatric patients for the approved indications within routine clinical practice

17.6.4. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/LEG 033

Applicant: Correvio

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a detailed analysis of a case of hypotension (KW-C14001-19-00239) including the CIOMS⁶⁵ form, causality assessment report

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0033 (without RMP)

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: Annual reassessment of the marketing authorisation

⁶⁵ Council for International Organisations of Medical Sciences

18.1.2. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0045 (without RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.3. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0078 (without RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Annual reassessment of the marketing authorisation

18.1.4. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0019 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.5. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0028 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.6. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0035 (without RMP)

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Autologous CD34⁺ cell enriched population that contains hematopoietic stem cells transduced with lentiglobin BB305 lentiviral vector encoding the beta-A-T87Q-globin gene - ZYNTEGLO (CAP) - EMEA/H/C/003691/R/0005 (without RMP)

Applicant: bluebird bio (Netherlands) B.V, ATMP⁶⁶

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.2.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0041 (without RMP)

Applicant: Otsuka Novel Products GmbH

⁶⁶ Advanced therapy medicinal product

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.2.3. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0022 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

18.2.4. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0018 (without RMP)

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.2.5. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/R/0016 (without RMP)

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/R/0044 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.2. Bortezomib - BORTEZOMIB ACCORD (CAP) - EMEA/H/C/003984/R/0022 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.3. Ceftolozane, tazobactam - ZERBAXA (CAP) - EMEA/H/C/003772/R/0026 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.4. Human alpha1-proteinase inhibitor - RESPREEZA (CAP) - EMEA/H/C/002739/R/0036 (without RMP)

Applicant: CSL Behring GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.5. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/R/0031 (with RMP)

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: 5-year renewal of the marketing authorisation

18.3.6. Lutetium (¹⁷⁷Lu) chloride - LUMARK (CAP) - EMEA/H/C/002749/R/0014 (with RMP)

Applicant: I.D.B. Holland B.V.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

18.3.7. Panobinostat - FARYDAK (CAP) - EMEA/H/C/003725/R/0020 (with RMP)

Applicant: Secura Bio Limited

PRAC Rapporteur: Sofia Trantza

Scope: 5-year renewal of the marketing authorisation

18.3.8. Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/R/0025 (without RMP)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

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 10-13 February 2020 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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No participation in final deliberations and voting on:	4.1.1. Macrogol 3350 (NAP); macrogol 4000 (NAP)
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	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:	17.2.3. Eluxadoline - TRUBERZI (CAP) 17.4.2. Colistimethate sodium - COLOBREATHE (CAP)
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislowski	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No restrictions applicable to this meeting	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
John Joseph Borg	Member - via telephone	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	3.3.1. Cyproterone acetate (NAP) 16.3.2. Dienogest, estradiol (NAP) 17.5.9. Radium-223 - XOFIGO (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member - via telephone	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	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
Birgitta Grundmark	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:	18.2.4. Obeticholic acid - OCALIVA (CAP)
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No participation in final deliberations and voting on:	6.3.4. Human plasma proteins (NAP)
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Flora Musuamba	Expert - in person*	Belgium	No interests declared	Full involvement
Martine Sabbe	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Benjamin Burrus	Expert - via telephone*	France	No interests declared	Full involvement
Pauline Dayani	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Camille De Kervasdoue	Expert - in person*	France	No interests declared	Full involvement
Emmanuel Doyen	Expert - via telephone*	France	No interests declared	Full involvement
Aude Le-Monnier	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Emilie Patras De Campaigno	Expert - via telephone*	France	No interests declared	Full involvement
Muriel Uzzan	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Faustine Vidil	Expert - in person*	France	No interests declared	Full involvement
Dennis Lex	Expert - in person*	Germany	No restrictions applicable to this meeting	Full involvement
Jens Reinhardt	Expert - in person*	Germany	No interests declared	Full involvement
Kate Browne	Expert - via telephone*	Ireland	No interests declared	Full involvement
Eleanor Carey	Expert - via telephone*	Ireland	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Donal O'Connor	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Sara Khosrovani	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Hanja de Kooter	Expert - in person*	The Netherlands	No restrictions applicable to this meeting	Full involvement
Bianca Mulder	Expert - in person*	The Netherlands	No restrictions applicable to this meeting	Full involvement
Johannes Ovelgonne	Expert - in person*	The Netherlands	No interests declared	Full involvement
Lies van Vlijmen	Expert - via telephone*	The Netherlands	No interests declared	Full involvement
Rune Kjekken	Expert - in person*	Norway	No restrictions applicable to this meeting	Full involvement
Bruno Miguel Nogueira Sepodes	Expert - in person*	Portugal	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Carin Bergquist	Expert - in person*	Sweden	No interests declared	Full involvement
Jolanta Gulbinovic	Expert - via telephone*	Sweden	No interests declared	Full involvement
Anders Sundström	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

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/>