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Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 30 September – 03 October 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 30 September – 03 October 2019 meeting by welcoming all participants.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.1](#)). All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Agenda of the meeting on 30 September – 03 October 2019

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

1.3. Minutes of the previous meeting on 02 - 05 September 2019

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 02 - 05 September 2019 were published on the EMA website on 4 February 2020 ([EMA/PRAC/60629/2020](#)).

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

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/A-20/1483

Applicant: Sanofi Belgium

PRAC Rapporteur: Brigitte Keller-Stanislawski; PRAC Co-rapporteur: Ulla Wändel Liminga

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for the review of Lemtrada (alemtuzumab) following new emerging and serious safety concerns referring to fatal cases, cardiovascular adverse events in close temporal association with infusion of the medicinal product as well as immune-mediated diseases such as auto-immune hepatitis, hepatic injury, auto-immune-mediated central nervous system disease and Guillain-Barre syndrome. The review assesses the impact of these safety concerns in the context of the benefit-risk balance of the medicinal product in the authorised indication(s). In April 2019 the PRAC recommended, until a thorough review is finalised, provisional measures to amend the product information. For further background, see [PRAC minutes April 2019](#) and [PRAC minutes July 2019](#).

Summary of recommendation(s)/conclusions

- The PRAC discussed the joint assessment report by the Rapporteurs.
- The PRAC received feedback from the Scientific Advisory Group on Neurology ([SAG-N](#)) meeting held on 5 September 2019.
- The PRAC adopted a second list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable ([EMA/PRAC/218954/2019 rev.2](#)).

3.2.2. Fluorouracil and related substances: capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP); CAPECITABINE TEVA (CAP); ECANSYA (CAP); XELODA (CAP); NAP flucytosine (NAP); 5-fluorouracil (5-FU) (NAP); tegafur (NAP); tegafur, gimeracil, oteracil – TEYSUNO (CAP) - EMEA/H/A-31/1481

Applicants: Accord Healthcare Limited (Capecitabine Accord), Krka, d.d., Novo mesto (Ecansya), Medac Gesellschaft für klinische Spezialpräparate mbH (Capecitabine medac), Nordic Group B.V. (Teysono), Roche Registration GmbH (Xeloda), Teva B.V. (Capecitabine Teva), various

PRAC Rapporteur: Jean-Michel Dogné; PRAC Co-rapporteur: Martin Huber

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 is ongoing for fluorouracil-, capecitabine- and tegafur-containing medicines for systemic use in order to review the genotyping and phenotyping methods as well as their availability across the EU for the detection of dihydropyrimidine dehydrogenase (DPD) deficiency responsible for severe and fatal toxicity. The ongoing procedure also reviews the value of the existing screening methods in identifying patients at increased risk of severe side effects as well as the need for updating existing recommendations for pre-treatment evaluation of DPD activity in patients to receive treatment with 5-fluorouracil (5-FU) or related substances. For further background, see [PRAC minutes March 2019](#) and [PRAC minutes July 2019](#).

Summary of recommendation(s)/conclusions

- The PRAC adopted the list of experts, including the addition of a patient representative, for the ad-hoc inter-Committee Scientific Advisory Group on Oncology ([SAG-O](#)) organised on 11 October 2019.
- The PRAC noted the responses from the Pharmacogenomics Working Party ([PgWP](#)) that will be further considered in the course of the review.

3.2.3. Tofacitinib - XELJANZ (CAP) - EMEA/H/A-20/1485

Applicant(s): Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan; PRAC Co-rapporteur: Amelia Cupelli

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for the review of Xeljanz (tofacitinib) following an increased risk of pulmonary embolism (PE) and overall mortality arising from study A3921133¹ in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily (BID). The review assesses the impact of the risk of thromboembolic events, in particular PE and deep venous thrombosis (DVT) in the context of the benefit-risk balance of the medicinal product in the authorised indications and doses. In May 2019, the PRAC recommended, until a thorough review is finalised, provisional measures to amend the product information. For further background, see [PRAC minutes May 2019](#) and [PRAC minutes September 2019](#).

Summary of recommendation(s)/conclusions

- The PRAC adopted the list of experts for the ad-hoc expert group meeting organised on 10 October 2019.

¹ A phase 3B/4 randomised safety endpoint study of 2 doses of tofacitinib (tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID) in comparison to a tumour necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis

3.3. Procedures for finalisation

3.3.1. Estradiol² (NAP) - EMEA/H/A-31/1482

Applicant(s): various

PRAC Rapporteur: Eva Jirsova; PRAC Co-rapporteur: Menno van der Elst

Scope: Review of the benefit-risk balance following notification by European Commission 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 estradiol-containing medicines (0.01% w/w) for topical use is to be concluded. This referral procedure was initiated following the partial annulment of the scientific conclusions reached in 2014 in a previous EU review based on procedural grounds. This previous review was initiated further to data showing that plasma levels of estradiol-containing medicines (0.01% w/w) for topical use are similar to those associated with the use of estradiol in systemic hormone replacement therapy (HRT), and these may lead to undesirable effects known for systemic HRT including venous thromboembolism, stroke, breast and endometrial cancer. The current procedure was initiated in April 2019 to review the data assessed in the previous referral procedure for medicinal products containing estradiol for topical use as well as any data that would have become available since 2014 in order to ensure that patients are not put at risks. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes April 2019](#) and [PRAC minutes July 2019](#).

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs.

The PRAC reviewed the totality of data submitted with regard to the risk of adverse drug reactions due to systemic absorption of estradiol. This includes the responses submitted by the MAHs, public literature and spontaneous reporting. In addition, the PRAC considered the outcome of the *ad-hoc* expert group composed of gynaecologists and patient representatives held on 17 September 2019.

The PRAC confirmed that the efficacy of estradiol-containing medicinal products (0.01% w/w) for topical use is favourable in the treatment of the symptoms of vaginal atrophy in postmenopausal women indication.

Nevertheless the PRAC considered, in view of the currently available data, that there is a systemic exposure above the normal post-menopausal range after topical use of estradiol-containing medicinal products (0.01% w/w) that warrants risk minimisation measures (RMMs). The PRAC requested that the contraindications and warnings are updated taking into consideration the current clinical knowledge on safety of systemic HRT especially regarding risks of thromboembolism events, breast and endometrial cancer. The product information should follow the elements for estrogen products for vaginal application of which the systemic exposure to the estrogen is higher than the normal post-menopausal range.

² 0.01%, topical use only

The Committee noted that data on long-term treatment as well as repeated use of estradiol-containing medicinal products (0.01% w/w) for topical use is not available. Therefore, and given the systemic exposure above normal post-menopausal range, these products should only be used for a single treatment period up to 4 weeks maximum.

In order to minimize the risk of prolonged use and to ensure patients' adherence to the recommended duration of use, the PRAC recommended that the maximum package size of the medicinal product(s) authorised should not exceed 25 g.

Finally, the PRAC concluded that the product information should be updated to provide further awareness on the strength of these medicinal products and on the maximum treatment period.

The Committee concluded that the benefit-risk balance of estradiol-containing medicinal products (0.01% w/w) for topical use is favourable subject to changes to the product information and other RMMS.

Summary of recommendation(s)/conclusions

- The PRAC adopted a recommendation to vary³ the terms of the marketing authorisation(s) for estradiol-containing products (0.01% w/w) for topical use to be considered by CMDh for a position – see EMA Press Release ([EMA/531250/2019](https://www.ema.europa.eu/en/press-room/2019/10/ema-press-release-2019-10-04)) entitled 'Four-week limit for use of high-strength estradiol creams' published on 4 October 2019.
- The PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

3.4. Re-examination procedures⁴

None

3.5. Others

None

4. Signals assessment and prioritisation⁵

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

4.2.1. Hormone replacement therapy (HRT): conjugated estrogens (NAP); conjugated estrogens, bazedoxifene - DUAVIVE

³ Update of SmPC sections 4.2 and 4.4 and in line with the core SmPC for hormone replacement therapy products. The labelling and package leaflet are updated accordingly

⁴ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

⁵ 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

(CAP); diethylstilbestrol (NAP); estradiol (NAP); estradiol, norethisterone (NAP); estriol (NAP); estrone (NAP); ethinylestradiol (NAP); promestriene (NAP); tibolone (NAP)

Applicant(s): Pfizer Europe MA EEIG (Duavive), various

PRAC Rapporteur: Menno van der Elst

Scope: New information on the known risk of breast cancer

EPITT 19482 – New signal

Lead Member State(s): DE, FI, FR, IT, NL, RO, SE

Background

Hormone replacement therapy (HRT) replaces hormones that a woman's body no longer produces because of the menopause and involves either taking both hormones, namely an estrogen and a progestogen (combined HRT) or estrogen alone (estrogen-only HRT).

Conjugated estrogens, diethylstilbestrol, estradiol, estriol, estrogen, estrone, ethinylestradiol, promestriene and tibolone are estrogens or agonists of estrogen receptors. Bazedoxifene, raloxifene, ospemifene, lasofoxifene, ormeloxifene are selective estrogen receptor modulators (SERMs). These active substances are among others contained in medicinal products indicated as HRT in post-menopausal women.

Following the publication of a meta-analysis of 58 published and unpublished epidemiological studies since 1992 by The Lancet and by the Collaborative Group on Hormonal Factors in breast cancer⁶, a signal of new information on the known risk of breast cancer was identified by The Netherlands. The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the new information on the known risk of breast cancer associated with the use of HRT medicinal products in post-menopausal women, the PRAC agreed to further assess the new information from this study, focusing on hormone replacement therapy medicinal products containing estrogens or estrogens and progestagens in combination, which were the focus of the meta-analysis.

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

Summary of recommendation(s)

- The Rapporteur should further assess the new information from the study.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Indapamide (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

⁶ Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet 2019; 394: 1159–68

Scope: Signal of choroidal effusion

EPITT 19468 – New signal

Lead Member State(s): DE

Background

Indapamide is a thiazide-like oral antihypertensive/diuretic. It is indicated for the treatment of essential hypertension.

The exposure for indapamide-containing products is estimated to have been more than 90.8 million patient-years worldwide, in the period from first authorisation in 2002 to 2015.

During routine signal detection activities, a signal of choroidal effusion was identified by Poland, based on the publication in the BMJ by *Phylactou et al*⁷ and 1 case retrieved from EudraVigilance. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the evidence from the case reports, including the positive de-challenge in the published case, the PRAC agreed that further assessment of the available evidence concerning all thiazide and thiazide-like diuretic-containing medicines is necessary, including a further review of data from EudraVigilance and the literature.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The Rapporteur should provide an assessment of case reports of choroidal effusion reported with thiazide and thiazide-like diuretic⁸-containing medicines in EudraVigilance and in the literature.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

- 4.3.1. Direct-acting antivirals (DAAV):
dasabuvir – EXVIERA (CAP) - EMEA/H/C/003837/SDA/020; elbasvir, grazoprevir – ZEPATIER (CAP) - EMEA/H/C/004126/SDA/012; glecaprevir, pibrentasvir – MAVIRET (CAP) - EMEA/H/C/004430/SDA/010; ledipasvir, sofosbuvir – HARVONI (CAP) - EMEA/H/C/003850/SDA/021; ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP) - EMEA/H/C/003839/SDA/022; sofosbuvir – SOVALDI (CAP) - EMEA/H/C/002798/SDA/027; sofosbuvir, velpatasvir – EPCLUSA (CAP) - EMEA/H/C/004210/SDA/012; sofosbuvir, velpatasvir, voxilaprevir – VOSEVI (CAP) - EMEA/H/C/004350/SDA/007
-

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Exviera, Maviret, Viekirax); Gilead Sciences Ireland UC (Eplusa, Harvoni, Sovaldi, Vosevi); Merck Sharp & Dohme B.V. (Zepatier)

⁷ Phylactou M, Matarazzo F and Jones E. Indapamide-induced bilateral choroidal effusion in pseudophakic patient. BMJ Case Rep. 2018 Jul 26;2018. pii: bcr-2018-225920

⁸ Bendroflumethiazide, chlorthalidone, cicletanine, clopamide, cyclopentiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, metipamide, metolazone, xipamide

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of autoimmune hepatitis

EPITT 19395 – Follow-up to May 2019

Background

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

The MAHs Gilead Sciences Ireland UC, Bristol-Myers Squibb Pharma EEIG, Merck Sharp & Dohme B.V. and AbbVie Deutschland GmbH Co. KG replied to the request for information on the signal of autoimmune hepatitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature and the responses from the MAHs, the PRAC agreed that a causal relationship between direct-acting antivirals (DAAV) against hepatitis C and the development of autoimmune hepatitis cannot be established at this stage. The PRAC agreed that no further regulatory actions are warranted at present.

