11 April 2019
EMA/PRAC/235021/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 12-15 March 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 12-15 March 2019 meeting by welcoming all participants at the first plenary meeting in Amsterdam, the Netherlands.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure (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.

The PRAC Chair welcomed Virginie Hivert as the new alternate representing patients' organisations and Raymond Anderson as the member representing healthcare professionals nominated and re-nominated respectively by the European Commission (EC). In addition, the PRAC noted that Cathalijne van Doorne was nominated as the member for patients' organisations and Ylva Böttiger as the alternate representing healthcare professionals. Their mandate started on 1 March 2019 for a term of three years. For further background, see Commission Decision (CD) dated 25 February 2019: C(2019) 1449 final.

1.2. Agenda of the meeting on 12-15 March 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 11-14 February 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 11-14 February 2019 were published on the EMA website on 8 April 2019 (EMA/PRAC/216303/2019).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

3.1.1. 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 fur klinische Spezialpraparate mbH (Capecitabine medac), Nordic Group B.V. (Teysuno), 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

5-fluorouracil (5-FU), capecitabine and tegafur belong to the class of fluoropyrimidines that are pyrimidine analogues and antineoplastic agents. Capecitabine and tegafur are prodrugs of 5-FU. 5-FU solution for injection or infusion is indicated for the treatment of malignancies, including gastrointestinal neoplasm malignant, head and neck cancer, epidermoid cancer, breast cancer, malignant respiratory tract neoplasm, liver tumour, cervix carcinoma, bladder cancer, ovarian cancer, prostate cancer and uterine carcinoma. Capecitabine is indicated, as Xeloda, Capecitabine Accord, Capecitabine Medac, Capecitabine Teva, Ecansya and other nationally approved products, for the treatment of malignancies including colon cancer, metastatic colorectal cancer, gastric cancer, advanced or metastatic breast cancer. Tegafur in combination with gimeracil, a

dihydropyrimidine dehydrogenase (DPD) inhibitor, and oteracil, an orotate phosphoribosyltransferase (OPRT) inhibitor, is indicated, as Teysuno, for the treatment of gastric cancer in combination with cisplatin under certain conditions.

The French Medicines Agency[1] (ANSM) sent a letter of notification dated 13 March 2019 of a referral under Article 31 of Directive 2001/83/EC for the review of 5-FU-, capecitabine- and tegafur-containing medicines for systemic use to review the genotyping and phenotyping methods and availability across the EU for the detection of DPD deficiency responsible for severe and fatal toxicity. The goal of the procedure is to review existing screening methods and their value in identifying patients at increased risk of severe side effects and to consider the need for updating existing recommendations for pre-treatment evaluation of DPD activity in patients to receive treatment with 5-FU or related substances. Therefore, it is considered in the interest of the Union to refer the matter to the PRAC for further evaluation.

Discussion

The PRAC noted the notification letter from the ANSM and discussed a list of questions (LoQ) to the MAHs to be addressed during the procedure as well as a timetable for conducting the review. In addition, based on the fact that the risk of systemic exposure of 5-FU after administration of topical formulation or after metabolism of flucytosine cannot be completely excluded, the PRAC discussed the possibility to extend the scope of the procedure to include these substance-containing products in the review. 5-FU for topical use and flucytosine are indicated for various skin conditions and in severe fungal infections respectively. The PRAC also discussed the possibility to collect further data at the EMA level as well as at national level from the National Competent Authorities (NCAs).

The PRAC appointed Jean-Michel Dogné as Rapporteur and Martin Huber as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

- The Committee agreed to extend the scope of the procedure to include 5-FU for topical use and flucytosine in the review.
- The Committee adopted a LoQ to the MAHs (EMA/PRAC/165648/2019) and a timetable for the procedure (EMA/PRAC/165647/2019).
- The EMA agreed to perform a EudraVigilance analysis of reports of DPD deficiency related toxicity with fluorouracil and related substances, as well as a literature review of any new publication in relation to the screening of DPD deficiency in patients treated with fluorouracil and related substances.
- The Committee agreed on the content of a non-urgent information request (NUI) to be distributed to the EU NCAs in order to collect information on availability of testing facilities, current clinical practice in relation to the evaluation of DPD activity in the treatment of cancer patients, and national recommendations concerning DPD deficiency.
- The PRAC discussed the option to conduct a public hearing in the context of the Article 31 procedure, according to the pre-defined criteria set out in the rules of

[1] Agence Nationale de Sécurité du Médicament et des Produits de Santé

procedure[2] (EMA/363479/2015). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure as needed.

See EMA press release (EMA/164425/2019) entitled 'EMA starts review on screening patients before treatment with fluorouracil, capecitabine, tegafur and flucytosine'.

Post-meeting note: Following requests from MAH(s) to extend the timelines for submission of the responses to the LoQ, the PRAC adopted on 01/04/2019 a revised timetable (EMA/PRAC/165647/2019 Rev.1) by written procedure.

3.2. Ongoing procedures

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

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

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

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for methotrexate-containing medicines (oral and parenteral formulations) following reports of overdose toxicity as a consequence of daily intake in error instead of weekly intake. The ongoing review also assesses the risk minimisation measures taken nationally over recent years to fully elucidate the issue and to take appropriate measures. For further background, see PRAC minutes April 2018, PRAC minutes October 2018, PRAC minutes January 2019 and PRAC minutes February 2019.

Summary of recommendation(s)/conclusions

- The PRAC received feedback from the stakeholders meeting held on 26 February 2019.

Post-meeting note: On 06 May 2019, the PRAC received the final report from the meeting with stakeholders.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[3]

None

[2] Rules of procedure on the organisation and conduct of public hearings at the PRAC
[3] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

3.5. Others

None

4. Signals assessment and prioritisation[4]

4.1. New signals detected from EU spontaneous reporting systems

None

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Ondansetron (NAP)

Applicant(s): various

PRAC Rapporteur: Gabriela Jazbec

Scope: Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications

EPITT 19353 – New signal

Lead Member State(s): SI

Background

Ondansetron is a 5-HT_3 receptor antagonist indicated for the treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of postoperative nausea and vomiting.

Following the recent publication of studies in Reproductive Toxicology by *Zambelli-Weiner et al.*[5] and in JAMA[6] by *Huybrechts KF et al.*[7], a signal of birth defects following in-utero exposure during the first trimester of pregnancy was identified by the United Kingdom, suggesting an association between early pregnancy ondansetron exposure (during the first trimester) and specific structural birth defects in offspring, especially cardiac defects and orofacial cleft defects. Slovenia confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of birth defects following in-utero exposure during the first trimester of pregnancy and concluded that this signal merits further investigation. The PRAC agreed to request the authors of both studies (*Zambelli-Weiner et al.* and *Huybrechts et al.*) to provide additional clarifications on the study

[4] 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
[5] Zambelli-Weiner A et al. First trimester ondansetron exposure and risk of structural birth defects. Reprod Toxicol. 2019 Jan;83:14-20
[6] Journal of the American Medical Association
[7] Huybrechts KF et al. Association of maternal first-trimester ondansetron use with cardiac malformations and oral clefts in offspring. JAMA. 2018 Dec 18;320(23):2429-2437

findings and requested responses to a list of questions (LoQ) from the MAH of the originator for ondansetron-containing product(s).

The PRAC appointed Gabriela Jazbec as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH Novartis for the originator ondansetron-containing product(s) should submit to the EMA, within 30 days, responses to a list of questions (LoQ) as adopted by the PRAC.
- The study authors of *Zambelli-Weiner et al.* and *Huybrechts KF et al.* are invited to submit to the EMA, within 30 days, additional clarifications on the studies, as per an agreed LoQ.
- A 60-day timetable was recommended for the assessment of these responses leading to a further PRAC recommendation.

4.2.2. Sodium-glucose co-transporter 2 (SGLT2) inhibitors: canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP); dapagliflozin – EDISTRIDE (CAP); dapagliflozin – FORXIGA (CAP); dapagliflozin, metformin – EBYMECT (CAP); dapagliflozin, metformin – XIGDUO (CAP); empagliflozin – JARDIANCE (CAP); empagliflozin, metformin – SYNJARDY (CAP); ertugliflozin – STEGLATRO (CAP); ertugliflozin, metformin – SEGLUROMET (CAP)

Applicant(s): AstraZeneca AB (Ebymect, Edistride, Forxiga, Xigduo), Boehringer Ingelheim International GmbH (Jardiance, Synjardy), Janssen-Cilag International NV (Invokana, Vokanamet), Merck Sharp & Dohme B.V. (Segluromet, Steglatro)

PRAC Rapporteur: Martin Huber

Scope: New information on the known association between sodium-glucose co-transporter 2 (SGLT2) inhibitors and diabetic ketoacidosis (DKA) in surgical patients

EPITT 19355 – New signal

Lead Member State(s): DE, ES, SE, NL, UK

Background

Invokana and Vokanamet, Ebymect, Edistride, Forxiga and Xigduo, Jardiance and Synjardy and Steglatro and Segluromet are centrally authorised products containing respectively canagliflozin, dapagliflozin, empaglifozin, and ertuglifozin that are sodium-glucose cotransporter-2 (SGLT2) inhibitors. They are indicated, alone or in combination with metformin, a biguanide oral hypoglycaemic agent, in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control as monotherapy or as add-on therapy under certain conditions.