Summary of recommendation(s)

- The MAHs for Exviera (dasabuvir), Zepatier (elbasvir/grazoprevir), Maviret (glecaprevir/pibrentasvir), Harvoni (ledipasvir/sofosbuvir), Viekirax (ombitasvir/paritaprevir/ritonavir), Sovaldi (sofosbuvir), Eplclusa (sofosbuvir/velpatasvir) and Vosevi (sofosbuvir/velpatasvir/voxilaprevir) should continue to monitor autoimmune hepatitis and other autoimmune disorders as part of routine safety surveillance.

4.3.2. Durvalumab – IMFINZI (CAP) – EMEA/H/C/004771/SDA/003

Applicant(s): AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of myasthenia gravis

EPITT 19451 – Follow-up to September 2019

Background

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

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

Discussion

Having considered the available evidence from EudraVigilance and the literature, as well as the comments from the MAH, the PRAC considered that there is sufficient evidence to establish a causal association between durvalumab and myasthenia gravis. The product information of Imfinzi (durvalumab) should be updated accordingly.

Summary of recommendation(s)

- The MAH for Imfinzi (durvalumab) should submit to EMA, within 60 days, a variation to update the product information⁹.
- In the next PSUR, the MAH should include a comprehensive cumulative review and analysis of other neurological immune-related adverse drug reactions (ADRs) from all sources (i.e. spontaneous reports, literature and clinical trials).

For the full PRAC recommendation, see [EMA/PRAC/532014/2019](#) published on 28 October 2019 on the EMA website.

4.3.3. Lithium (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of drug induced lichenoid reaction

EPITT 19389 – Follow-up to May 2019

Background

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

The MAH Teofarma replied to the request for information on the signal of drug-induced lichenoid reaction and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence including case reports with positive de-challenge and positive re-challenge, the PRAC agreed that there is sufficient evidence to establish a causal association between lithium and the occurrence of lichenoid skin reaction. The PRAC agreed that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAHs for lithium-containing medicinal products should submit to relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update the product information¹⁰.

For the full PRAC recommendation, see [EMA/PRAC/532014/2019](#) published on 28 October 2019 on the EMA website.

4.3.4. Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/SDA/007

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of nephrotic syndrome

EPITT 19410 – Follow-up to May 2019

Background

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

⁹ Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is to be updated accordingly

¹⁰ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

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

Discussion

Having considered the available evidence from EudraVigilance case reports and further clarifications regarding the case reports from the MAH, the PRAC agreed that although a causal association between Kanuma (sebelipase alfa) and nephrotic syndrome is possible in one case, there is insufficient evidence at present to warrant further regulatory actions.

Summary of recommendation(s)

- The MAH for Kanuma (sebelipase alfa) should continue to monitor nephrotic syndrome as part of routine safety surveillance and report any new significant information 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. Adalimumab - EMEA/H/C/004879

Scope: Treatment of juvenile idiopathic arthritis, paediatric plaque psoriasis, Crohn's disease, paediatric Crohn's disease, hidradenitis suppurativa (HS), adolescent HS, paediatric uveitis, rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, ulcerative colitis, uveitis, paediatric uveitis

5.1.2. Brolocizumab - EMEA/H/C/004913

Scope: Treatment of neovascular (wet) age-related macular degeneration (AMD)

5.1.3. Cholera vaccine, oral, live - EMEA/H/C/003876

Scope: Active immunisation against disease caused by *Vibrio cholerae* serogroup O1 in adults and children aged 6 years and older

5.1.4. Entrectinib - EMEA/H/C/004936

Scope: Treatment of adult and paediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive locally advanced or metastatic solid tumours and treatment of

patients with ROS1¹¹-positive, advanced non-small cell lung cancer (NSCLC)

5.1.5. Givosiran - EMEA/H/C/004775, Orphan

Applicant: Alnylam Netherlands B.V.

Scope (accelerated assessment): Treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older

5.1.6. Imipenem, cilastatin, relebactam - EMEA/H/C/004808

Scope: Treatment of bacterial infections due to gram-negative microorganisms

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

See also Annex I 15.2.

5.2.1. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/II/0114

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 25.0) with data on extended interval dosing, including an update to key elements for inclusion of the physician information and management guidelines. In order to align with the changes in the RMP, the MAH submitted changes to sections 4.4 and 5.1 of the SmPC and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

Background

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α 4-subunit of human integrins. It is indicated, as Tysabri, as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or for patients with rapidly evolving severe RMMS 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.

The PRAC is evaluating a type II variation procedure for Tysabri, a centrally authorised medicine containing natalizumab, to update the RMP with data on extended interval dosing (EID), including an update to key elements for inclusion of the physician information and management guidelines. In June 2019, the PRAC concurred that further analysis was needed in order to conclude on the safety of EID versus standard interval dosing (SID) in the conclusion of LEG 066.3 procedure. Further analyses were requested as part of the current variation. 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 June 2019](#) and [PRAC minutes July 2019](#).

¹¹ Proto-oncogene tyrosine-protein kinase

Summary of advice

- The RMP version 25.0 for Tysabri (natalizumab) in the context of the variation under evaluation by the PRAC and CHMP is considered acceptable as detailed in the adopted assessment report.
- The PRAC adopted an outcome by majority¹² to update the RMP and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' as well as the 'special warnings and precautions for use' and 'pharmacodynamic properties' sections of the product information¹³ in order to include meaningful information about the potential use of EID, including the additional risk minimisation activities, namely educational materials for physicians.

5.2.2. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/II/0040

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated RMP (version 13) in order to remove the healthcare professional survey from the list of additional pharmacovigilance activities and to remove several safety concerns from the list of important identified and potential risks and missing information in line with revision 2 of GVP module V on 'Risk management systems' and in line with the conclusions of variation II/28 finalised in February 2019

Background

Vandetanib is an inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2), epidermal growth factor receptor (EGFR) and RET¹⁴ tyrosine kinases, as well as a sub-micromolar inhibitor of vascular endothelial receptor-3 tyrosine kinase. It is indicated, as Caprelsa, in adults, children and adolescents aged 5 years and older for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

The PRAC is evaluating a type II variation procedure for Caprelsa, a centrally authorised medicine containing vandetanib, to update the RMP in order to remove from the list of additional pharmacovigilance activities the PASS (listed as a category 3 study in the RMP) set-up to assess the usefulness of existing educational material and physician's knowledge and understanding of the risks of vandetanib and to update as well the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation.

Summary of advice

- The RMP (version 13.0) for Caprelsa (vandetanib) in the context of the variation under evaluation is considered acceptable.
- The PRAC supported the removal of the PASS in question from the list of additional pharmacovigilance activities in light of the results that showed the usefulness of the

¹² Thirty one members voted in favour of the outcome whilst two members had divergent views (Rhea Fitzgerald, Ulla Wändel Liminga). The Norwegian PRAC alternate did agree with the outcome

¹³ Update of SmPC sections 4.4 and 5.1

¹⁴ Rearranged during transfection

educational material. The educational material should continue to be distributed to healthcare professionals (HCPs) who are expected to prescribe and deliver Caprelsa (vandetanib). In addition, the PRAC agreed with the update of the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'.

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

See also Annex I 15.3.

5.3.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/II/0063

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4 and 4.9 of the SmPC in order to reflect the availability of a reversal agent for apixaban following the recent approval of andexanet alfa in the EU. The package leaflet and labelling are updated accordingly. The RMP (version 20) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template). As a result, the list of safety concerns is updated and a number of safety concerns listed as missing information have been reclassified/removed from the RMP. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to update the information in the SmPC and package leaflet in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

Background

Apixaban is a direct and selective active site inhibitor of factor Xa. It is indicated, as Eliquis, for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery as well as for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. It is also indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age \geq 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA¹⁵ class \geq II).

The CHMP is evaluating a type II variation for Eliquis, a centrally authorised product containing apixaban, proposing to update the product information in order to reflect the availability of a reversal agent for apixaban following the recent approval of andexanet alfa in the EU. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 20.1 for Eliquis (apixaban) in the context of the variation procedure under evaluation by the CHMP is considered acceptable.
- The PRAC supported the update of the patient alert card with 'an agent to reverse the anti-factor Xa activity of apixaban is available'.

¹⁵ New York Heart Association

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension of indication to extend the approved therapeutic indication of Rezolsta (darunavir/cobicistat) to include a new population, namely the adolescent population aged 12 years old and older with a body weight at least 40 kg. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 6.0) are updated accordingly. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to update section 4.2 of the SmPC in line with recommendations for other human immunodeficiency virus (HIV) products with regards to administration Rezolsta (darunavir/cobicistat) in case of vomiting

Background

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the human immunodeficiency virus-1 (HIV-1) protease. Cobicistat is a mechanism-based inhibitor of cytochromes P450 of the CYP3A¹⁶ subfamily. In combination, darunavir/cobicistat is indicated as Rezolsta, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in adults aged 18 years or older.

The CHMP is evaluating a type II variation for Rezolsta, a centrally authorised product containing darunavir/cobicistat, proposing to extend the approved indication to the adolescent population aged 12 years old and older with a body weight at least 40 kg. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Rezolsta (darunavir/cobicistat) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 6.0 is submitted.
- The PRAC agreed with the proposed changes to the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems'. Nevertheless, 'safety in patients with cardiac conduction disorders' should be maintained as missing information as this population was excluded from clinical trials and this is in consideration of the finding about cardiac abnormalities in *ex vivo* rabbit studies.

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.

¹⁶ Cytochrome P450, family 3, subfamily A

6.1.1. Cholic acid¹⁷ - KOLBAM (CAP) - PSUSA/00010182/201903

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: Evaluation of a PSUSA procedure

Background

Cholic acid is one of the two main bile acids in humans. It is indicated, as Kolbam, for the treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis (CTX)) deficiency, 2- (or α -) methylacyl-coenzyme A (CoA) racemase (AMACR) deficiency or cholesterol 7 α -hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Kolbam (cholic acid) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of hepatotoxicity with the use of cholic acid and extending the need for close monitoring and stopping rules to patients with pre-existing hepatic impairment related to the primary disease. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH should provide a full review of the risk of hepatotoxicity of cholic acid treatment for patients with or without pre-existing liver disease, providing data from all sources including literature during pre- and post-marketing. The MAH should also monitor and review cases of haemorrhages, use in pregnancy, cases with a fatal outcome, seizures/epilepsy, malignancies and reports of lack of efficacy.

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

6.1.2. Degarelix - FIRMAGON (CAP) - PSUSA/00000944/201902

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

¹⁷ Indicated in the treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α -) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7 α -hydroxylase (CYP7A1) deficiency

¹⁸ Update of SmPC sections 4.2 and 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Firmagon is a centrally authorised product containing degarelix, a gonadotrophin releasing hormone (GnRH) antagonist. It is indicated, as Firmagon, for the treatment of adult male patients with advanced hormone-dependent prostate cancer.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Firmagon, a centrally authorised medicine containing degarelix 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 Firmagon (degarelix) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include rhabdomyolysis as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.
- In the next PSUR, the MAH should closely monitor cases of dementia/Alzheimer's disease, provide a cumulative review and analysis of interstitial lung disease (ILD)/pulmonary fibrosis/interstitial pneumonitis, bullous conditions, detailed analysis on all relevant cases of acute renal failure and continue monitoring gastrointestinal perforation, ulceration, haemorrhage and obstruction.

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

6.1.3. Fingolimod - GILENYA (CAP) - PSUSA/00001393/201902

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

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

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

¹⁹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to refine the existing warning on progressive multifocal leukoencephalopathy (PML) and the warning and undesirable effect on lymphoma. In addition, autoimmune haemolytic anaemia is added as an undesirable effect with a frequency 'not known' and weight decreased with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁰.
- In the next PSUR, the MAH should provide a further detailed discussion on PML risk factors, provide a review of cryptococcal infection and propose an update of the product information as regards cryptococcal meningitis as warranted. In addition, the MAH should provide a discussion on the risk of preterm birth associated with fingolimod exposure during pregnancy or peri-last menstrual period. Furthermore, the MAH should submit cumulative reviews of cases of pancytopenia, exostosis, cancer, infections, convulsions and unexplained death.

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

6.1.4. Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/201903

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

Background

Galcanezumab is a humanised immunoglobulin G4 (IgG4) monoclonal antibody that binds calcitonin gene-related peptide (CGRP). It is indicated, as Emgality, for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Emgality, a centrally authorised medicine containing galcanezumab 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 Emgality (galcanezumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on serious hypersensitivity reactions including cases of anaphylaxis, angioedema and to add as undesirable effects anaphylaxis and angioedema with a frequency 'rare' and rash with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should provide detailed reviews of cardiovascular and cerebrovascular events and of cases of use in pregnancy.

²⁰ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²¹ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/201903

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor. It is indicated, as Yervoy, for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yervoy, a centrally authorised medicine containing ipilimumab, 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 Yervoy (ipilimumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on transient vision loss as a potential consequence of ipilimumab-related ocular inflammations and to add serous retinal detachment as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied²².
- In the next PSUR, the MAH should provide a review and causality assessment of the cases reporting hemophagocytic lymphohistiocytosis (HLH) with combination therapy with ipilimumab and nivolumab and propose to update the product information as warranted.

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

6.1.6. Mifamurtide - MEPACT (CAP) - PSUSA/00002059/201903

Applicant: Takeda France SAS

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Mifamurtide is a specific ligand of nucleotide-binding oligomerisation domain 2 (NOD2) which serves as a potent activator of monocytes and macrophages. It is indicated, as Mepact, for

²² Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection, in combination with post-operative multi-agent chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mepact, a centrally authorised medicine containing mifamurtide 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 Mepact (mifamurtide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pericardial effusion as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²³.

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

6.1.7. Naldemedine - RIZMOIC (CAP) - PSUSA/00010753/201903

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Naldemedine is an antagonist of opioid binding at the mu-, delta-, and kappa-opioid receptors. It is indicated, as Rizmoic, for the treatment of opioid-induced constipation in adult patients who have previously been treated with a laxative.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rizmoic, a centrally authorised medicine containing naldemedine 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 Rizmoic (naldemedine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on the risk of gastrointestinal perforation and to add gastrointestinal perforation as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁴.
- In the next PSUR, the MAH should provide a comprehensive update on the key safety findings from the ongoing study investigating the risk of major adverse cardiovascular events with naldemedine comparing to other treatments and provide a robust scientific

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

²⁴ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

discussion on the potential risk of 'anti-analgesic effect due to centrally mediated opioid receptor antagonism'.

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

6.1.8. Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/201903

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20²⁵-expressing B cells. It is indicated, as Ocrevus, for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features and for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ocrevus, a centrally authorised medicine containing ocrelizumab 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 Ocrevus (ocrelizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- Nevertheless, the product information should be updated to revise the existing warning on the risk of hepatitis B reactivation. Therefore, the current terms of the marketing authorisation(s) should be varied²⁶.
- In the next PSUR, the MAH should provide an updated cumulative review of cases of sepsis including urosepsis from clinical studies and post-marketing surveillance, including a comparison with background data from placebo-groups and from the literature. In addition, the MAH should provide a comparison of the age groups and cause of deaths in the post-marketing setting of ocrelizumab with published data on multiple sclerosis (MS) mortality. Furthermore, a comprehensive cumulative review of cases of agranulocytosis should be submitted together with a systematic review of late-onset and persistent neutropenia associated with ocrelizumab, proposing adequate risk minimisation measures, 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.

²⁵ B cell differentiation antigen

²⁶ Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.9. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201903

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Oritavancin is a lipoglycopeptide antibiotic. It is indicated, as Orbactiv, for the treatment of acute bacterial skin and skin structure infections in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Orbactiv, a centrally authorised medicine containing oritavancin 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 Orbactiv (oritavancin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on the risk of anaphylactic reactions including anaphylactic shock and to add anaphylactic reaction as an undesirable effect with a frequency 'uncommon' and anaphylactic shock with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁷.

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

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

See also Annex I 16.2.

6.2.1. Vardenafil - LEVITRA (CAP); VIVANZA (CAP); NAP - PSUSA/00003098/201903

Applicant(s): Bayer AG (Levitra, Vivanza), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Vardenafil is an inhibitor of the cGMP specific phosphodiesterase type 5 (PDE5). It is indicated for the treatment of erectile dysfunction in adult men.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Levitra and Vivanza, centrally authorised medicines containing vardenafil, and nationally authorised

²⁷ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

medicines containing vardenafil and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of vardenafil-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on serious cardiovascular events including sudden death, tachycardia, myocardial infarction, ventricular tachyarrhythmia, angina pectoris, and cerebrovascular disorders and to include as undesirable effects sudden death with a frequency 'not known', transient ischaemic attack with a frequency 'rare' and cerebral haemorrhage with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied²⁸.
- In the next PSUR, the MAH should closely monitor cases of hypotension, arrhythmias and specifically arrhythmias related to QT prolongation, non-arteritic ischaemic optic neuropathy (NAION), epilepsy/seizures/convulsions, sudden deafness, as well as central nervous system haemorrhages and cerebrovascular accidents, and interactions with anticoagulants.

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

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

See also Annex I 16.3.

6.3.1. Acetylsalicylic acid (NAP) - PSUSA/00000039/201902

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Background

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

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

Summary of recommendation(s) and conclusions

²⁸ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the benefit-risk balance of acetylsalicylic acid-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on the drug-drug interaction between acetylsalicylic acid and metamizole. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.
- In the next PSUR, all MAHs should provide a cumulative review of all cases of malignant melanoma. The MAH Bayer should further monitor the safety concern of 'increase in cancer-related mortality' and provide an overview of all relevant data.

Additionally, the PRAC agreed that the above updates of the product information are also relevant for fixed-dose combinations of acetylsalicylic acid, including acetylsalicylic acid/clopidogrel. Further consideration should be given at the level of CHMP and 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. Cabergoline (NAP) - PSUSA/00000477/201903

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Cabergoline is an ergot derivative and a dopamine D2-agonist indicated for the inhibition of physiologic lactation soon after parturition and suppression of established lactation, the treatment of hyperprolactinaemic disorders and for the management of Parkinson's disease as monotherapy, or as an adjunct to levodopa.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing cabergoline 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 cabergoline-containing medicinal product(s) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on serious cardio-cerebrovascular, neurologic and psychiatric events. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, all MAHs should monitor and describe new cases from any source of cardiovascular, neurologic and psychiatric adverse events for the indication in inhibition or suppression of physiological lactation and provide a detailed analysis of cases of

²⁹ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³⁰ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

medication errors. The MAH Pfizer should provide a detailed analysis of the use of cabergoline in pregnant women and the occurrence of abortion, premature delivery and congenital abnormalities.

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.

6.3.3. Dorzolamide (NAP) - PSUSA/00003168/201902

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Dorzolamide is an inhibitor of human carbonic anhydrase II in the ciliary processes of the eye indicated for the treatment of elevated intra-ocular pressure in patients with ocular hypertension, open-angle glaucoma, pseudo-exfoliative glaucoma and as adjunctive therapy to beta-blockers, or as monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contraindicated.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing dorzolamide 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 dorzolamide-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include palpitations as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.
- In the next PSUR, the MAH(s) should provide a comprehensive analysis of cases of blindness or transient blindness, ocular/conjunctival hyperemia or cataract, a review of cases of thrombocytopenia as well as a review of cardiorespiratory distress, bradycardia, angina pectoris, heart rate irregular, arrhythmia, tachycardia, hypertension, blood pressure increased, blood pressure decreased and heart rate increased.

Additionally, the PRAC considered that the risk of palpitations is also relevant for all fixed-dose combination product(s) containing dorzolamide and that the product information of these medicinal products should be updated accordingly. 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.

³¹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.4. Gabapentin (NAP) - PSUSA/00001499/201902

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gabapentin is an anti-epileptic drug indicated as monotherapy and as adjunctive therapy in the treatment of partial seizures with and without secondary generalisation and for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, subject to certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gabapentin 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 gabapentin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH Pfizer should discuss data regarding the abuse potential of gabapentin taken concomitantly with an opioid, including data from a clinical trial investigating this risk for the related substance pregabalin³². In addition, all MAHs should provide a cumulative review of pregnancy outcomes and congenital malformations as well as a cumulative review of cases reporting suicidal action/behaviour/ideation.

Additionally, the PRAC considered that a detailed analysis of reported cases of suicidality related to gabapentin/gabapentinoids should be performed. Therefore, the MAH for the originator gabapentin-containing product (Pfizer) should be requested to discuss in detail the feasibility to conduct an epidemiological study to further investigate the suicidal risk of gabapentin, taking into account the recently published study by *Molero et al*³³. Additionally, the PRAC considered that MAH Pfizer should perform a population-based cohort study on gabapentin pregnancy outcomes and a study protocol submitted accordingly for assessment. 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.

6.3.5. Levothyroxine (NAP) - PSUSA/00001860/201901

Applicant(s): various

³² Study 1118-4: evaluation of the abuse potential of pregabalin taken concomitantly with an opioid

³³ Molero Y, Larsson H, D'Onofrio BM, Sharp DJ, Fazel S. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population-based cohort study in Sweden. *BMJ* 2019; 365:l2147

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Levothyroxine is a synthetic thyroid hormone indicated for the treatment of hypothyroidism.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing levothyroxine 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 levothyroxine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on circulatory collapse in very low birth weight pre-term neonates and to ensure haemodynamic parameters are monitored when the therapy with levothyroxine is initiated in this population. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, all MAHs should include thyroid imbalance due to switching from one levothyroxine containing-product to another levothyroxine containing-product (including new formulation, new packaging or new storage conditions of the same product) as an important identified risk in PSUR safety concerns and should analyse cases related to a switch to a new formulation. In addition, the MAHs should provide a cumulative review of psychiatric disorders, including depression and suicide, self-injury, panic attack, mania and acute psychosis. Furthermore, an updated review on coagulation disorders should be provided as well as a discussion on the impact of biotin interference with clinical laboratory tests on levothyroxine. Moreover, the MAHs should provide a discussion on the relevance of the drug interaction between levothyroxine and St John's Wort (*Hypericum perforatum*), as well as levothyroxine and antimalarials (in particular chloroquine, proguanil). Based on the reviewed analysis on the large number of reported adverse drug reactions (ADRs), despite being within the known safety profile, the MAH Merck should expand their existing analysis comparing the safety profile of the old and new formulation of Levothyrox/Euthyrox (levothyroxine) in each EU Member State where the new formulation was introduced.

The PRAC considered that the product information of levothyroxine-containing products for which the product information has not been already updated should be revised to include the need for a clinical and biological monitoring in case of switching between medicinal products. 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.

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

6.3.6. Lisdexamfetamine (NAP) - PSUSA/00010289/201902

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Lisdexamfetamine is a non-catecholamine sympathomimetic with central nervous system (CNS) stimulant activity indicated for the treatment of attention deficit hyperactivity disorder (ADHD) from 6 years of age.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lisdexamfetamine 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 lisdexamfetamine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information based on the experience with the use of lisdexamfetamine, amfetamine and dexamfetamine³⁵ during pregnancy. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.

Additionally, the PRAC considered that the risks from use during pregnancy and after intrauterine exposure are also relevant for amphetamine- and dexamfetamine-containing medicinal products and should be included in their product information. 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.

6.4. Follow-up to PSUR/PSUSA procedures

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)³⁷

See also Annex I 17.1.