The exposure for Invokana (canaglifozin) is estimated to have been more than 3.17 million person-years worldwide, in the period from first authorisation in 2013 to 2018. The exposure for Forxiga (dapaglifozin) is estimated to have been more than 3 million patient-years, in the period from first authorisation in 2012 to 2017. The exposure for Jardiance (empaglifozin) is estimated to have been more than 3.1 million patient-years, in the period from first authorisation in 2014 to 2018. The exposure for Steglatro (ertuglifozin) is estimated to have been more than 9,732 patient-years, in the period from first authorisation in 2017 to 2018.

During routine signal detection activities, a signal of diabetic ketoacidosis (DKA) in surgical patients was identified by the EMA, based on communication from the FDA[8] and 53 cases retrieved from EudraVigilance. Germany and Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of DKA in surgical patients and agreed that further evaluation of the signal on DKA following surgery in T2DM patients and SLGT-2 inhibitors as a class is warranted. The PRAC agreed to request cumulative reviews of DKA in surgical patients from the MAHs of SGLT-2 inhibitor-containing products, and a review whether an update of the product information for these medicines is warranted.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for canagliflozin-, dapagliflozin-, empaglifozin-, and ertuglifozin-containing products should submit to the EMA, within 60 days, a cumulative review of the signal, including an analysis of all case reports of DKA following surgery from all sources (i.e. spontaneous reports, literature and clinical trials), and a discussion on the need for risk minimisation measures (e.g. amendment of the product information).
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.3. Tofacitinib - XELJANZ (CAP)

Applicant(s): Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of increased risk of pulmonary embolism and overall mortality arising from a post-authorisation safety study in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily

EPITT 19382 – New signal

Lead Member State(s): NL

Background

Tofacitinib is a selective inhibitor of the Janus kinase (JAK) family. Xeljanz (tofacitinib) is a centrally authorised product indicated alone or in combination with methotrexate (MTX) for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. It is also indicated in combination with MTX for the treatment of active psoriatic arthritis (PsA) and moderately to severely active ulcerative colitis (UC), under certain conditions.

The exposure for Xeljanz (tofacitinib) is estimated to have been more than 165,170 patient-years worldwide, in the period from first authorisation in 2012 to 2018.

During routine signal detection activities, a signal of increased risk of pulmonary embolism and overall mortality arising from a post-authorisation safety study in patients with

[8] US Food & Drug Administration

cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily was identified by the Netherlands, based on information arising from ongoing PASS A3921133[9]. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the findings of a statistically and clinically important difference in the occurrence of pulmonary embolism (PE) with the tofacitinib 10 mg twice-daily treatment arm compared to the active tumour necrosis factor (TNF)-α inhibitor control arm and an increase in overall mortality. The PRAC noted that the studied 10 mg dose twice-daily is not authorised in the EU for the treatment of RA but is authorised for the treatment of UC. The PRAC agreed that the signal warrants further investigation and agreed to request responses to a list of questions (LoQ). Additionally, considering the potential for an increased risk of PE with tofacitinib 10 mg twice-daily in the authorised UC indication, and that at this stage the concern cannot be excluded for the tofacitinib 5 mg twice-daily, the PRAC agreed on the need to disseminate a direct healthcare professional communication (DHPC).

Summary of recommendation(s)

- The MAH for Xeljanz (tofacitinib) should submit to the EMA, within 30 days, responses to a LoQ as agreed by the PRAC.
- The PRAC agreed on the distribution of a DHPC. The PRAC agreed the content of the DHPC together with a communication plan.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/SDA/032.1

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of pancreatitis

EPITT 19265 – Follow-up to January 2019

Background

For background information, see PRAC minutes January 2019.

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

Discussion

Having considered the available evidence provided by the MAH, the PRAC agreed that the likelihood of a causal relationship between the use of apixaban and pancreatitis is not

[9] A phase 3b/4 randomized safety endpoint study of 2 doses of tofacitinib in comparison to a tumour necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis (EudraCT number: 2013-003177-99) (PASS listed as a category 3 study in the EU RMP)

sufficiently strong at this stage. Therefore, the PRAC concurred that no regulatory action is currently warranted.

Summary of recommendation(s)

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

4.3.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/SDA/029.1

Applicant(s): GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of lupus nephritis

EPITT 19174 – Follow-up to October 2018

Background

For background information, see PRAC minutes October 2018.

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

Discussion

Having considered the available information, including clinical data and spontaneous reports, the PRAC concluded that there is currently insufficient evidence to establish a causal association between the use of belimumab and *de novo* development or aggravation of lupus nephritis in patients treated with belimumab for systemic lupus erythematosus. Therefore, the PRAC concurred that no regulatory action is currently warranted.

Summary of recommendation(s)

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

4.3.3. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/SDA/035

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of hypoparathyroidism

EPITT 19310 – Follow-up to November 2018

Background

For background information, see PRAC minutes November 2018 (29-31 October 2018).

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

Discussion

Having considered the available evidence from the cumulative review provided by the MAH, the PRAC agreed that there is a reasonable likelihood of a causal relationship

between nivolumab and hypoparathyroidism and that healthcare professionals (HCPs) should be made aware of the potential risk for hypocalcaemia and other symptoms of hypoparathyroidism that may be associated with the use of nivolumab. The PRAC agreed that the product information of Opdivo (nivolumab) should be updated accordingly.

Summary of recommendation(s)

- The MAH for Opdivo (nivolumab) should submit to EMA, within 60 days, a variation to amend the product information[10].

For the full PRAC recommendation, see EMA/PRAC/157165/2019 published on 08/04/2017 on the EMA website.

4.3.4. Paracetamol (NAP)

Applicant(s): various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus

EPITT 17796 – Follow-up to November 2018

Background

For background information, see PRAC minutes November 2018 (29-31 October 2018).

The MAHs Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Sanofi and Teva provided comments on the proposed product information update on the signal of paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus. The responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the literature, including non-clinical and epidemiological studies, regarding the signal of prenatal exposure to paracetamol and the impact on the urogenital apparatus or neurodevelopmental disorders in offspring, the comments received from the MAHs and the analysis of observational studies performed by EMA, the PRAC concluded that the results of the available studies are inconclusive. Nevertheless, the product information of paracetamol-containing medicinal products should be amended in order to reflect the current state of scientific knowledge. The PRAC welcomed the intention to publish the results of the EMA's analysis in a peer-reviewed journal to help disseminate the findings and the methodological considerations.

Summary of recommendation(s)

- The MAHs for paracetamol-containing products[11] should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 90 days, a variation to amend the product information[12].

For the full PRAC recommendation, see EMA/PRAC/157165/2019 published on 08/04/2017 on the EMA website.

[10] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[11] All paracetamol-containing products independently of the route of administration/formulation
[12] Update of SmPC sections 4.6 and 5.3. The package leaflet is to be updated accordingly

4.3.5. Paracetamol (NAP)

Applicant(s): various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of paracetamol use during pregnancy and premature ductus arteriosus closure in offspring

EPITT 19297 – Follow-up to November 2018

Background

For background information, see PRAC minutes November 2018 (29-31 October 2018).

The MAHs Aurobindo, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Novartis, Sanofi, Stada and Teva replied to the request for information on the signal of paracetamol use during pregnancy and premature ductus arteriosus closure in offspring and the responses were assessed by the Rapporteur.

Discussion

Having considered all the available evidence, including non-clinical data and spontaneous reports, the PRAC concluded that there is currently insufficient evidence to establish a causal relationship between in-utero paracetamol exposure and premature ductus arteriosus closure in the offspring. Therefore, the PRAC concurred that no regulatory action is currently warranted.

Summary of recommendation(s)

- The MAHs of paracetamol-containing products should continue to monitor these events as part of routine safety surveillance.
- Premature closure/constriction of ductus arteriosus when used in third trimester of pregnancy should be added as a safety concern to be followed up in PSURs of paracetamol-containing products, and be re-evaluated in the next PSUR with a cumulative review including all available non-clinical and clinical data.

4.3.6. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/SDA/053

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of psoriasis

EPITT 19273 – Follow-up to September 2018

Background

For background information, see PRAC minutes September 2018.

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

Discussion

Having considered the available evidence from the literature, clinical trial data and spontaneous reports and epidemiological data, the PRAC agreed that the likelihood of a

causal relationship between tocilizumab and psoriasis is not sufficiently strong at this stage. Therefore, the PRAC concurred that no regulatory action is currently warranted.

Summary of recommendation(s)

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

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Angiotensin II - EMEA/H/C/004930

Scope: Treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy

5.1.2. Ciprofloxacin - EMEA/H/C/004394

Scope: Treatment of non-cystic fibrosis bronchiectasis (NCFBE) patients with chronic lung infection with *Pseudomonas aeruginosa* (*P. aeruginosa*)

5.1.3. L-lysine hydrochloride, L-arginine hydrochloride - EMEA/H/C/004541

Scope: Reduction of renal radiation exposure during peptide-receptor radionuclide therapy (PRRT) with lutetium (^{177}Lu) oxodotreotide

5.1.4. Larotrectinib - EMEA/H/C/004919, Orphan

Applicant: Bayer AG

Scope: Treatment of adult and paediatric patients with locally advanced or metastatic solid tumours

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

See also Annex I 15.2.