³⁵ Lisdexamfetamine is a prodrug of dexamfetamine which is an isomer of amfetamine

³⁶ Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

³⁷ In accordance with Article 107n of Directive 2001/83/EC

Applicant: Kite Pharma EU B.V., ATMP³⁸

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to PSP/S/0079 [protocol for a long-term, non-interventional study in patients taking Yescarta (axicabtagene ciloleucel) for the treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma to evaluate the safety of patients, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinaemia and pregnancy outcomes in female patients of childbearing potential] as per the request for supplementary information (RSI) adopted in May 2019 and following discussion in September 2019

Background

Yescarta is a centrally authorised medicine containing axicabtagene ciloleucel, an engineered autologous T-cell immunotherapy product. Yescarta (axicabtagene ciloleucel) is indicated for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

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 non-interventional PASS based on a registry should be conducted to assess the safety profile including long term safety in patients with B-lymphocyte malignancies treated with axicabtagene ciloleucel in the post marketing setting. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted a protocol for a PASS entitled: 'long term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma' for which PRAC adopted in May 2019 a request for supplementary information (RSI). The PRAC is responsible for evaluating the PASS protocol. For further background, see [PRAC minutes May 2019](#) and [PRAC minutes September 2019](#).

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 1.1 dated 03 July 2019 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Yescarta (axicabtagene ciloleucel). The PRAC considered that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage. In particular, the MAH should ensure that cumulative safety data analysis including patient-level discussion and causality assessments of adverse event of special interest (AESI) following every quarterly data transfer from the European Society for Blood and Marrow Transplantation (EBMT) to the MAH should be submitted. In addition, the MAH should ensure that the educational material is provided to healthcare professionals (HCPs), stressing the importance of the spontaneous reporting system as the primary safety-data entry point, not substitutable by the reporting to the EBMT as part of this PASS. The MAH is requested also to describe the procedures, under their responsibility, for training and qualifying centres with a special focus on facilitating spontaneous reporting from the HCPs. Furthermore, the MAH is requested not to restrict the study size, but to include all eligible patients from the EBMT registry.

³⁸ Advanced therapy medicinal product

- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 day-assessment timetable will be followed.

7.1.2. Iron^{39, 40} (NAP) - EMEA/H/N/PSA/J/0042

Applicant(s): Mesama Consulting (on behalf of a consortium) (Cosmofer, Ferinject, Monofer, Venofer)

PRAC Rapporteur: Ghania Chamouni

Scope: Amendment to a previously agreed protocol in September 2017 (PSP/J/0053.1) for a joint PASS evaluating the risk of severe hypersensitivity reactions with intravenous (IV) iron use

Background

Intravenous (IV) iron-containing medicines are indicated in iron deficiency situations when the oral route is insufficient or poorly tolerated especially in chronic kidney disease (CKD) patients, but also in pre- or post-operative situations, or in case of intestinal absorption disorders.

The obligation to conduct a non-interventional imposed PASS study in accordance with Article 107o of Directive 2001/83/EC to be performed with intravenous iron products aiming to assess the risk of anaphylactic or severe immediate hypersensitivity reactions was imposed on MAHs in 2013 as an outcome of the referral under Article 31 of Directive 2001/83/EC for IV iron-containing medicines ([EMEA/H/A-31/1322](#)). For further information see [PRAC minutes March 2017](#).

Substantial amendments of the protocol were presented for review by the PRAC, reflecting the proposed changes to the analysis plan due to the very low number of events identified through preliminary descriptive analyses.

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 2.1 in accordance with Article 107n of Directive 2001/83/EC, endorsed the study protocol.

7.1.3. Tisagenlecleucel - KYMRIA⁴¹ (CAP) - EMEA/H/C/PSP/S/0066.2

Applicant: Novartis Europharm Ltd, ATMP⁴¹

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0066.1 [protocol for non-interventional study CCTL019B2401 with secondary use of data from two registries conducted by the European Society for Blood and Marrow Transplantation (EBMT) and Centre for International Blood and Marrow Transplant Research (CIBMTR) to evaluate the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel (chimeric antigen receptor (CAR)-T cell therapy) in a real-world setting] as per the request for supplementary information (RSI) adopted in April 2019 and following discussion in September 2019

³⁹ Intravenous applications only

⁴⁰ Iron(III)-hydroxide dextran complex, iron sucrose complex/iron(III)-hydroxide sucrose complex, ferric carboxymaltose complex, iron(III) isomaltoside complex, sodium ferric gluconate complex

⁴¹ Advanced therapy medicinal product

Background

Kymriah is a centrally authorised medicine containing tisagenlecleucel, an engineered autologous T-cell immunotherapy product. Kymriah (tisagenlecleucel) is indicated for treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse and treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

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 non-interventional PASS based on a registry should be conducted to further characterise the safety, including long-term safety. In accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted a protocol for study CCTL019B2401 with secondary use of data from two registries conducted by the European Society for Blood and Marrow Transplantation (EBMT) and Centre for International Blood and Marrow Transplant Research (CIBMTR) to evaluate the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel (chimeric antigen receptor (CAR)-T cell therapy) in a real-world setting. In April 2019, the PRAC adopted a further request for supplementary information (RSI). The PRAC is responsible for evaluating the PASS protocol. For further background, see [PRAC minutes December 2018](#), [PRAC minutes May 2019](#) and [PRAC minutes September 2019](#).

Endorsement/Refusal of the protocol

- The PRAC, having considered protocol version 02 dated 18 July 2019 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for Kymriah (tisagenlecleucel). The PRAC considered that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage. In particular, the MAH should ensure that cumulative safety data analysis including patient level discussion and causality assessments of adverse event of special interest (AESI) following every quarterly data transfer from the European Society for Blood and Marrow Transplantation (EBMT) to the MAH. The MAH should also describe the procedures under the MAH's responsibility to qualify and train centres, highlighting the importance of spontaneous reporting from HCPs to regulatory authorities or the MAH.
- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 day-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴²

See also Annex I 17.2.

7.2.1. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/MEA 003.1

Applicant: Kite Pharma EU B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 003 [protocol for study KT-EU-471-0116: a prescriber survey to assess the prescribers' understanding of serious neurologic adverse reactions and

⁴² 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

cytokine release syndrome (CRS)] as per the request for supplementary information (RSI) adopted in June 2019

Background

Yescarta is a centrally authorised medicine containing axicabtagene ciloleucel, an engineered autologous T-cell immunotherapy product. Yescarta (axicabtagene ciloleucel) is indicated for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

As part of the RMP for Yescarta (axicabtagene ciloleucel), the MAH was required to conduct a prescriber survey to assess the prescribers' understanding of serious neurologic adverse reactions and cytokine release syndrome (CRS) in order to mitigate the risk of CRS for Yescarta (axicabtagene ciloleucel). The MAH submitted a protocol for the evaluation, which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Yescarta (axicabtagene ciloleucel) version 1.1 dated 15 February 2019 could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to the EMA before finalisation of the procedure.
- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 60 day-assessment timetable will be followed.

7.2.2. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/MEA 010

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 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

Background

Latuda is a centrally authorised medicine containing lurasidone, a second-generation oral atypical antipsychotic used in the treatment of schizophrenia in adults aged 18 years and over.

As part of the RMP for Latuda, the MAH was required to conduct a study to evaluate the safety profile of lurasidone using administrative claims databases in order to characterise and mitigate the risks of lurasidone treatment. The MAH submitted a protocol for a study (as part of the RMP but outside the scope of Article 107n of Directive 2001/83/EC) for the evaluation which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Having considered the protocol for study 151(A)PO19107, the PRAC agreed that the MAH's proposal not to pursue the PASS study using a UK primary care database (i.e. Clinical Practice Research Datalink (CPRD) as agreed at the time of initial marketing authorisation(s)), and to replace it with an US observational study, is acceptable. The

PRAC agreed that the protocol for this study in the US administrative claims database is adequate.

7.2.3. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/MEA 011

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 151(A)PO19056: a drug utilisation study (DUS) to evaluate the characteristics of lurasidone-treated patients in real world clinical practice in the United Kingdom

Background

Latuda is a centrally authorised medicine containing lurasidone, a second-generation oral atypical antipsychotic used in the treatment of schizophrenia in adults aged 18 years and over.

As part of the RMP for Latuda (lurasidone), the MAH was required to conduct a drug utilisation study (DUS) to evaluate the characteristics of lurasidone-treated patients in real world clinical practice in order to characterise and mitigate the risks of lurasidone treatment. The MAH submitted a protocol for a study for the evaluation which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- Having considered the protocol for study 151(A)PO19056, the PRAC supported to not pursue the study the low patient exposure to lurasidone in the UK and in the EU which would not allow for a meaningful study. In addition, the PRAC confirmed that routine pharmacovigilance activities are sufficient to characterise the clinically relevant risks for lurasidone that are all mitigated via routine risk minimisation measures.

7.3. Results of PASS imposed in the marketing authorisation(s)⁴³

See Annex I 17.3.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁴

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.

⁴³ In accordance with Article 107p-q of Directive 2001/83/EC

⁴⁴ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

7.6. Others

7.6.1. Pantoprazole - CONTROLOC CONTROL (CAP) - EMEA/H/C/001097/LEG 018

Applicant: Takeda GmbH

PRAC Rapporteur: Rugile Pilviniene

Scope: Feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population, as requested in the conclusions of variation WS/1422 finalised in January 2019

Background

Controloc Control is a centrally authorised medicine containing pantoprazole, a proton pump inhibitor indicated for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

The MAH was requested to conduct a feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population. The MAH submitted a feasibility assessment for the DUS assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the feasibility assessment submitted by the MAH.

Summary of advice

- Having considered the feasibility report for a drug utilisation study (DUS), the PRAC agreed that whereas it is feasible to conduct a DUS on oral use of pantoprazole in the paediatric population from a technical perspective, considering the very low use of pantoprazole in children in most countries, the study is unlikely to reveal any additional significant information to help inform clinical decision making.

7.6.2. Pantoprazole - PANTOLOC CONTROL (CAP) - EMEA/H/C/001100/LEG 017

Applicant: Takeda GmbH

PRAC Rapporteur: Rugile Pilviniene

Scope: Feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population, as requested in the conclusions of variation WS/1422 finalised in January 2019

Background

Pantoloc Control is a centrally authorised medicine containing pantoprazole, a proton pump inhibitor indicated for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

The MAH was requested to conduct a feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population. The MAH submitted a feasibility assessment for the DUS assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the feasibility assessment submitted by the MAH.

Summary of advice

- Having considered the feasibility report for a drug utilisation study (DUS), the PRAC agreed that whereas it is feasible to conduct a DUS on oral use of pantoprazole in the paediatric population from a technical perspective, considering the very low use of pantoprazole in children in most countries, the study is unlikely to reveal any additional significant information to help inform clinical decision making.

7.6.3. Pantoprazole - PANTOZOL CONTROL (CAP) - EMEA/H/C/001013/LEG 018

Applicant: Takeda GmbH

PRAC Rapporteur: Rugile Pilviniene

Scope: Feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population, as requested in the conclusions of variation WS/1422 finalised in January 2019

Background

Pantozol Control is a centrally authorised medicine containing pantoprazole, a proton pump inhibitor indicated for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

The MAH was requested to conduct a feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population. The MAH submitted a feasibility assessment for the DUS assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the feasibility assessment submitted by the MAH.

Summary of advice

- Having considered the feasibility report for a drug utilisation study (DUS), the PRAC agreed that whereas it is feasible to conduct a DUS on oral use of pantoprazole in the paediatric population from a technical perspective, considering the very low use of pantoprazole in children in most countries, the study is unlikely to reveal any additional significant information to help inform clinical decision making.

7.6.4. Pantoprazole - SOMAC CONTROL (CAP) - EMEA/H/C/001098/LEG 023

Applicant: Takeda GmbH

PRAC Rapporteur: Rugile Pilviniene

Scope: Feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population, as requested in the conclusions of variation WS/1422 finalised in January 2019

Background

Somac Control is a centrally authorised medicine containing pantoprazole, a proton pump inhibitor indicated for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

The MAH was requested to conduct a feasibility assessment for a protocol for a drug utilisation study (DUS) to assess the extent of off-label use in the paediatric population. The MAH submitted a feasibility assessment for the DUS assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the feasibility assessment submitted by the

MAH.

Summary of advice

- Having considered the feasibility report for a drug utilisation study (DUS), the PRAC agreed that whereas it is feasible to conduct a DUS on oral use of pantoprazole in the paediatric population from a technical perspective, considering the very low use of pantoprazole in children in most countries, the study is unlikely to reveal any additional significant information to help inform clinical decision making.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Etonogestrel (NAP) - NL/H/0150/001/II/050

Applicant(s): N.V. Organon (Implanon NXT)

PRAC Lead: Menno van der Elst

Scope: PRAC consultation on a type II variation procedure referred to the CMDh under Article 13(1) of EC/1234/2008 relating to an update of the SmPC on the implant insertion and removal instructions and risk minimisation measures on intravascular insertion and neurovascular injury, on request of the Netherlands

Background

Etonogestrel is a progestogen indicated for use as a hormonal contraceptive implant.

In the context of the evaluation of a type II variation procedure on the implant insertion, removal instructions and risk minimisation measures for managing the risk of intravascular insertion and neurovascular injury, The Netherlands as the reference member state (RMS) requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the RMS's assessment and agreed that migration of the implant into a pulmonary artery can occur any time after its implantation. The PRAC agreed that the currently proposed risk minimisation measures (RMMs) in the type II variation are not sufficient to minimise the risk of migration of the implant. The PRAC advised that the patient information leaflet (PIL) should include a recommendation for regular self-examination whether the implant is palpable and at the correct place and that healthcare professionals (HCPs) should be informed about the change of the insertion site of Implanon (etonogestrel), the accompanying additional RMM (video) and the need for regular self-examination via an EU-wide direct healthcare professional communication (DHPC). The PRAC agreed that routine pharmacovigilance activities are sufficient to monitor the effectiveness of the RMMs introduced in the current procedure.

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) – consultation procedure: update and practical aspects

In line with the [PRAC work plan 2019](#), the EMA Secretariat updated the PRAC on the practical aspects of the PRAC consultation for procedures of the Scientific Advice Working Party (SAWP), including the usual timelines and the expected contribution by the PRAC.

12.4. Cooperation within the EU regulatory network

12.4.1. Communication harmonisation within the network - naming convention

The EMA Secretariat informed the PRAC of the naming convention for messages exchanges between the EU regulatory network during assessment of procedures for human medicines, in order to allow an automated triage of received emails.

12.4.2. European Network Training Centre (EU NTC) - Pharmacovigilance - Training curriculum (TC) – Update on training activities

The EMA Secretariat further updated the PRAC on the progress of the training activities in context of the pharmacovigilance training curriculum, including the composition of the four

priority areas.

12.5. Cooperation with International Regulators

12.5.1. International Conference on Harmonisation (ICH) E2B(R3) guideline on electronic transmission of individual case safety reports - data elements and message specification - stakeholder readiness for mandatory use

As a follow-up to the last discussion (for further background, see [PRAC minutes July 2019](#)), the PRAC adopted recommendation that the International Organization for Standardization (ISO) individual case safety report (ICSR) standard as referred to in Article 26(2)(a) of the Commission Implementing Regulation (EU) No 520/2012, the modalities on how to use this ISO ICSR standard defined in the ICH E2B(R3) documentation, and related ISO standard terminology for routes of administration (RoAs) and pharmaceutical dose forms (PDFs) referred to in Article 25(1)(f) of Commission Implementing Regulation (EU) No 520/2012 shall become mandatory as of 30 June 2022 in relation to reporting obligations to EudraVigilance (pre- and post-authorisation). The recommendation will be further considered at the EMA Management Board (MB) for confirmation and announcement in December 2019.

Post-meeting note: On 19 December 2019, the EMA MB confirmed and announced that ISO ICSR standard, the modalities on how to use this ISO ICSR standard defined in the ICH E2B(R3) documentation, and the ISO terminology on pharmaceutical dose forms and routes of administration shall become mandatory as of 30 June 2022 relation to reporting obligations to EudraVigilance. For details, please refer to the [announcement](#).

12.5.2. International Conference on Harmonisation (ICH) E2D guideline on post-approval safety data management: definitions and standards for expedited reporting - revision

At the organisational matters (ORGAM) teleconference on 17 October 2019, the PRAC was informed of the preparation for the revision of the International Conference on Harmonisation (ICH) E2D guideline on post-approval safety data management, which was originally finalised by ICH in 2003 and adopted in the EU in May 2004. The revision will take into account the new data sources and technologies which have led to a major increase in volume of adverse events to be collected, analysed, and reported with the aim to increase harmonisation and focus on consistent data collection for signal detection purposes. PRAC members were invited to send written comments on the concept paper by 30 October 2019.

12.5.3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-E19 on 'optimisation of safety data collection' – draft guideline

As a follow up the last discussion in September 2019, the PRAC adopted the PRAC response to the consultation on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E19 guideline on 'optimisation of safety data collection'. For further background see [PRAC minutes September 2019](#).

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

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the GPAG progress highlights. In particular, the PRAC was updated on the development of the EURD tool.

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 October 2019, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for

upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of October 2019, the updated EURD list was adopted by the CHMP and CMDh at their October 2019 meetings and published on the EMA website on 23 October 2019, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

At the organisational matters (ORGAM) teleconference on 17 October 2019, the PRAC was updated on the progress of activities related to the Methods work stream of the working group, including the re-prioritisation of topics for 2019.

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 7 October 2019, see:

[Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.14.3. Good pharmacovigilance practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' – revision 3

PRAC lead: Sabine Straus

In line with the [PRAC work plan 2019](#), the EMA Secretariat presented to PRAC a proposed scope and planned timelines for revising GVP module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators'. PRAC members were invited to express interest to volunteer by 18 October 2019 to contribute to revision 3.

Post-meeting note: The following delegates volunteered: Raymond Anderson, Ghania Chamouni, Hedvig Marie Egeland Nordeng, Birgitta Grundmark, Martin Huber, Adrien Inoubli, Željana Margan Koletić, Jana Lukacisinova, Liana Gross-Martirosyan, Antoine Pariente, Eva Segovia, Sofia Trantza, Maia Uusküla, Menno van der Elst, Cathalijne van Doorne and Ulla Wändel Liminga.

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. Biosimilar medicines and identification – update

The PRAC was updated on the progress of a study investigating the identification of biosimilar medicines in reports of adverse drug reactions, using their brand name and batch number, as required by the legislation. A further update is foreseen at PRAC in December 2019.

12.20.2. Capacity-building activities in human and veterinary pharmacovigilance - EMA survey for its staff and the EU network on 02-11 October 2019

The EMA Secretariat informed the PRAC about a survey to collect information on capacity-building activities in human and veterinary pharmacovigilance performed by EMA for its staff and the EU network. The electronic survey is due for completion by 11 October 2019.

12.20.3. Drug-induced hepatotoxicity – review

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

In line with the [PRAC work plan 2019](#), the PRAC is undertaking a review of drug-induced hepatotoxicity to facilitate detection and assessment of signals of hepatotoxicity. The PRAC was updated on the progress from the working group, together with a proposal for the content of a guidance document. A further discussion at PRAC is expected in Q4 2019.

12.20.4. EMA pre-submission activities - European Ombudsman enquiry outcome

The EMA Secretariat informed the PRAC of the development of an action plan and planned timelines to reflect the findings from the European Ombudsman's independent [enquiry](#) into EMA pre-submission activities.

12.20.5. EMA relocation to new building, Amsterdam, the Netherlands – update

Following the update in September 2019 on the planned timelines for the new permanent EMA headquarters in Amsterdam, the Netherlands (for further background, see [PRAC minutes September 2019](#)), the PRAC was updated on further practical information relating to the new EMA building.

12.20.6. Good Pharmacovigilance Practice (GVP) Guideline on product or population specific considerations III: pregnancy and breastfeeding – draft guideline

PRAC lead: Ulla Wändel Liminga

As a follow-up to the last discussion in September 2019 (for further background, see [PRAC minutes September 2019](#)), the PRAC was presented with an overview of the latest comments on the draft guideline. At the organisational matters teleconference on 17 October 2019, the PRAC discussed the final draft document.

Post meeting note: On 18 October 2019, the PRAC adopted the guideline via written procedure.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁴⁵

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 timetables⁴⁶.

14.1.1. Bevacizumab – AVASTIN (CAP); MVASI (CAP); ZIRABEV (CAP)

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 – New signal

Lead Member State(s): DK

14.1.2. Nivolumab – OPDIVO (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of haemophagocytic lymphohistiocytosis

EPITT 19467 – New signal

⁴⁵ 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

⁴⁶ 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

Lead Member State(s): DE

14.1.3. Vismodegib – ERIVEDGE (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Signal of pancreatitis

EPITT 19470 – New signal

Lead Member State(s): SE

14.2. New signals detected from other sources

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Azacitidine - EMEA/H/C/005147

Scope: Treatment of myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML), acute myeloid leukaemia (AML) and AML with >30% marrow blasts according to the WHO⁴⁷ classification

15.1.2. Azacitidine - EMEA/H/C/005075

Scope: Treatment of myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML)

15.1.3. Budesonide, formoterol fumarate dihydrate - EMEA/H/C/004882

Scope: Treatment of asthma and chronic obstructive pulmonary disease (COPD)

15.1.4. Cinacalcet - EMEA/H/C/005236

Scope: Treatment of secondary hyperparathyroidism and hypercalcaemia

15.1.5. Pegfilgrastim - EMEA/H/C/005312

Scope: Treatment of neutropenia

⁴⁷ World Health Organization

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. Adalimumab - IDACIO (CAP) - EMEA/H/C/004475/WS1651/0003; KROMEYA (CAP) - EMEA/H/C/005158/WS1651/0003

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 4.0) for Idacio (adalimumab) and KromeYA (adalimumab) in order to align it with the reference product containing adalimumab. The risk minimisation measures of Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' are also updated. The MAH took the opportunity to introduce minor linguistic changes/corrections to the product information in German, French, Hungarian (Idacio only) and Slovenian

15.2.2. Autologous CD34⁺ enriched cell fraction that contains CD34⁺ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/II/0022, Orphan

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP⁴⁸

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 2.0) in order to introduce changes to the design of the post-authorisation study STRIM-002: methodology study to investigate the utility of retroviral insertion site analysis in samples from subjects treated with Strimvelis gene therapy, from a prospective to a retrospective study. In addition, the RMP is brought in line with revision 2 of the guidance on the format of RMP in the EU (template) and the timelines for study STRIM-001: evaluation of referring healthcare professionals (HCPs)' and parents'/carers' understanding of specific risks associated with Strimvelis treatment, are updated

15.2.3. Everolimus - AFINITOR (CAP) - EMEA/H/C/001038/WS1671/0063; VOTUBIA (CAP) - EMEA/H/C/002311/WS1671/0059

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 14.0) for Afinitor (everolimus) and Votubia (everolimus) in order to implement some safety concerns, to reflect the completion of several pharmacovigilance studies, namely: study CRAD001Y2201: a phase 2 study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in the treatment of postmenopausal women with oestrogen receptor positive (ER+) locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole (Afinitor, variation II/58 finalised in September 2018),

⁴⁸ Advanced therapy medicinal product

CRAD001M2304: a three-arm, randomised, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures (Votubia, variation II/51 finalised in July 2018), CRAD001J2301: a randomised phase 3, double-blind, placebo-controlled multicentre trial of everolimus in combination with trastuzumab and paclitaxel, as first line therapy in women with human epidermal growth factor receptor 2 (HER2) positive locally advanced or metastatic breast cancer (Afinitor, variation II/51G finalised in March 2017), RAD00W2301: a randomised phase 3, double-blind, placebo-controlled multicentre trial of everolimus in combination with trastuzumab and vinorelbine, in pretreated women with human epidermal growth factor receptor 2 (HER2)/neu over-expressing locally advanced or metastatic breast cancer (Afinitor, variation II/51G finalised in March 2017); and to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template), as requested in the conclusions of the periodic safety update report single assessment (PSUSA) procedure PSUSA/00010268/201703 finalised in October 2017

15.2.4. Filgrastim - ACCOFIL (CAP) - EMEA/H/C/003956/II/0037

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of an updated RMP (version 4.0) in order to update the section of additional pharmacovigilance activities to remove the Severe Chronic Neutropenia International Registry (SCNIR) and the 'European Society for Blood and Marrow Transplantation' (EBMT) registries following the conclusion of the SCNIR and EBMT combined analysis report. The MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.5. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/II/0115