5.2.1. Dexamethasone - NEOFORDEX (CAP) - EMEA/H/C/004071/II/0008

Applicant: Laboratoires CTRS

PRAC Rapporteur: Ghania Chamouni

Scope: Update of the RMP (version 4.0) in order to propose the 'removal of the score line for subdivision of the 40 mg tablet and consequent deletion of the 20 mg posology' as a category 3 activity. In addition, the MAH updated the other category 3 activity on 'development of a 20 mg oral dosage form'. Furthermore, 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)

Background

Dexamethasone is a synthetic glucocorticoid indicated for the treatment of symptomatic multiple myeloma in combination with other medicinal products.

The PRAC is evaluating a type II variation procedure for Neofordex, a centrally authorised medicine containing dexamethasone, to update the RMP in order to remove a category 3 activity on the 'removal of the score line for subdivision of the 40 mg tablet and consequent deletion of the 20 mg posology' as well as to update the category 3 activity on 'development of a 20 mg oral dosage form'. 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 September 2018.

Summary of advice

- The RMP for Neofordex (dexamethasone) version 4.2 in the context of the variation procedure under evaluation is considered acceptable.
- The PRAC agreed that the MAH provided sufficient reassurance on the authorisation of a 20 mg oral dosage form in the Member States. Therefore, the PRAC agreed with the removal of the category 3 activity on the 'development of a 20 mg oral dosage form' from the RMP. With regard to the category 3 activity on the 'removal of the score line for sub-division of the 40 mg tablet, and consequent deletion of the 20 mg posology', the PRAC concluded that the MAH's rationale to remove the category 3 activity is not acceptable. It was considered that the rationale does not address at this stage the main objective of the requested activity to eliminate the possibility to break tablets and to ensure their use as one dose. The removal of this activity is to be considered at the time of approval of the appropriate variation procedures to eliminate the score line for Neofordex (dexamethasone) 40 mg tablets. Finally, the PRAC considered that the revised list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' is acceptable. The important potential risk 'medication error related to administration of 20 mg dose' should be maintained in the RMP.

5.2.2. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0068

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of the RMP (version 23.1) in order to discuss the effectiveness of the educational materials put in place for Keytruda (pembrolizumab) at the time of the initial marketing authorisation, to provide a proposal to update these materials and to revise the safety specification as requested in the outcome of the PSUR single assessment procedure (PSUSA/00010403/201803) finalised in October 2018

Background

Pembrolizumab is a humanised monoclonal antibody programmed cell death-1 (PD-1) receptor inhibitor, indicated, as Keytruda, in monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection, for the first line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) under certain conditions, for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 under certain conditions, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) under certain conditions, for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy or who are not eligible for cisplatin-containing chemotherapy and for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) and progressing on or after platinum-containing chemotherapy.

The PRAC is evaluating a type II variation procedure for Keytruda, a centrally authorised medicine containing pembrolizumab, to update the RMP in order to discuss the effectiveness of the current educational materials and to revise the safety specification as requested by PRAC in the outcome of the PSUSA procedure (PSUSA/00010403/201803) finalised in October 2018. 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 October 2018.

Summary of advice

- The RMP for Keytruda (pembrolizumab) in the context of the variation procedure under evaluation could be considered acceptable provided that an update to RMP version 23.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- In terms of safety specification, the PRAC did not support the removal of immune-related risks as, despite being reflected in the product information, they continue to require additional risk minimisation measures (aRMMs). The MAH should group immune-related adverse drug reactions (ADRs) under the umbrella term 'immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, endocrinopathies, myositis, and myocarditis)' considering the common aetiology and management strategy. With regard to the removal of important potential risks and in particular the proposal to remove the risk of gastrointestinal perforation secondary to colitis, the PRAC considered that before drawing firm conclusion, the MAH should provide a detailed review of this risk from all sources with a proposal to update the product information as warranted. The remaining important potential risks need further characterisations and are currently studied in a number of ongoing studies. Therefore these risks should remain as important potential risks in the RMP. The proposal to remove all missing information except 'long term safety' is accepted.
- In terms of aRMMs, the PRAC agreed that educational material for healthcare professionals (HCPs) is not warranted any longer in light of the knowledge gained by HCPs over time on the risk and management of immune related reactions and infusion related reactions with pembrolizumab and other immune check point inhibitors. These have become part of clinical practice through the product

information, scientific publications, treatment protocols as well as European and international guidelines. The educational material for patients should remain in place.

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

See also Annex I 15.3.

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

Applicant: Teva B.V.

PRAC Rapporteur: Ghania Chamouni

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

Background

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

The CHMP is evaluating an extension of application to add a new strength. An update to the RMP is proposed to include in particular 'medication errors related to possible confusion between the two presentations' as a new important potential risk and to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes September 2018 and PRAC minutes January 2019.

Summary of advice

- The RMP for Trisenox (arsenic trioxide) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 2.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) in order to minimise the risk of 'medication error' due to the introduction of 2mg/mL concentration. The PRAC agreed the content of the DHPC together with a communication plan.

5.3.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0065

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on

suicidality and depression based on interim results from study BEL115467 (listed in Annex II): a randomized, double-blind, placebo-controlled 52-week study to assess adverse events of special interest in adults with active, autoantibody-positive systemic lupus erythematosus receiving belimumab. The package leaflet and the RMP (version 30) are updated accordingly. In addition, the MAH is proposing a direct healthcare professional communication (DHPC) and a communication plan

Background

Belimumab is a human immunoglobulin (Ig)G1λ monoclonal antibody indicated, as Benlysta, as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy.

The CHMP is evaluating a type II variation for Benlysta, a centrally authorised product containing belimumab, in order to add a warning on suicidality and depression based on interim results from imposed study BEL115467. 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 Benlysta (belimumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 30 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) in order to warn healthcare professionals (HCPs) on the risk of depression, suicidal ideation or behaviour, self-injury. The PRAC agreed the content of the DHPC together with a communication plan.

5.3.3. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/II/0150

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on data from: 1) study 20070782: a phase 3, randomized, double-blind, placebo-controlled, non-inferiority study in subjects with chemotherapy-induced anaemia receiving multi-cycle chemotherapy for the treatment of advanced stage non-small cell lung cancer (NSCLC); 2) study EPO-ANE-3010: a randomized, open-label, multicentre, phase 3 study of epoetin alfa plus standard supportive care versus standard supportive care in anaemic patients with metastatic breast cancer receiving standard chemotherapy; 3) the company core data sheet (CCDS). In addition, section 4.6 of the SmPC is revised as requested in the outcome of the PSUR single assessment procedure (PSUSA/00000932/201710) finalised in June 2018. The package leaflet and the RMP (version 9.3) are updated accordingly. Furthermore, the MAH took the opportunity to introduce minor editorial changes, update the information on local representatives and align the product information (PI) with the QRD template (version 10.0)

Background

Darbepoetin alfa is erythropoiesis-stimulating agent (ESA) indicated, as Aranesp, for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adults

and paediatric patients and for the treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

The CHMP is evaluating a type II variation for Aranesp, a centrally authorised product containing darbepoetin alfa, in order to update the product information to address the potential risk of increased mortality and adverse tumour outcomes with ESAs in the oncology setting and warning for patients with a history of venous thromboembolic events (VTE), based on the results of studies 20070782 and EPO-ANE-3010. 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 Aranesp (darbepoetin alfa) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 9.3 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the 'risk of mortality and/or tumour progression or recurrence in patients with cancer or a history of cancer' should be maintained as a safety concern in the RMP. In addition, the MAH should discuss the way to further evaluate this risk. With regard to the pregnancy surveillance programme, the MAH should implement pregnancy-follow-up questionnaires in order to gain sufficient information regarding pregnancy cases.

5.3.4. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/II/0006, Orphan

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to optimise the starting dose of niraparib and clarify dose modification information, modify the existing warning on haematologic adverse reactions, amend the description of thrombocytopenia and amend existing efficacy and pharmacokinetics information, respectively. The changes are based on the integrated population clinical report that contains information from: 1) completed phase 3 study NOVA (submitted as part of the initial application): a phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer; 2) supportive information from ongoing study PR-30-5020-C (QUADRA): a phase 2, open-label, single-arm study to evaluate the safety and efficacy of niraparib in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received three or four previous chemotherapy regimens; 3) study 300-PN-162-01-001 (TOPACIO): a phase 1/2 clinical study of niraparib in combination with pembrolizumab (MK-3475) in patients with advanced or metastatic triple-negative breast cancer and in patients with recurrent ovarian cancer. The package leaflet and the RMP (version 1.1) are updated accordingly. The RMP is also updated in line with revision 2 of the guidance on the format of RMP in the EU (template) and the outcome of the PSUR single assessment procedure (PSUSA/00010655/201803) finalised in October 2018

Background

Niraparib is a poly(adenosine diphosphate (ADP)-ribose) polymerase (PARP) enzyme inhibitor indicated, as Zejula, in monotherapy for the maintenance treatment of adult

patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The CHMP is evaluating a type II variation for Zejula, a centrally authorised product containing niraparib on the proposal to optimise starting dose of niraparib to reduce adverse events. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see PRAC minutes December 2018 (26-29 November 2018).

Summary of advice

- The RMP for Zejula (niraparib) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 2.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- In light of the recommended change in dose due to safety reasons, the PRAC supported to request the MAH to provide a draft direct healthcare professional communication (DHPC) as an additional risk minimisation measure to inform healthcare professionals of the reduced recommended starting dose in order to optimise the safe and effective use of niraparib as well as to prevent and mitigate adverse events and medication error that may arise as a result of the product use.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Dabrafenib - TAFINLAR (CAP) - PSUSA/00010084/201808

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Dabrafenib is a RAF kinase inhibitor indicated, as Tafinlar, in monotherapy or in combination with trametinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation and in combination with trametinib for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. Dabrafenib in combination with trametinib is also indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tafinlar, a centrally authorised medicine containing dabrafenib 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 Tafinlar (dabrafenib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include severe cutaneous reactions (SCARs) as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[13].

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

The PRAC considered that the risk of SCARs could also be relevant for trametinib-containing product(s) which is used in combination with Tafinlar (dabrafenib). The MAH for trametinib-containing product(s) should update its product information as applicable.

6.1.2. Glimepiride, pioglitazone hydrochloride - TANDEMACT (CAP); metformin, pioglitazone - COMPETACT (CAP), GLUBRAVA (CAP); pioglitazone - ACTOS (CAP), GLUSTIN (CAP) - PSUSA/00002417/201807 (with RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Glimepiride is a sulfonylurea, pioglitazone a thiazolidinedione oral anti-diabetic agent and metformin a biguanide. Pioglitazone alone, as Actos and Glustin, and in combination glimepiride/pioglitazone, as Tandemact, and in combination metformin/pioglitazone, as Competact and Glubrava, are indicated for the treatment of type 2 diabetes mellitus (T2DM) under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Tandemact, Competact and Glubrava and Actos and Glustin, centrally authorised medicines containing glimepiride/pioglitazone, metformin/pioglitazone and pioglitazone, respectively 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 Tandemact (glimepiride/pioglitazone), Competact and Glubrava (metformin/pioglitazone) and Actos and Glustin (pioglitazone) in the approved indication(s) remains unchanged.
- Nevertheless, the 'conditions or restrictions with regard to the safe and effective use of the medicinal product' should be updated to remove the requirement for educational pack for healthcare professionals (HCPs) and the prescriber guide as additional risk minimisation measures as the knowledge gathered over the years amongst HCPs is considered sufficient to mitigate the relevant risk(s) in clinical

[13] 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

practice. Therefore, the current terms of the marketing authorisation(s) should be varied[14].

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

6.1.3. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201809

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Pembrolizumab is a humanised monoclonal antibody and antineoplastic agent, indicated, as Keytruda, in monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection, for the first line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) under certain conditions, for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 under certain conditions, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) under certain conditions, for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy or who are not eligible for cisplatin-containing chemotherapy and for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) and progressing on or after platinum-containing chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Keytruda, a centrally authorised medicine containing pembrolizumab 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 Keytruda (pembrolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include haemophagocytic lymphohistiocytosis as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should provide cumulative reviews of second B-cell lymphoma, acantholytic dermatosis and glomerulonephritis, taking into account all available information from studies, spontaneous sources and literature. Proposals to update the product information should be provided as warranted.

[14] Update of Annex II on 'conditions or restrictions with regard to the safe and effective use of the medicinal product'. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[15] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

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

See Annex I 16.2.

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

See also Annex I 16.2.

6.3.1. Adapalene (NAP) - PSUSA/00000058/201807

Applicant(s): various

PRAC Lead: Ronan Grimes

Background

Adapalene is a retinoid indicated for the topical treatment of acne.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing adapalene 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 adapalene-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'anaphylactic reaction', 'angioedema', 'application site burn', 'skin hyperpigmentation' and 'skin hypopigmentation' as undesirable effects with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH Galderma should provide a detailed overview of cases of 'medication error' split per geographical regions and formulations, including the over the counter (OTC) formulation available in the US. The MAHs Galderma and PharmaSwiss should also provide a cumulative review of severe burns, including a detailed description of cases that are indicative of causality and a discussion regarding aetiology.

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.

[16] Update of SmPC section 4.8. The package leaflet is updated accordingly regarding application site burn, skin hyperpigmentation and skin hypopigmentation. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.2. Alprostadil[17] (NAP) - PSUSA/00010021/201807

Applicant(s): various

PRAC Lead: Daniela Philadelphy

Scope: Evaluation of a PSUSA procedure

Background

Alprostadil is a prostaglandin E1 (PGE1) indicated to temporarily maintain the patency of ductus arteriosus until corrective or palliative surgery can be performed in neonates who have congenital heart defects.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing alprostadil 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 alprostadil-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypokalaemia as an undesirable effect with frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

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

6.3.3. Atorvastatin, ezetimibe (NAP) - PSUSA/00010385/201807

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Atorvastatin is a selective, competitive inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase and ezetimibe a lipid modifying agent. In combination, atorvastatin/ezetimibe is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease, for the reduction of elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides and non-high-density lipoprotein cholesterol, and to increase high-density lipoprotein cholesterol in patients with primary hypercholesterolemia or mixed hyperlipidaemia and for the reduction of elevated total-cholesterol and low-density lipoprotein (LDL)-cholesterol levels in patients with homozygous familial hypercholesterolemia.

[17] Indicated for maintaining the patency of the ductus arteriosus
[18] 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

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing atorvastatin/ezetimibe 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 atorvastatin/ezetimibe-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the package leaflet should be updated to include red-brown discolouration of urine as a symptom to known undesirable effects of hepatitis, hepatic failure and rhabdomyolysis. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should present a review of drug interaction with Niemann-Pick C1-like 1 (NPC1L1) protein substrates related to atorvastatin/ezetimibe and atorvastatin as a single substance and should closely monitor cases of 'lichen planus' and present any new data.
- The PRAC considered that urine discolouration is also relevant for inclusion in the package leaflet of medicinal product(s) containing atorvastatin as a single substance and all other fixed dose combination product(s). Further consideration is to be given at the level of CMDh.

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

6.3.4. Colchicine (NAP) - PSUSA/00000858/201807

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Colchicine is an anti-inflammatory agent indicated for the treatment and prophylaxis of acute gout attacks. It is also indicated in some EU countries for the treatment of acute pericarditis and prevention on recurrent pericarditis, Behcet's disease, familial Mediterranean fever, prevention of coronary heart disease and other acute attacks due to microcrystalline deposits.

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

Summary of recommendation(s) and conclusions

[19] Update of package leaflet section 4. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Based on the review of the data on safety and efficacy, the benefit-risk balance of colchicine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hepatotoxicity as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, MAHs should provide the outcomes of all pregnancy cases following colchicine exposure and submit a detailed review of all post-marketing cases of severe cutaneous adverse reactions (SCARs) associated with colchicine. In addition, the MAHs should provide a review of all cases of 'medication error' and a review of cases of intentional overdose in paediatric population (<18 years). Additionally, the MAHs should provide the number and case details of all fatal cases occurring during the reporting period as well as a causality assessment. Finally, the MAHs should closely monitor adverse events related to lichenoid eruptions.
- The PRAC considered that hepatotoxicity as an undesirable effect is also relevant for inclusion in the product information of fixed dose combination product(s) containing colchicine. Further consideration is to be given at the level of CMDh.

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

6.3.5. Everolimus[21] (NAP) - PSUSA/00010269/201807

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Everolimus is a selective mammalian target of rapamycin (mTOR) inhibitor indicated[22] for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant and in patients receiving a hepatic transplant.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing everolimus in these indication(s) 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 everolimus-containing medicinal products in the approved indication(s) [23] remains unchanged.

[20] 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
[21] Indicated for the prevention of rejection of transplanted organs only
[22] Indicated for the prevention of rejection of transplanted organs only
[23] Indicated for the prevention of rejection of transplanted organs only

- Nevertheless, the product information should be updated to include lymphoedema as an undesirable effect with frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should include a detailed review of pregnancy outcome, including pregnancies with paternal everolimus exposure.

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

6.3.6. Montelukast (NAP) - PSUSA/00002087/201807

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Montelukast is a selective leukotriene antagonist indicated for the treatment of asthma as add-on therapy in patients with mild to moderate persistent asthma, and for the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing montelukast 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 montelukast-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on neuropsychiatric events. In addition, dysphemia should be added as an undesirable effect with frequency 'very rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[25].