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 12) in order to revise the lists of safety concerns and to bring it in line with revision 2 of GVP module V on 'Risk management systems'

15.2.6. Irinotecan hydrochloride trihydrate - ONIVYDE (CAP) - EMEA/H/C/004125/II/0015, Orphan

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP (version 2.7) in order to update the RMP in line with the conclusions of periodic safety update report single assessment (PSUSA) procedures PSUSA/00010534/201804 finalised in November 2018 and PSUSA procedure PSUSA/00010534/201810 finalised in May 2019. The RMP is also updated in line with revision 2 of GVP module V on 'Risk management systems'

15.2.7. [Measles, mumps, rubella and varicella vaccine \(live\) - PROQUAD \(CAP\) - EMEA/H/C/000622/II/0134](#)

Applicant: MSD Vaccins

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 6.1) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.8. [Pioglitazone - ACTOS \(CAP\) - EMEA/H/C/000285/WS1680/0082; GLUSTIN \(CAP\) - EMEA/H/C/000286/WS1680/0081; Pioglitazone, glimepiride - TANDEMACT \(CAP\) - EMEA/H/C/000680/WS1680/0060; Pioglitazone, metformin - COMPETACT \(CAP\) - EMEA/H/C/000655/WS1680/0074; GLUBRAVA \(CAP\) - EMEA/H/C/000893/WS1680/0060](#)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 27) in order to update and consolidate within a single RMP the RMPs for pioglitazone-containing product(s), pioglitazone/metformin-fixed dose combination (FDC) and pioglitazone/glimepiride-FDC. The list of safety concerns is revised in line with the conclusions of periodic safety update report single assessment (PSUSA) procedure PSUSA/00002417/201807 finalised in March 2019 with regards to the discontinuation of the additional risk minimisation measures (aRMMs)

15.2.9. [Posaconazole - NOXAFIL \(CAP\) - EMEA/H/C/000610/II/0057](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 15.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' with the consequent applicable re-evaluation of some safety concerns. In addition, the MAH took the opportunity to include data from the completed clinical trial in paediatric subjects PN097: a phase 1B study of the safety, tolerability, and pharmacokinetics of intravenous (IV) and powder for oral suspension formulations of posaconazole (POS) in immunocompromised paediatric subjects, and to update the due date for submission of the final report of the ongoing post-marketing efficacy trial PN069: a phase 3 randomised study on the efficacy and safety of posaconazole versus voriconazole for the treatment of invasive aspergillosis in adults and adolescents from December 2019 to Q4 2020

15.2.10. [Ribavirin - REBETOL \(CAP\) - EMEA/H/C/000246/II/0086](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 5.1) in order to revise safety concerns for ribavirin in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the MAH took the opportunity to revise the safety concerns of ribavirin in light of the

current era of interferon (IFN) free regimen, as requested in a previous PSUSA procedure (EMA/H/C/PSUSA/00010007/201707) concluded in March 2018

15.2.11. Sunitinib - SUTENT (CAP) - EMA/H/C/000687/II/0073

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

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

15.2.12. Umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMA/H/C/002751/WS1586/0028; LAVENTAIR ELLIPTA (CAP) - EMA/H/C/003754/WS1586/0031

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of an updated RMP (version 8.0) following the completion of the annual renewal procedures (R/0022 and R/0025) in November 2018 concluding on the commitments to remove the important identified risks of 'hypersensitivity' and 'paradoxical bronchospasm' from the list of safety concerns and to update all relevant sections of the RMP in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH proposed to remove some additional risks ('narrow angle glaucoma', 'bladder outflow obstruction and urinary retention', 'safety in pregnancy and lactation', 'safety in long-term use' and 'safety in severe hepatic impairment')

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. Afatinib - GIOTRIF (CAP) - EMA/H/C/002280/II/0031

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add gastrointestinal (GI) perforation as an additional side effect based on summaries of clinical trial and post-marketing safety data. The package leaflet is updated accordingly. In addition, the RMP (version 8.0) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template), taking also into consideration recommendations part of the conclusions of renewal procedure R/0026 adopted in March 2018. Furthermore, the MAH took the opportunity to correct some typographical errors in the German, Austrian and Spanish product information and to update the list of the local representatives for Austria in the package leaflet

15.3.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0075

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to reflect changes in the existing warning on immunogenicity and immunomodulation and to add new clinical information on infantile onset Pompe disease (IOPD) patients' immune tolerance induction based on data on use of immune tolerance induction in IOPD patients from two exploratory phase 4 studies, namely: study AGLU03707/MS12817: an exploratory study of the safety and efficacy of immune tolerance induction (ITI) in patients with Pompe disease who have previously received Myozyme (alglucosidase alfa); and companion study AGLU03807/MS12892: open-label, exploratory study of the safety and efficacy of prophylactic ITI in alglucosidase alfa-naïve cross reactive immunologic material (CRIM)(-) patients with IOPD, as well as the Duke Center of Excellence observational study (01562): open-label, retrospective cohort study of ITI regimens in combination with alglucosidase alfa in patients with CRIM(-) IOPD. The RMP (version 9.0) is updated accordingly

15.3.3. 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

15.3.4. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0070, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

EMA resources: PM: Irene Papadouli; RMS: Daniel Becker; EPL: Irene Papadouli

Scope: Extension of indication to add Adcetris (brentuximab vedotin) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for the treatment of adult patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 15.1) are updated accordingly

15.3.5. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/II/0010

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an in vitro metabolism study report for study R188-A15. The RMP (version 1.6) is updated accordingly

15.3.6. 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

15.3.7. Cobicistat - TYBOST (CAP) - EMEA/H/C/002572/II/0051

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to modify the approved therapeutic indication to include new population, namely adolescents aged 12 years and older, weighing at least 35 kg for the treatment of human immunodeficiency virus 1 (HIV-1). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.1) are updated accordingly

15.3.8. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0029, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to extend the existing therapeutic indication for Darzalex (daratumumab) in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 6.0 s1) are updated accordingly

15.3.9. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0047/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) for Xtandi (enzalutamide) in combination with androgen deprivation therapy (ADT). As a consequence, sections 4.1, 4.7, 4.8, 5.1, 5.3 and 6.6 of the SmPC are updated. Furthermore the MAH took the opportunity to introduce minor corrections to section 4.7. The package leaflet and the RMP (version 13.0) are updated accordingly; 2) update of section 5.1 of the SmPC based on the 5-year overall survival (OS) results obtained from study MDV310003 (PREVAIL), a phase 3 study of enzalutamide in chemotherapy naïve patients with metastatic prostate cancer that progressed on ADT

15.3.10. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0064

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to remove the limitation of use in patients with moderate renal impairment (creatinine clearance [CrCl] 30 to 50 mL/min) based on pooled data from 8 EQW (exenatide once weekly)/EQWS (exenatide once weekly suspension) studies undertaken in patients with mild renal impairment/chronic kidney disease stage 2 or moderate renal impairment/chronic kidney disease stage 3, and on supportive data from study D5551C00003/BCB109 (EXSCCEL): a randomised, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus, including a subset of patients with moderate renal impairment. In addition, the MAH took the opportunity to introduce glomerular filtration rate (GFR) as the main indicator of renal function rather than CrCl. The package leaflet is updated accordingly and the MAH took the opportunity to implement some minor changes in the labelling. The RMP (version 34) is updated accordingly and includes a proposal for removing acute renal failure (ARF) as an important identified risk based on revision 2 of GVP module V on 'Risk management systems'. As requested in the conclusions of variation II/54 finalised in April 2019, the MAH also introduced a pan-EU epidemiological study as an additional pharmacovigilance activity to monitor events of pancreatic cancer

15.3.11. Fidaxomicin - DIFICLIR (CAP) - EMEA/H/C/002087/X/0034/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped application consisting of: 1) extension application to introduce a new pharmaceutical form associated with new strength (40 mg/mL granules for oral suspension); 2) extension of indication to include paediatric use of Dificlir (fidaxomicin) in children from birth to less than 18 years of age. The RMP (version 11.0) is updated accordingly. The SmPC of Dificlir (fidaxomicin) 200 mg film-coated tablet, labelling and package leaflet are updated accordingly. In addition, the MAH took the opportunity to update the package leaflet with the statement on 'sodium-free' in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, the MAH updated the details of the local representative in Czech Republic

15.3.12. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/X/0004

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Extension application to include the new strength of 100 mg/mL solution for injection in pre-filled syringe for Emgality (galcanezumab) associated with a new indication to include treatment of episodic cluster headache. The RMP (version 1.1) is updated accordingly

15.3.13. Human fibrinogen, human thrombin - VERASEAL (CAP) - EMEA/H/C/004446/II/0006/G

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Grouped variations consisting of; 1) addition of a new CE marked applicator tip as a replacement for the current application cannula which allows the application of the product both by dripping and spraying without gas assistance. The RMP (version 4.0) is updated accordingly; 2) modification of the syringe holder to a sterilised plastic cartridge, to allow the connection of the syringe holder to the new applicator tip; 3) changes to the blister packaging and removal of the outer pouch; 4) minor change in the manufacturing process

15.3.14. Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) - GARDASIL 9 (CAP) - EMEA/H/C/003852/II/0033

Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.2, 4.6, 4.8 and 5.1 of the SmPC in order to update the safety and immunogenicity information based on final results from study V503-P004 (listed as a category 3 study in the RMP): an open-label phase 3 clinical trial to study the immunogenicity and tolerability of Gardasil 9 in adult women (27 to 45 year-olds) compared to young adult women (16 to 26 year-olds) (in fulfilment of MEA007). The package leaflet and the RMP (version 4.1) are updated accordingly. In addition, the MAH took the opportunity to update section 4.4 of the SmPC in line with the 'Guideline on quality aspects included in the product information for vaccines for human use (EMA/CHMP/BWP/133540/2017)' and to include editorial changes in section 5.1 of the SmPC

15.3.15. Insulin glargine - TOUJEO (CAP) - EMEA/H/C/000309/II/0108

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to the treatment of diabetes mellitus in adolescents and children from the age of 6 years based on the 6-month on-treatment data of study EFC13597: a 6-month, multicentre, randomised, open-label, 2-arm, parallel-group study comparing the efficacy and safety of a new formulation of insulin glargine and Lantus (insulin glargine) injected once daily in children and adolescents age 6-17 years with type 1 diabetes mellitus (T1DM) with a 6-month safety extension period study. 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 6.0) are updated accordingly

15.3.16. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/II/0011

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment in combination with metformin of adults

with type 2 diabetes mellitus (T2DM) to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or basal insulin, based on phase 3 study EFC13794: a 26-week randomised, open-label, active controlled, parallel-group study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with type 2 diabetes inadequately controlled on glucagon-like peptide-1 (GLP-1) receptor agonist and metformin (alone or with pioglitazone and/or sodium-glucose co-transporter-2 (SGLT2) inhibitors), followed by a fixed ratio combination single-arm 26-week extension period. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in Denmark, the Netherlands and the UK in the package leaflet and to implement minor editorial changes in Annexes

15.3.17. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/II/0130

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final clinical study report (CSR) from study HUBIN_L_05335 (listed as a category 3 study in the RMP): a phase 3 study covering the evaluation of Insuman Implantable 400 IU/mL (insulin human) in patients with type 1 diabetes treated with the Medtronic MiniMed Implantable Pump System using Insuplant 400 IU/mL (in fulfilment of post-authorisation measure (PAM) MEA040). The RMP (version 4.0) is updated accordingly and includes the amended protocol (version 2) of the ongoing study HUBIN_C_06380: an European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman Implantable 400 IU/mL (insulin human) in Medtronic MiniMed implantable pump as endorsed by PRAC in procedure MEA 047.5 in May 2018