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

[24] 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
[25] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.4.1. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/LEG 010.2

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to LEG 010.1 [overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the effectiveness of each measure in place to minimise any risk (including educational material and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017] as per the request for supplementary information (RSI) adopted in September 2018

Background

Bosentan is a dual endothelin receptor antagonist (ERA) indicated, as Stayveer, for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO[26] functional class III, as well as to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit a detailed description of the educational materials with the controlled distribution systems implemented at national levels in order to assess the effectiveness of each measure in place to minimise any risk, and hence measure whether the risk minimisation measures (RMMs) in place are still relevant. Following assessment, the PRAC requested the MAH to submit a variation to update Annex II in order to delete from the additional risk minimisation measures (aRMMs) the requirement to distribute a prescriber kit to healthcare professionals (HCPs). For further background, see PRAC minutes July 2017, PRAC minutes February 2018 and PRAC minutes September 2018. In December 2018, the MAH submitted responses to justify the non-submission of the requested variation. These responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 60 days, a variation[27] to update Annex II on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to delete from the aRMMs the requirement to distribute a prescriber kit to HCPs as these have been implemented for a long period of time and it is considered that HCPs are well trained and aware of the management of the risks of bosentan-containing product(s). In addition, some RMMs have become part of standard clinical practice and are no longer necessary in view of the knowledge gained over the years. Nevertheless, the PRAC advised to maintain the patient alert card as it is a significant tool to ensure that patient are aware of the risk of hepatotoxicity and the recommendation for adequate use of contraceptive method.

6.4.2. Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/LEG 086.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

[26] World Health Organization
[27] Annex II. The RMP is to be updated accordingly

Scope: MAH's response to LEG 086.1 [overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the effectiveness of each measure in place to minimise any risk (including educational material and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017] as per the request for supplementary information (RSI) adopted in September 2018

Background

Bosentan is a dual endothelin receptor antagonist (ERA) indicated, as Tracleer, for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO[28] functional class III, as well as to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit a detailed description of the educational materials with the controlled distribution systems implemented at national levels in order to assess the effectiveness of each measure in place to minimise any risk, and hence measure whether the risk minimisation measures (RMMs) in place are still relevant. Following assessment, the PRAC requested the MAH to submit a variation to update Annex II in order to delete from the additional risk minimisation measures (aRMMs) the requirement to distribute a prescriber kit to healthcare professionals (HCPs).. For further background, see PRAC minutes July 2017, PRAC minutes February 2018 and PRAC minutes September 2018. In December 2018, the MAH submitted responses to justify the non-submission of the requested variation. These responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice / conclusion(s)

- The MAH should submit to EMA, within 60 days, a variation[29] to update Annex II on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to delete from the aRMMs the requirement to distribute a prescriber kit to HCPs as these have been implemented for a long period of time and it is considered that HCPs are well trained and aware of the management of the risks of bosentan-containing product(s). In addition, some RMMs have become part of standard clinical practice and are no longer necessary in view of the knowledge gained over the years. Nevertheless, the PRAC advised to maintain the patient alert card as it is a significant tool to ensure that patient are aware of the risk of hepatotoxicity and the recommendation for adequate use of contraceptive method.

6.4.3. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/LEG 014

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Review of cases of meningioma associated with estradiol/nomegestrol use including a thorough discussion on whether the individual dose of each component and interactions between oestrogens and progestogens could limit the extrapolation from nomegestrol monocomponent to Zoely (estradiol/nomegestrol acetate) in relation to this

[28] World Health Organization
[29] Annex II. The RMP is to be updated accordingly

risk, as requested in the conclusions of PSUSA/00002182/201801 adopted in October 2018

Background

Nomegestrol acetate is a progestogen and estradiol is a natural oestrogen identical to the endogenous human 17β-estradiol. In combination, estradiol/nomegestrol acetate is indicated, as Zoely, for oral contraception.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on cases of meningioma associated with estradiol/nomegestrol use including a thorough discussion on whether the individual dose of each component and interactions between oestrogens and progestogens could limit the extrapolation from nomegestrol monocomponent to Zoely (estradiol/nomegestrol acetate) in relation to this risk. For further background, see PRAC minutes October 2018. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice / conclusion(s)

- The MAH should submit to EMA, within 60 days, a variation to update the product information to include a contraindication regarding the presence or history of meningiomas, and a warning on the occurrence of meningiomas. In addition, as the risk of meningioma is not yet fully characterised with this fixed dose combination and it could have an impact on the risk-benefit balance, the MAH should include this risk in the summary of safety concern involving the use of specific adverse reaction follow-up questionnaires. Moreover, the MAH should include the risk of meningioma as an important potential risk in the RMP.

6.4.4. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/LEG 027

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Reviews of cases of ‘medication errors’, ‘vomiting’ and ‘blurred vision’ as requested in the conclusions of PSUSA/00003103/201802 adopted in October 2018

Background

Velaglucerase alfa is a glycoprotein indicated, as Vpriv, for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on ‘medication errors’, cases where ‘vomiting’ is reported as well as a cumulative review of cases of ‘blurred vision’. For further background, see PRAC minutes October 2018. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice / conclusion(s)

- The MAH should submit to EMA, within 60 days, a variation to update the product information to include ‘blurred vision’ within the existing warning on infusion-related reactions as well as vomiting and vision blurred as undesirable effects with frequency ‘uncommon’.

- In the next PSUR (data lock point (DLP): 25/02/2020), the MAH should provide detailed information on patient characteristics as available from the distribution sources, including age, weight, dosing scheme and reported adverse events (AEs) together with the time to onset for the documented AEs from the patient's logbook or from the distribution sources. In addition, the MAH should provide further information whether there are intended or unintended deviations from the authorised dosing scheme based on available information.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[30]

See also Annex I 17.1.

7.1.1. Radium (Ra223) dichloride - XOFIGO (CAP) - EMEA/H/C/PSP/S/0076

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Protocol for a PASS to estimate the incidence rate of symptomatic bone fractures among users of Xofigo (Ra-223) in routine clinical practice

Background

Xofigo is a centrally authorised medicine containing radium (Ra223) dichloride, a radiopharmaceutical. Xofigo (radium (Ra223) dichloride) is indicated in monotherapy or in combination with luteinising hormone releasing hormone analogue for the treatment of castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

Following the recent referral procedure under Article 20 of Regulation (EC) No 726/2004 for Xofigo (radium-223 dichloride) completed in 2018, the obligation to conduct a PASS was imposed as a condition to the marketing authorisation(s) of Xofigo (radium-223 dichloride) in order to further characterise its safety and efficacy. For background information, see PRAC minutes July 2018.

In order to fulfil the obligation to conduct the study, the MAH Bayer AG submitted a protocol for the PASS entitled 'PRECISE, rates of bone fractures and survival in castration-resistant prostate cancer (CRPC) patients treated with radium-223 in routine clinical practice in Sweden' for review by the PRAC.

Endorsement / Refusal of the protocol

- The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol as the Committee considered that that the design of the study does not fulfil the study objectives at this stage.
- The MAH should revise the protocol to align the objectives with the findings of study ERA-223[31], include a suitable comparison group to allow the assessment whether

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

fractures and mortality occur more frequently as a result of the exposure to radium (Ra223) dichloride as well as discuss how similar the Prostate Cancer data Base Sweden (PCBaSe) patient population is to the patients from respective clinical trials (ALSYMPCA[32] and ERA-223). In addition, the MAH should consider extending the follow-up period to increase the sample size, further clarify the definitions of exposure and outcome and to include both symptomatic and asymptomatic fractures for the main analysis as well as collect information on the cause of death to allow the analyses on mortality among users of Xofigo (radium (Ra223) dichloride). Furthermore, the MAH should include the number of previous fractures, number of metastases, time since detection of first metastases and number of symptomatic skeletal events (SEE) as baseline covariates and the MAH should a priori define which co-variates will be used for stratification of incidence rates. Moreover, the MAH should provide more details on criteria of feasibility to conduct the study in various databases.

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be followed.

7.1.2. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/PSP/S/0077

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a study evaluating the long-term safety of Adynovi (rurioctocog alfa pegol) in adults and adolescents ⩾12 years of age with haemophilia A

Background

Adynovi is a centrally authorised medicine containing rurioctocog alfa pegol, a pegylated recombinant human factor VIII. Adynovi (rurioctocog alfa pegol) is indicated for the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).

In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Baxalta Innovations GmbH submitted a protocol for a PASS entitled: 'evaluation of long-term safety of Adynovi/Adynovate (antihaemophilic factor [recombinant] PEGylated, rurioctocog alfa pegol) in adults and adolescents ≥12 years of age with haemophilia A' for review by the PRAC.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol, as the Committee considered that the design of the study does not fulfil the study objectives at this stage.
- The PRAC recommended that the MAH includes annual interim reports as milestones and revises the primary objective to: 'assess the long term safety of prophylaxis with

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

[32] ALSYMPCA: a double-blind, randomised, multiple dose, phase 3, multicentre study of alpharadin in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases. NCT00699751. EudraCT number: 2007-006195-11

Adynovi/Adynovate in patients with haemophilia A in the real-world setting through the collection and analysis of adverse events (AEs) of special interest potentially indicative of PEG[33] accumulation, AEs, serious adverse events (SAEs), and adverse reactions (ARs)'. In addition, the PRAC recommended including as a secondary objective 'to monitor the clinical effects of long-term exposure of prophylaxis with Adynovi/Adynovate in patients with haemophilia A, including assessments of kidney and liver function parameters, neurological function, and patients' PEG plasma levels'. Furthermore, the MAH should revise the inclusion and exclusion criteria to ensure similar data collection for recently approved pegylated coagulation factors and should discuss which measures will be taken to assure completeness of data collection. The MAH is requested to discuss how data regarding PEG plasma levels will be obtained. Furthermore, the MAH should provide further information on the statistical analysis methods, stratification of data and adjustment for confounders.