15.3.18. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0064

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC in order to update the safety information following final results from study CA184143 (listed as a category 3 study in the RMP (post-authorisation measure MEA 017.11)): a multi-national, prospective, observational study in patients with unresectable or metastatic melanoma. The RMP (version 26.0) is updated accordingly. In addition, the MAH took the opportunity to update the RMP in regards to already assessed MEA 036.1 concerning protocol synopsis on the extension of the Dutch Melanoma Treatment Registry (DMTR) to paediatric melanoma patients treated with ipilimumab. Furthermore the MAH took the opportunity to request a 6-month shift in the dates associated to the next implementation steps of the DMTR extension (registration of paediatric patients in the DMTR register and final clinical study report (CSR) submission). Finally, the MAH introduced some editorial changes in section 5.1 of the SmPC to provide more clarity on whether studies relate to melanoma or renal cell carcinoma (RCC) and to monotherapy or combination therapy with nivolumab

15.3.19. 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 (PI)

15.3.20. Nalotimagene carmaleucel - ZALMOXIS (CAP) - EMEA/H/C/002801/II/0016, Orphan

Applicant: MolMed S.p.A, ATMP⁴⁹

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Proposal to terminate study TK008 (listed as a category 2 study, specific condition to the conditional marketing authorisation): a phase 3, randomised trial of haploidentical hematopoietic cell transplantation (HCT) with or without an add back strategy of human herpes simplex virus thymidine kinase type 1 gene (HSV-Tk) donor lymphocytes in patients with high risk acute leukaemia, and replace it with study TK013: a two-step study consisting in an initial feasibility study, followed by a single-arm trial with matched-pair controls from the European Society for Blood and Marrow Transplantation (EBMT) registry. The RMP (version 8.1) is updated accordingly

15.3.21. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0033

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to support the use of Lynparza (olaparib) tablets (100 mg and 150 mg) for the maintenance treatment of germline BRCA⁵⁰ mutation (gBRCAm) metastatic pancreatic cancer based on the results from pivotal study POLO: a phase 3 randomised, double blind, placebo controlled, multicentre study of maintenance olaparib monotherapy in patients with gBRCA mutated metastatic pancreatic cancer whose disease has not progressed on first line platinum based chemotherapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 18) are updated accordingly. In addition, the MAH took the opportunity to update section 4.8 for Lynparza (olaparib) hard capsules 50 mg to revise the list of adverse drug reactions (ADR) based on the pooled safety data analysis. Furthermore, the MAH took the opportunity to update the product information on sodium content in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. Finally, the MAH introduced some minor editorial changes throughout the

⁴⁹ Advanced therapy medicinal product

⁵⁰ BRCA Cancer gene

product information (PI)

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, randomised trial 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, randomised 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. Pasireotide - SIGNIFOR (CAP) - EMEA/H/C/002052/II/0041/G, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.8 of the SmPC based on the final clinical study report (CSR) from study CSOM230B2219 (listed as a category 3 study in the RMP): a multicentre, randomised, open-label, phase 4 study to investigate the management of pasireotide-induced hyperglycaemia with incretin based therapy or insulin in adult patients with Cushing's disease or acromegaly. The RMP (version 7.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.24. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0080

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC on the safety information for immune-related endocrinopathies following a safety review for Addison's disease/primary adrenal insufficiency. The RMP (version 26.1) is updated accordingly. The MAH also took the opportunity to include changes in Annex II in line with the latest quality review of documents (QRD) template (version 10.1) and to update the list of local representatives of Portugal in the package leaflet

15.3.25. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0033

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Cyramza (ramucirumab) in combination with erlotinib for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations. 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 9) are updated accordingly

15.3.26. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0162

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Extension of indication to include the treatment of paediatric patients (aged ≥ 2 to <18 years old) with active polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) for the 100 mg and 500 mg concentrate for solution based on efficacy and safety data from study WA25615: a phase 2A, international, multicentre, open-label, uncontrolled study to evaluate the safety and pharmacokinetics of 4×375 mg/m² intravenous rituximab in paediatric patients with severe granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis (PePRS). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC is updated. The package leaflet and the RMP (version 20.0) are updated accordingly. In addition, the product information is brought in line with the latest quality review document (QRD) template (version 10) and the opportunity is taken to combine the SmPC and package leaflet for the 100 mg and 500 mg concentrate for solution presentations. Furthermore, the MAH took the opportunity to implement minor editorial changes in the SmPC

15.3.27. 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 mg 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 accordingly. In addition, the MAH took the opportunity to implement minor linguistic corrections throughout the product information (PI)

15.3.28. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/X/0049/G, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped application consisting of: extension application to introduce a new strength (61 mg soft capsules, pack-size of 30 and 90 capsules) including an extension of indication to include treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation (ATTR-CM); update of section 4.6 of the SmPC of 20 mg soft capsules to reflect some wording pertaining to the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme. The RMP (version 9.0) is updated accordingly, including proposed new dosage/indication, review of the additional data collected from the ATTR-CM

clinical programme and post marketing reporting, a reclassification of the safety concerns and the removal of healthcare professional (HCP) educational leaflet. Annex II is updated in accordance. In addition, the MAH proposed to update the information in Braille of Annex III-A on 'labelling' to differentiate between the dosage forms

15.3.29. Telotristat ethyl - XERMELO (CAP) - EMEA/H/C/003937/II/0015, Orphan

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 5.1 of the SmPC based on final results from study LX1606.1-302.CS (TELEPATH) (listed as a category 3 study in the RMP): a multicentre, phase 3, long-term extension study to further evaluate the safety and tolerability of telotristat etiprate in patients with carcinoid syndrome (CS). The RMP (version 4.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.30. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0020

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: Update of sections 4.8 and 5.1 of the SmPC based on safety information from interim results at week 48 of study GS-US-320-4018 (listed as a category 3 study in the RMP): a phase 3, randomised, double blind study conducted to evaluate the efficacy and safety of switching from tenofovir disoproxil fumarate (TDF) 300 mg once a day (QD) to tenofovir alafenamide (TAF) 25 mg QD in subjects with chronic hepatitis B (CHB) who are virologically suppressed. The package leaflet and the RMP (version 4.1) are updated accordingly

15.3.31. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0086/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of sections 4.8 of the SmPC to change the frequency for anaphylaxis (fatal) and Stevens-Johnson syndrome to 'rare'. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to sections 4.2, 4.8 and 5.1 of the SmPC, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the package leaflet; 2) submission of an updated RMP (version 25.2) in order to remove the reference to the neutropenia guided questionnaire in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to introduce minor changes to the RMP, including the removal of study WA22479 (British Society of Rheumatology Biologics Register (BSRBR)) (in fulfilment of post-authorisation measure (PAM) MEA-045), inclusion of study ZUMA-8 (KTE-X19-108): a phase 1/2 multicentre study evaluating KTE-X19 in patients with relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL), as requested in the conclusions of variation II/0076 finalised in September 2018

15.3.32. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0073

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication to include a new population for Stelara (ustekinumab) solution for injection in children aged 6 to 12 years with moderate to severe psoriasis based on the results of study CNTO1275PSO3013: a phase 3 open-label study to assess the efficacy, safety, and pharmacokinetics of subcutaneously administered ustekinumab in the treatment of moderate to severe chronic plaque psoriasis in paediatric subjects greater than or equal to 6 to less than 12 years of age. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Section 4.8 of the SmPC for Stelara (ustekinumab) concentrate for solution for infusion is updated accordingly. The package leaflet and the RMP (version 15.0) are updated accordingly. The MAH also updated the RMP to add 'follow-up of pregnancy registry'. The MAH took the opportunity to introduce minor editorial changes to section 4.5 for both formulations and to update the list of local representatives in the package leaflet

15.3.33. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0023/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include Venclyxto (venetoclax) in combination with an anti-CD20 antibody (obinutuzumab) for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) based on the results of pivotal study CLL14/BO25323: a prospective, open-label, multicentre randomised phase 3 trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax (GDC-0199/ABT-199) versus obinutuzumab and chlorambucil in previously untreated patients with CLL and coexisting medical conditions. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.1) are updated accordingly. Furthermore, section 5.3 of the SmPC is updated based on the 6 month-carcinogenicity mouse study report, supported by the 4 week dose ranging study in mice and embryo-foetal development (EFD) data. The MAH took the opportunity to introduce minor editorial changes throughout the product information (PI)

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

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

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

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

16.1.1. Apremilast - OTEZLA (CAP) - PSUSA/00010338/201903

Applicant: Celgene Europe BV
PRAC Rapporteur: Eva Segovia
Scope: Evaluation of a PSUSA procedure

16.1.2. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/201903

Applicant: Merck Europe B.V.
PRAC Rapporteur: Hans Christian Siersted
Scope: Evaluation of a PSUSA procedure

16.1.3. Belimumab - BENLYSTA (CAP) - PSUSA/00009075/201903

Applicant: GlaxoSmithKline (Ireland) Limited
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

16.1.4. Bosutinib - BOSULIF (CAP) - PSUSA/00010073/201903

Applicant: Pfizer Europe MA EEIG
PRAC Rapporteur: Martin Huber
Scope: Evaluation of a PSUSA procedure

16.1.5. Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/201903

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

16.1.6. Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/201902

Applicant: Ablynx NV
PRAC Rapporteur: Jan Neuhauser
Scope: Evaluation of a PSUSA procedure

16.1.7. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/201903

Applicant: Merck Sharp & Dohme B.V.
PRAC Rapporteur: Adam Przybylkowski
Scope: Evaluation of a PSUSA procedure

16.1.8. Cyclosporin⁵¹ - IKERVIS (CAP); VERKAZIA (CAP) - PSUSA/00010362/201903

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.9. Cinacalcet - MIMPARA (CAP) - PSUSA/00000756/201902

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.10. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/201903

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.11. Damoctocog alfa pegol - JIVI (CAP) - PSUSA/00010732/201902

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.12. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - PSUSA/00010646/201903

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.13. Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/201903

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.14. Doravirine - PIFELTRO (CAP) - PSUSA/00010729/201902

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

⁵¹ Topical use only

16.1.15. [Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO \(CAP\) - PSUSA/00010731/201902](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.16. [Eftrenonacog alfa - ALPROLIX \(CAP\) - PSUSA/00010499/201903](#)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.17. [Eluxadoline - TRUBERZI \(CAP\) - PSUSA/00010528/201903](#)

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.18. [Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY \(CAP\) - PSUSA/00010514/201902](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.19. [Ferric citrate coordination complex - FEXERIC \(CAP\) - PSUSA/00010418/201903](#)

Applicant: Akebia Europe Limited c/o Matheson

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.20. [Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA \(CAP\); TRELEGY ELLIPTA \(CAP\) - PSUSA/00010653/201903](#)

Applicant(s): GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.21. [Glycopyrronium⁵² - SIALANAR \(CAP\) - PSUSA/00010529/201903](#)

Applicant: Proveca Pharma Limited

⁵² Centrally authorised product(s) only, indicated for the treatment of severe sialorrhoea (chronic pathological drooling)

PRAC Rapporteur: Zane Neikena
Scope: Evaluation of a PSUSA procedure

16.1.22. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/201903

Applicant: Shire Pharmaceuticals Ireland Limited
PRAC Rapporteur: Maria del Pilar Rayon
Scope: Evaluation of a PSUSA procedure

16.1.23. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/201903

Applicant: BPL Bioproducts Laboratory GmbH
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

16.1.24. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - FLUCELVAX TETRA (CAP) - PSUSA/00010737/201903

Applicant: Seqirus Netherlands B.V.
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

16.1.25. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201903

Applicant: Basilea Pharmaceutica Deutschland GmbH
PRAC Rapporteur: Adam Przybylkowski
Scope: Evaluation of a PSUSA procedure

16.1.26. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/201903

Applicant: Eli Lilly Nederland B.V.
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

16.1.27. Lapatinib - TYVERB (CAP) - PSUSA/00001829/201903

Applicant: Novartis Europharm Limited
PRAC Rapporteur: Annika Folin
Scope: Evaluation of a PSUSA procedure

16.1.28. Lusutrombopag - MULTPLEO (CAP) - PSUSA/00010755/201903

Applicant: Shionogi B.V.
PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.29. Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/201902

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.30. Niraparib - ZEJULA (CAP) - PSUSA/00010655/201903

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.31. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁵³) - EMEA/H/W/002300/PSUV/0042

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUR procedure

16.1.32. Ribociclib - KISQALI (CAP) - PSUSA/00010633/201903

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.33. Rolapitant - VARUBY (CAP) - PSUSA/00010592/201902