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[34]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[35]

See Annex I 17.3.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[36]

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

[33] Polyethylene glycol
[34] 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
[35] In accordance with Article 107p-q of Directive 2001/83/EC
[36] 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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Ibrutinib – IMBRUVICA (CAP) – EMEA/H/C/003791/II/0048

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Update of section 4.4 of the SmPC in order to add a warning under 'bleeding-related events' based on the final clinical study report results for study PCYC-PMR-2060-4 (listed as a category 3 study in the RMP): a non-interventional PASS exploring the risk of serious haemorrhage. In addition, the MAH took the opportunity to include minor editorial changes in the list of local representatives in the package leaflet

Background

Ibrutinib is an orally administered small-molecule inhibitor of Bruton's tyrosine kinase indicated, as Imbruvica, for the treatment of adult patients with relapsed or refractory mantle cell lymphoma, adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and adult patients with Waldenström's macroglobulinaemia under certain conditions. It is also indicated, alone or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

A type II variation proposing to update the product information of Imbruvica (ibrutinib) on the risk of major haemorrhages is under evaluation at the CHMP (II/0048). This variation assesses the outcome of a non-interventional PASS evaluating the risk of major haemorrhage with ibrutinib, conducted as an additional pharmacovigilance activity. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC considered that the current data are limited and insufficient to justify the proposal from the MAH to remove the recommendation against concomitant use of warfarin or other vitamin K antagonists with Imbruvica (ibrutinib) as part of the product information on 'special warnings and precautions for use'[37].
- The PRAC advised that the current product information wording should be maintained until further data on patients with concomitant vitamin K antagonists becomes available. In addition, the PRAC supported to request the MAH to repeat the analysis of aggregate clinical study data in the near future once more recent clinical data becomes available. The inclusion of data on different populations, e.g. patients with concomitant use of anti-platelet agents into this analysis, is advised.
- The PRAC agreed that the current pharmacovigilance activities and risk minimisation measures are sufficient to minimise the risk of the medicinal product in the approved indications.

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

None

10.3. Other requests

None

[37] SmPC section 4.4

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Carbetocin (NAP) - UK/H/PSUFU/000546/201706

Applicant(s): Ferring Pharmaceuticals (Pabal 100 micrograms/ml solution for injection), Laboratorios GP Pharm (Carbetocin 100 micrograms solution for injection in pre-filled syringe)

PRAC Lead: Julie Williams

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on the review of the risk of myocardial ischaemia, arrhythmia and angina pectoris and on the review of the risk of anaphylaxis in patients with latex allergy as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on carbetocin (PSUSA/00000546/201706) concluded in March 2018, on request of the United Kingdom

Background

Carbetocin is a synthetic long-lasting oxytocin agonistic analogue which binds selectively to oxytocin receptors in the smooth muscle of the uterus and is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by caesarean section (CS) under epidural or spinal anaesthesia.

Based on the assessment of the PSUR single assessment (PSUSA) procedure for carbetocin (PSUSA/00000546/201706) concluded in March 2018, the PRAC considered that the risk of myocardial ischaemia, arrhythmia and angina pectoris and the risk of anaphylaxis in patients with latex allergy needed to be further assessed. For further background, see PRAC minutes March 2018. The MAH(s) for carbetocin-containing product(s) were requested by CMDh to submit cumulative reviews and characterisation of the risk of myocardial ischaemia, arrhythmia and angina pectoris and the risk of anaphylaxis in patients with latex allergy, as a worksharing PSUR follow-up (PSU FU) procedure. In the context of the evaluation of the worksharing PSU FU procedure on these reviews (UK/H/PSUFU/000546/201706), the United Kingdom as lead Member State (LMS) requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions of the LMS and concurred that the product information of carbetocin-containing

product(s) should be updated to include tachycardia as an undesirable effect[38] with a frequency 'not known' causally associated with carbetocin and to also list several cardiac disorders as having been reported with oxytocin to which carbetocin is structurally related. Regarding the risk of anaphylaxis in patients with latex allergy, the PRAC agreed with the LMS that the current evidence is insufficient to support a causal association with carbetocin. Therefore, no update of the product information is warranted at this stage.

- The PRAC supported to request the MAH(s) to provide in the next PSUR (data lock point (DLP): 30/06/2022) cumulative reviews of all cases of bradycardia, arrhythmia, myocardial ischaemia and QT prolongation as well as a cumulative review of all cases of hypersensitivity reactions and anaphylaxis, including all case narratives, as well as a discussion whether an update to the product information is warranted. Moreover, the MAH(s) should provide reviews of all available data regarding uterine hypertonus, tetanic contractions of uterus and the rupture of uterus and hyponatraemia and water intoxication, including all cases narratives and stratification by carbetocin dose, together with a discussion whether an update of the product information is warranted.

11.2.2. Levonorgestrel (NAP) - DE/H/PSUFU/00001856/201712/I

Applicants: Bayer AG (Mirena, Jaydess/Luadei, Kyleena), Mithra Pharmaceuticals (Levosert)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on detailed analyses on the effectiveness of the current educational material for levonorgestrel-containing intrauterine device (IUDs) and reviews of the educational material safety concerns and key elements' as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on levonorgestrel (PSUSA/00001856/201712) concluded in September 2018, on request of Germany

Background

Levonorgestrel is a second generation progestin (synthetic progesterone) indicated in oral contraception, heavy menstrual bleeding (hypermenorrhea, idiopathic menorrhagia) and emergency contraception. It is also indicated in some EU Member States for the protection from endometrial hyperplasia during oestrogen replacement therapy.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure on levonorgestrel (PSUSA/00001856/201712) concluded in September 2018, the PRAC considered that the effectiveness and necessity of the currently available educational materials for levonorgestrel-containing intrauterine device (IUDs) should be re-evaluated. For further background, see PRAC minutes September 2018. The concerned MAH(s) for levonorgestrel-containing product(s) were requested by CMDh to submit detailed analyses on the effectiveness of the current educational material for levonorgestrel-containing IUDs and reviews of the educational material safety concerns and key elements, as a worksharing PSUR follow-up (PSU FU) procedure. In the context of the evaluation of the worksharing PSU FU procedure (DE/H/PSUFU/00001856/201712/I), Germany as lead Member State (LMS) requested PRAC advice on its assessment.

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

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions of the LMS and concurred that an update of existing RMP or a RMP for the medicinal product(s) with none in place should be submitted to the relevant National Competent Authorities (NCAs) of the Member States for all levonorgestrel-containing IUDs, within 180 days of the finalisation of this PSU FU procedure to reflect the changes/requirements in relation to additional risk minimisation measures for the important identified risk of ectopic pregnancy and important potential risk of medication errors. The PRAC supported the implementation of a healthcare professional brochure with agreed defined key elements for all levonorgestrel-containing IUDs with the aim to minimise the risk of ectopic pregnancy and the risk of medication error in order to better distinguish features and/or avoid inadvertent mix ups between different levonorgestrel-containing IUD products. Additionally, the PRAC supported the development and implementation of a patient reminder card, with agreed defined key elements, to be delivered with every package for all levonorgestrel-containing IUDs, unless other measures to capture and convey this information to patients are already in place at the national levels. This is to be agreed with the respective National Competent Authorities (NCAs).

11.2.3. Levonorgestrel (NAP) - DE/H/PSUFU/00001856/201712/II

Applicants: Bayer AG (Mirena, Jaydess/Luadei, Kyleena), Mithra Pharmaceuticals (Levosert)

PRAC Lead: Martin Huber

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on detailed analyses of the 'risk of expulsion of levonorgestrel-containing intrauterine device (IUDs) in obese women' as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on levonorgestrel (PSUSA/00001856/201712) concluded in September 2018, on request of Germany

Background

Levonorgestrel is a second generation progestin (synthetic progesterone) indicated in oral contraception, heavy menstrual bleeding (hypermenorrhea, idiopathic menorrhagia) and emergency contraception. It is also indicated in some EU Member States for the protection from endometrial hyperplasia during oestrogen replacement therapy.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure on levonorgestrel (PSUSA/00001856/201712) concluded in September 2018, the PRAC considered that the risk of expulsion of levonorgestrel-containing intrauterine device (IUDs) in obese women should be further assessed. For further background, see PRAC minutes September 2018. The concerned MAH(s) for levonorgestrel-containing product(s) were requested by CMDh to submit cumulative reviews and characterisation of the risk of expulsion of levonorgestrel-containing IUDs in obese women, as a worksharing PSUR follow-up (PSU FU) procedure. In the context of the evaluation of the worksharing PSU FU procedure (DE/H/PSUFU/00001856/201712/II), Germany as lead Member State (LMS) requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions of the LMS and agreed that further assessment of the risk of expulsion of levonorgestrel-containing IUDs in obese women is warranted once the final data from the post-marketing study APEX IUD[39] required by FDA become available. In light of the new data the MAH(s) should discuss any risk factors which could be associated with an increased risk of expulsion and discuss whether an update of the product information is warranted.
- The PRAC agreed with the LMS conclusions to request the MAH Bayer to submit as part of a work-sharing variation the final report of the APEX-IUD study and to discuss the need for an update of the product information.

11.2.4. Tramadol (NAP) - UK/H/PSUFU/00003002/201705

Applicants: various

PRAC Lead: Julie Williams

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on the review of cases of anorgasmia reported with tramadol therapy as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on tramadol (PSUSA/00003002/201705) concluded in January 2018, on request of the United Kingdom

Background

Tramadol is an opioid analgesic indicated for the treatment of moderate to severe pain.

Based on the assessment of the PSUR single assessment (PSUSA) procedure for tramadol (PSUSA/00003002/201705) concluded in January 2018, the PRAC considered that cases of anorgasmia reported with tramadol therapy required further investigation. For further background, see PRAC minutes January 2018. The MAH(s) for tramadol-containing product(s) were requested by CMDh to submit cumulative reviews and characterisation of the risk of anorgasmia, as a worksharing PSUR follow-up (PSU FU) procedure. In the context of the evaluation of the worksharing PSU FU procedure (UK/H/PSUFU/00003002/201705) on cases of anorgasmia, the United Kingdom as lead Member State (LMS) requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions of the LMS and concurred that at present, there is insufficient evidence to support a causal association between administration of tramadol and onset of anorgasmia. The PRAC concurred that no changes to the product information were warranted at this stage. The PRAC also agreed with the LMS conclusions that anorgasmia in patients receiving tramadol should be kept under close monitoring and should be re-evaluated in the next PSUR (data lock point (DLP): 22/05/2020), in the context of a wider cumulative review of cases of sexual dysfunction.

[39] A study on the association of uterine perforation and intrauterine device (IUD) expulsion with breastfeeding status at the time of IUD insertion and postpartum timing of IUD insertion in electronic medical record databases

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Brexit – Rapporteurship transfer and EMA knowledge sharing package to support UK portfolio transfer

In the context of the regular status updates to Committees on 'Brexit preparedness business continuity plan including Committees' operational preparedness activities in view of the withdrawal of the UK from the European Union' (for further background, see PRAC minutes May 2018 and PRAC minutes December 2018 (26-29 November 2018)), the EMA Secretariat presented to PRAC further instructions for accessing the 'knowledge sharing package to support UK portfolio transfer'. The reallocation of UK PRAC Rapporteurship and Leads was noted.

12.4.2. Handling of confidential information within the EU network

The EMA Secretariat reminded the PRAC of the best practice for sharing information within the EU network and of the recommended tools to safeguard the confidentiality of the shared information.

12.4.3. PRAC Strategic Review and Learning Meeting (SRLM) under the Romanian presidency of the European Union (EU) Council – Bucharest, Romania, 22-23 May 2019 - agenda

PRAC lead: Roxana Stroe, Alexandra Spurni

The PRAC was presented with a consolidated agenda for the 'PRAC strategic review and learning meeting (SRLM)', to be held jointly with the Co-ordination Group for Mutual Recognition and Decentralised procedures - Human (CMDh), on 22-23 May 2019 in Bucharest, under the Romanian presidency of the Council of the EU.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

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.

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list, version March 2019, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting in March 2019, the updated EURD list was adopted by the CHMP and CMDh at their March 2019 meetings and published on the EMA website on 03/04/2019, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

The PRAC noted that the March 2019 meeting of the working group was cancelled. The PRAC was updated on the practical preparations regarding the knowledge transfer for substances with the UK as Lead Member states (LMS) to other MSs due to the UK's planned withdrawal from the European Union.

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 27/03/2019 on the EMA website (see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[40]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[41].

14.2. New signals detected from other sources

14.2.1. Levomethadone (NAP), methadone (NAP)

Applicant(s): various

PRAC Rapporteur: Ronan Grimes

Scope: Signal of opioid toxicity in infants exposed to levomethadone and/or methadone via breast milk

EPITT 19372 – New signal

Lead Member State(s): AT, IE

14.2.2. Natalizumab – TYSABRI (CAP)

Applicant(s): Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of psoriasis

EPITT 19365 – New signal

Lead Member State(s): DE

14.2.3. Pirfenidone – ESBRIET (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of hyponatraemia

EPITT 19373 – New signal

Lead Member State(s): UK

14.2.4. Pirfenidone – ESBRIET (CAP)

Applicant(s): Roche Registration GmbH

[40] 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

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

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of herpes viral infections

EPITT 19374 – New signal

Lead Member State(s): IE, UK

14.2.5. Tocilizumab – ROACTEMRA (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

EPITT 19360 – New signal

Lead Member State(s): DE

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. Posaconazole - EMEA/H/C/005028

Scope: Treatment of fungal infections in adults

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. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0023

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Update of the RMP (version 11.0) in order to reclassify and/or rename the known safety concerns associated with the use of Otezla (apremilast) in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

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

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

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

15.2.3. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/II/0015

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 2.0) in order to revise the objectives, address the safety concerns and the milestones for study ARCANGELO (listed as a category 3 study in the RMP): a multicentre, retrospective, observational study of patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor (Italian prospective study on cangrelor). The protocol synopsis of the PASS is included in the Annex to the RMP. In addition, the RMP and the list of safety concerns are revised in line with revision 2 of the guidance on the format of RMP in the EU (template)

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

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

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

15.2.5. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP) - EMEA/H/C/000703/II/0081

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 13.1) in order to update the list of safety concerns by removing all remaining important identified and potential risks and missing information in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.2.6. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0099

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 5.1) in order to add study 20160176 (listed as category 3 in the RMP): a retrospective cohort study of female breast cancer patients aged 66 years and over selected from the US Surveillance, Epidemiology and End Results (SEER)-Medicare database to investigate the association between granulocyte colony stimulating factor (G-CSF) use and myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML), as a new pharmacovigilance activity. In addition, the MAH submitted a draft protocol for study 20160176

15.2.7. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0028

Applicant: Amgen Europe B.V., ATMP[42]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 4.0) in order to reflect changes in the categorisation of safety concerns and missing information in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.3. 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. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/X/0019/G

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to introduce a new presentation of 40 mg/0.8 mL solution for injection in vials, to allow the administration to paediatric patients requiring less than a full 40mg dose; 2) update of the product information for the pre-filled syringe (EU/1/17/1216/001-004) and pre-filled pen (EU/1/17/1216/005-008) presentations in line with the dosage regimen changes introduced with the extension application. The RMP (version 3.0) is updated accordingly. In addition, the applicant took the opportunity to implement minor editorial changes in Module 3.2. Quality - Product

[42] Advanced therapy medicinal product

15.3.2. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0064/G

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of section 4.4 of the SmPC in order to add a warning on pulmonary events based on post-marketing data. The package leaflet is updated accordingly. Consequently, the important potential risks and the list of target medical events in the RMP (version 4.6) are updated to include pulmonary events and a specific follow-up questionnaire is introduced. The RMP is also revised in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the due date for submission of the final study report for study Sobi ANAKIN-302 (listed as a category 3 in the RMP): 'a non-interventional study to follow-up long term safety including macrophage activation syndrome (MAS) in paediatric patients with Still's disease (PRINTO/Pharmachild registry)' is proposed to be extended. Furthermore, the MAH took the opportunity to move the text about MAS and malignancies from section 4.8 to section 4.4 of the SmPC

15.3.3. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/II/0017

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Update of section 4.4 of the SmPC in order to add a warning on the risk of anaphylactic reaction and update the safety information following a safety review. The package Leaflet and the RMP (version 2.0) are updated accordingly

15.3.4. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/II/0043

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Update of section 4.2 of the SmPC in order to provide dosing recommendations for a high-dose regimen of ceftaroline fosamil in paediatric patients from 2 months to less than 18 years of age for the treatment of complicated skin and soft tissue infections (cSSTI) for which *Staphylococcus aureus* is known or suspected of having minimum inhibitory concentrations (MIC) of 2 or 4 mg/L based on the final study report of extrapolation study PMAR-EQDD-C266b-DP4-826. The RMP (version 18.0) is updated accordingly

15.3.5. Ceftolozane, tazobactam - ZERBAXA (CAP) - EMEA/H/C/003772/II/0020

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of nosocomial pneumonia, including ventilator associated pneumonia for Zerbaxa (ceftolozane/tazobactam) based on results from study CXA-NP-11-04 (PN008): a prospective, randomised, double-blind, Phase 3 Study to assess the safety and efficacy of intravenous ceftolozane/tazobactam compared with meropenem in adult patients with ventilated nosocomial pneumonia. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated.