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.34. Sodium zirconium cyclosilicate - LOKELMA (CAP) - PSUSA/00010675/201903

Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

⁵³ 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)

16.1.35. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/201903

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.36. Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/201903

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.37. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/201903

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/201902

Applicant(s): Clinigen Healthcare B.V. (Savene), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.2.2. Orlistat - ALLI (CAP); XENICAL (CAP); NAP - PSUSA/00002220/201902

Applicant(s): GlaxoSmithKline Dungarvan Ltd (Alli), Cheplapharm Arzneimittel GmbH (Xenical), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.2.3. Trientine - CUPRIOR (CAP); NAP - PSUSA/00010637/201903

Applicant(s): GMP-Orphan SA (Cuprior), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Amitriptyline hydrochloride, chlordiazepoxide (NAP) - PSUSA/00000171/201902

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Amlodipine, atorvastatin (NAP) - PSUSA/00000177/201901

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.3. Cilostazol (NAP) - PSUSA/00010209/201902

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.4. Dorzolamide, timolol (NAP) - PSUSA/00001166/201902

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.5. Ethanol, orthophenylphenol (NAP) - PSUSA/00010416/201902

Applicant(s): various

PRAC Lead: Jana Lukačšínová

Scope: Evaluation of a PSUSA procedure

16.3.6. Glipizide (NAP) - PSUSA/00001535/201901

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.7. Human coagulation factor VIII⁵⁴ (NAP) - PSUSA/00009174/201902

Applicant(s): various

⁵⁴ Inhibitor bypassing fraction

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.3.8. Hydroxyethyl starch (NAP) - PSUSA/00001694/201903

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.9. Interferon gamma (NAP) - PSUSA/00001760/201901

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.10. Mesterolone (NAP) - PSUSA/00010551/201901

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.11. Octenidine dihydrochloride, 1-propanol, 2-propanol (NAP) - PSUSA/00010417/201901

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.12. Trandolapril (NAP) - PSUSA/00003004/201902

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

None

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁵⁵

17.1.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSP/S/0071.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: MAH's response to PSP/S/0071 [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 May 2019

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁵⁶

17.2.1. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/MEA 001.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 001 [protocol for study 20160264 (ABP 501) - British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR): an observational study to evaluate long term safety of Amgevita (adalimumab) in patients with rheumatoid arthritis [final report due date: Q3 2027]] as per the request for supplementary information (RSI) adopted in April 2019

17.2.2. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 003.2

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Amendment to a previously agreed protocol in November 2018 for study D3250R00026 'the benralizumab pregnancy exposure study': a post-marketing surveillance study on vaccines and medications in pregnancy surveillance system (VAMPSS)

17.2.3. Brigatinib - ALUNBRIG (CAP) - EMEA/H/C/004248/MEA 002.1

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 002 [protocol for study Brigatinib-5007: a cohort study to describe the occurrence of early-onset pulmonary events in patients with anaplastic lymphoma kinase-positive (ALS+) advance non-small cell lung cancer (NSCLC) treated with brigatinib] as per the request for supplementary information (RSI) adopted in June 2019

⁵⁵ In accordance with Article 107n of Directive 2001/83/EC

⁵⁶ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.4. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 006

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Protocol for study H9X-MC-B013: a non-interventional retrospective study to estimate the incidence rates of events of interest among type 2 diabetes mellitus (T2DM) patients treated with dulaglutide compared to other glucagon-like peptide 1 (GLP-1) receptor agonists in order to better characterise the safety profile of dulaglutide in terms of acute pancreatitis, pancreatic and thyroid malignancies

17.2.5. Mexiletine - NAMUSCLA (CAP) - EMEA/H/C/004584/MEA 001.1

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: MAH's response to MEA 001 [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 May 2019

17.2.6. Radium-223 - XOFIGO (CAP) - EMEA/H/C/002653/MEA 014.1

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's response to MEA 014 [protocol for a drug utilisation study (DUS) of Xofigo (radium-223) under routine clinical practice in Europe to investigate the risk of off-label use, as requested in the conclusions of the referral procedure on Xofigo (radium-223) under Article 20 of Regulation (EC) No 726/2004 (EMA/H/A-20/1459) finalised in 2018] as per the request for supplementary information (RSI) adopted in May 2019

17.2.7. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.5

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 044.4 [Amendment to a previously agreed protocol in February 2017 (MEA 044.2) for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)] as per the request for supplementary information (RSI) adopted in June 2019

17.3. Results of PASS imposed in the marketing authorisation(s)⁵⁷

17.3.1. Valproate (NAP) - EMEA/H/N/PSR/J/0021

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

⁵⁷ In accordance with Article 107p-q of Directive 2001/83/EC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSR/J/0021 [results for a joint drug utilisation study (DUS) of valproate and related substances, in Europe, using databases to describe the prescribing practices before and after the dissemination of risk minimisation measures (RMMs) (i.e. educational materials and direct healthcare professional communication (DHPC) between December 2014 and June 2015) and to assess the effectiveness of these measures, as imposed in the outcome of the referral procedure on valproate and related substances (EMA/H/A-31/1387) concluded in 2014] as per the request for supplementary information (RSI) adopted in May 2019

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁵⁸

17.4.1. Dasabuvir - EXVIERA (CAP) - EMA/H/C/003837/WS1663/0046/G; Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMA/H/C/003839/WS1663/0055/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped variations consisting of: 1) submission of final report from study P15-421, (listed as a category 3 study in the RMP): a prospective, observational cohort study utilising the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine aminotransferase (ALT) elevations in patients being treated for hepatitis C with paritaprevir and ritonavir (paritaprevir/r), ombitasvir and dasabuvir (3-direct acting antiviral (DAAV) regimen) or paritaprevir/r and ombitasvir (2-DAAV regimen) with or without ribavirin for hepatitis C infection (HCV); 2) change in the final due date for the prospective safety study report in order to evaluate the recurrence of hepatocellular carcinoma associated with Exviera (dasabuvir) and Viekirax (ombitasvir/paritaprevir/ritonavir) from Q2 2021 to Q2 2023. Annex II of the product information and the RMP (version 5.0) are updated accordingly.

17.4.2. Deferasirox - EXJADE (CAP) - EMA/H/C/000670/II/0068

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final report related to the physician survey (NO6987) conducted for Exjade (deferasirox) to assess the impact of educational materials on the prescribers' awareness of doses and biological monitoring recommendations and to assess the awareness and appropriate use of both formulations (dispersible tablets and film-coated tablets). The RMP (version 17.1) is updated accordingly

17.4.3. Etanercept - ENBREL (CAP) - EMA/H/C/000262/WS1614/0227; Etanercept - LIFMIOR (CAP) - EMA/H/C/004167/WS1614/0021

Applicant: Pfizer Europe MA EEIG

⁵⁸ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study B1801035 (081X1-4654) (listed as a category 3 study in the RMP): a non-interventional, multicentre, prospective, observational, cohort study conducted to evaluate the long-term safety and effectiveness of etanercept prescribed by dermatologists to paediatric patients for the treatment of plaque psoriasis (Paediatric Registry of Psoriasis and Enbrel - The PURPOSE Study)

17.4.4. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0016, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final report from study SNT-CRS-002 (listed as a specific obligation (SOB10, former SOB2) in Annex II): a historical case record survey (CRS) of visual acuity data from patients with Leber's hereditary optic neuropathy (LHON) aiming at generating a natural history group to serve as a comparator group of idebenone-naïve patients for open-label study SNT-IV-005: an external natural history controlled, open-label intervention study to assess the efficacy and safety of long-term treatment with Raxone (idebenone) in LHON. Annex II and the RMP (version 1.8) are updated accordingly.

17.4.5. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/II/0037

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report for drug utilisation study (DUS) register EUPAS5766 in EuroSIDA cohort (listed as a category 3 study in the RMP): an observational cohort study to assess rilpivirine (RPV) utilisation. The RMP (version 9.0) is updated accordingly

17.4.6. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0043

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report for study INC424AIC01T (listed as a category 3 study in the RMP): a non-interventional, observational PASS in order to provide real-world safety data on patients with myelofibrosis (MF) who were exposed and non-exposed to ruxolitinib and provide insights into disease management and the safety profile of ruxolitinib. The RMP (version 11) is updated accordingly

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

17.5.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/MEA 042

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Interim report for an observational registry of abatacept in patients with juvenile idiopathic arthritis (JIA) in order to describe the long-term safety of abatacept treatment for

JIA in routine clinical practice by quantifying the incidence rates of serious infections, autoimmune disorders, and malignancies (from R/055)

17.5.2. Everolimus - VOTUBIA (CAP) - EMEA/H/C/002311/MEA 014.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Fifth interim analysis for a sub-study of PASS CRAD001MIC03 (TOSCA): an international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex (TSC)

17.5.3. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.5

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: Eighth annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal (filgrastim) and Zarzio (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) expected date: December 2019]

17.5.4. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.5

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Eighth annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal (filgrastim) and Zarzio (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) expected date: December 2019]

17.5.5. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 012.8

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Eighth annual interim pooled report for studies D2403 (a long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started on fingolimod once daily or treated with another approved disease-modifying therapy), D2404 (multinational Gilenya pregnancy exposure registry in multiple sclerosis (MS)), D2406 (a long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS newly initiated on fingolimod once daily or treated with another approved disease-modifying therapy) and study D2409 (a long-term, open-label, multicentre study assessing long-term cardiovascular risks in patients treated with fingolimod). This procedure also includes an annual report for the pregnancy intensive monitoring (PRIM) study

17.5.6. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP) - EMEA/H/C/000703/MEA 086

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Yearly interim results for study P070 (listed as category 3 study in the RMP): a post-licensure safety study in males to monitor safety signals through a systematic evaluation in a research database

17.5.7. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 060.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Six-monthly summary report of medication error events reported with the on body injector in the EU market, as requested in the conclusions of variation II/093/G finalised in February 2018

17.5.8. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/MEA 003.9

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Ninth annual interim report for the Kuvan Adult Maternal Paediatric European registry (KAMPER), study EMR700773-001: a non-imposed, non-interventional exploring the long-term safety of Kuvan (sapropterin) use in patients with hyperphenylalaninaemia (HPA) as well as information on Kuvan use during pregnancy in women with HPA and data regarding childhood growth and neurocognitive outcomes

17.6. Others

17.6.1. Lusutrombopag - MUPLEO (CAP) - EMEA/H/C/004720/MEA 002

Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Feasibility assessment for a protocol for study VV-REG-090246: a PASS exploring the hepatic safety of lusutrombopag Shionogi in patients with Child-Pugh class C liver disease (from initial opinion/MA) [final study report expected in December 2025]

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. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0010 (without RMP)

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.2. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/S/0016 (without RMP)

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.3. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0048 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/R/0009 (without RMP)

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0026 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A., ATMP⁵⁹

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

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

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.4. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0041 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/R/0020 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.2. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/R/0022 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.3. Fosnetupitant, netupitant, palonosetron - AKYNZEO (CAP) - EMEA/H/C/003728/R/0024 (without RMP)

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.4. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/002789/R/0022 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A.

⁵⁹ Advanced therapy medicinal product

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.5. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/R/0024 (without RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.6. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/R/0031 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

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 30 September – 03 October 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	No interests declared	Full involvement
Eva Jirsovà	Member	Czech Republic	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 restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Member - via telephone	Greece	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
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
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
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Alexandra-Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Jasmina Klopčič	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
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
Martin Zahle Larsen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Florent Arinal	Expert - in person*	France	No interests declared	Full involvement
Serge Bakchine	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Anissa Benlazar	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Jeremie Botton	Expert - in person*	France	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
Pauline Dayani	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Mariem Loukil	Expert - in person*	France	No interests declared	Full involvement
Tiphaine Vaillant	Expert - in person*	France	No interests declared	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
Elena Wolff-Holz	Expert - in person*	Germany	No interests declared	Full involvement
Ruchika Sharma	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Bianca Mulder	Expert - in person*	Netherlands	No restrictions applicable to this meeting	Full involvement
Anja van Haren	Expert - in person*	Netherlands	No interests declared	Full involvement
Tania López Garrido	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Darius Matusevicius	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Karin Nylén	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

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

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

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

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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

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