The package leaflet and the RMP (version 2.1) are updated accordingly. The MAH also took the opportunity to implement editorial changes in sections 5.2 of the SmPC and to bring section 4.4 of the SmPC and section 2 of the package leaflet in line with the latest Annex to the European Union (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.6. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/II/0062/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of section 4.4 of the SmPC to provide additional information on switching from etelcalcetide to Mimpara (cinacalcet) as requested by PRAC in the conclusions of the PSUR single assessment procedure for etelcalcetide (PSUSA/00010533/201711) adopted in May 2018; 2) update of section 6.1 of the SmPC to replace the term 'silica, dental type' by 'amorphous silicon dioxide'. The RMP is updated (version 9.0) in order to reflect changes in the categorisation of safety concerns in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.7. Collagenase clostridium histolyticum - XIAPEX (CAP) - EMEA/H/C/002048/II/0107

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update the efficacy and safety information following the final results from study AUX-CC-810 (listed as a category 3 study in the RMP): a long-term safety, curvature deformity, characterisation, and immunogenicity over time in subjects previously treated with collagenase clostridium histolyticum (AA4500) for Peyronie's disease in the following studies: 1) study AUX-CC-802: an open-label 9-month phase 3 study including patients with Peyronie's disease from the EU; 2) study AUX-CC-803: a multicentre 12-month phase 3 study including patients with Peyronie's disease from the United States; 3) study AUC-X-CC-804: a multicentre 12-month phase 3 study including patients with Peyronie's disease from Australia; 4) study AUX-CC-806: an open-label phase 3 study to support the results of studies AUX-CC-803 and AUX-CC-804. The RMP (version 14.1) is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to SmPC and package leaflet

15.3.8. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/II/0009/G

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update the safety information based on results from pharmacokinetic (PK) study ELX-PK-01 (listed as a category 3 study in the RMP): a single-dose, open-label, PK study of eluxadoline in healthy subjects with normal renal function and patients with renal impairment; 2) update of sections 4.4 and 4.8 of the SmPC following an update of the company core data sheet (CCDS) based on the review of clinical safety

data and post-marketing safety data. In addition, the MAH took the opportunity to introduce minor changes throughout the SmPC, in particular the MAH updated section 4.3 to add clarification in line with section 4.4 as well as section 5.1 to add the pharmacotherapeutic group and anatomical therapeutic chemical (ATC) code. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.9. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS1461/0017; Linagliptin - TRAJENTA (CAP) - EMEA/H/C/002110/WS1461/0035 Linagliptin, metformin - JENTADUETO (CAP) - EMEA/H/C/002279/WS1461/0047

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC to update the warnings related to acute pancreatitis and bullous pemphigoid as well as the efficacy and safety information based on the final results from study CARMELINA (listed as a category 3 study in the RMP): a multicentre, international, randomised, parallel group, double blind, placebo-controlled CArdiovascular Safety & Renal Microvascular outcomE study with LINAgliptin, 5 mg once daily in patients with type 2 diabetes mellitus (T2DM) at high vascular risk. The RMP is updated accordingly (Trajenta and Jentadueto version 12, Glyxambi version 4.0) and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.10. Fluciclovine (^{18}F) - AXUMIN (CAP) - EMEA/H/C/004197/II/0011

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include diagnosis and continuing assessment of glioma in adult patients. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 5.1, 5.2 and 11 of the SmPC and Annex II are updated. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.11. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - GARDASIL (CAP) - EMEA/H/C/000703/II/0080

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to update the information related to the effectiveness and immunogenicity of the immune response of Gardasil (human papillomavirus vaccine [types 6, 11, 16, 18]) based on the final results from the long-term follow-up of study V501-P015-21 (listed as a category 3 study in the RMP): study designed to evaluate the effectiveness, immunogenicity and safety of the quadrivalent human papillomavirus (qHPV) vaccine for at least 10 years. The package leaflet is updated accordingly. The RMP (version 12.1) is also updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH is taking the opportunity to implement minor editorial changes in the product information (SmPC, labelling and package leaflet)

15.3.12. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/X/0062

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension application to introduce a solution for injection as a new pharmaceutical form, 120 mg as a new strength and subcutaneous use as a new route of administration. The RMP (version 9.1) is updated accordingly

15.3.13. 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

15.3.14. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0014/G, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of 1) submission of the final report of progression free survival (PFS) in fulfilment of study C16019 (SOB004): a phase 3, randomized, placebo-controlled, double-blind study of oral ixazomib citrate maintenance therapy in patients with multiple myeloma following autologous stem cell transplant; 2) request for an extension of the due date for study C16014 (SOB003): a phase 3, randomized, double-blind, multicentre study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma (NDMM). As a result, Annex II is amended. The RMP (version 4.0) is updated accordingly

15.3.15. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0102/G, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped applications consisting of: 1) extension of indication to include the treatment in combination with bortezomib and dexamethasone of adult patients with

previously untreated multiple myeloma; 2) addition of 7-capsule pack sizes for the 7.5 mg, 20 mg and 25 mg strengths of Revlimid (lenalidomide) to support the proposed posology and lenalidomide dose modification. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated. The package leaflet and the RMP (version 36.1) are updated accordingly. Additionally, minor editorial changes are introduced throughout the product information and Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' on key elements of the risk minimisation measures (RMM) to include information on timing of blood and semen donation in line with section 4.4 of the SmPC

15.3.16. Liraglutide - VICTOZA (CAP) - EMEA/H/C/001026/II/0049

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of children and adolescents (age 10-17 years) with type 2 diabetes mellitus (T2DM) based on results from 1) study NN2211-1800: a phase 1 clinical pharmacology, multicentre, randomised, double-blind placebo controlled trial, and 2) study NN2211-3659: a phase 3a efficacy and safety, multicentre, randomised, parallel group, placebo controlled trial with a 26-week double blind period followed by a 26-week open label period (main part). 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 30) are updated accordingly. Furthermore, the MAH took the opportunity to include a warning on sodium in section 4.4 of the SmPC and the package leaflet in line with the revised European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.17. Macitentan - OPSUMIT (CAP) - EMEA/H/C/002697/II/0029, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), based on: 1) pivotal study MERIT-1 (AC-055E201): a prospective, randomized, placebo-controlled, double-blind, multicentre, parallel-group, 24-week study to assess the efficacy, safety and tolerability of macitentan in subjects with inoperable CTEPH; 2) 6 months of efficacy and safety data (cut-off date 17 October 2017) from its ongoing open-label extension study MERIT-2 (AC-055E202): a long term, multicentre, single-arm, open-label extension study of the merit-1 study, to assess the safety, tolerability and efficacy of macitentan in subjects with inoperable CTEPH; 3) drug-drug interaction (DDI) study AC-055-122: a single-centre, open-label, one-sequence, two-treatment study to investigate the effect of macitentan at steady state on the pharmacokinetics (PK) of rosuvastatin in healthy male subjects; 4) DDI study AC-055-123: a single-centre, open-label, one-sequence, two-treatment study to investigate the effect of macitentan at steady state on the PK of riociguat in healthy male subjects; 5) observational data from the OPUS registry (OPsumit USers Registry; cut-off date of 17 April 2018): safety and tolerability of macitentan in a real-world setting. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 are updated. The package leaflet and the RMP (version 9.2) are updated accordingly. In addition, the MAH took the opportunity to implement editorial changes, to align the annexes with the latest QRD

template and to update the contact details of the local representatives in the package leaflet

15.3.18. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0021

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information based on the final results from study 200363 part B and two open label extension (OLE) studies namely study 201312 and study MEA115666 (listed as category 3 studies in the RMP). These are interventional PASS conducted to assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to patients aged 6 to 11 years old with severe eosinophilic asthma (study 200363 Part B), to describe the long-term safety profile of mepolizumab (MEA115666), and to provide extended treatment to subjects from study MEA115661 and further describe long-term safety in these subjects (study 201312). The RMP (version 5.0) is updated accordingly and brought in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.19. Netupitant, palonosetron - AKYNZEO (CAP) - EMEA/H/C/003728/X/0018

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Extension application to introduce the new pharmaceutical form 'powder for concentrate for solution for infusion' and a new strength for the fixed combination of fosnetupitant (pro-drug of netupitant)/palonosetron of 235 mg/0.25 mg, to be administered intravenously (new route of administration). The RMP (version 2.4) is updated accordingly

15.3.20. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0060/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of an update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include information from the following studies: 1) study CA209171: a phase 2, single-arm, open-label, multicentre clinical trial with nivolumab monotherapy in subjects with advanced or metastatic squamous (Sq) cell non-small cell lung cancer (NSCLC) who have received at least one prior systemic regimen for the treatment of stage IIIb/IV Sq NSCLC; 2) study CA209172: a phase 2, single-arm, open-label, multicentre clinical trial with nivolumab monotherapy in subjects with histologically confirmed stage III (unresectable) or stage IV melanoma progressing after prior treatment containing an anti-CTLA-4 monoclonal antibody. In addition, the MAH took the occasion to update Annex II to reflect the already fulfilled requirement regarding biomarkers data (ANX 005.3, ANX 006, ANX 023, ANX 024, ANX 026 and ANX 027). The RMP (version 13.4) is updated accordingly

15.3.21. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/II/0093

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.6 of the SmPC based on the data from the Xolair Pregnancy Registry (EXPECT): an observational study of the use and safety of Xolair (omalizumab) during pregnancy; and the final study report for study Q2952g (listed as a category 3 study in the RMP): an observational study to evaluate pregnancy outcomes and estimate the incidence of spontaneous foetal loss in pregnant women exposed to omalizumab prenatally and to explore the potential risk to newborn infants exposed via breast milk. The package leaflet and the RMP (version 14.0) are updated accordingly

15.3.22. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0065

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include Keytruda (pembrolizumab) as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults; based on the results from KEYNOTE-048: a randomized, multicentre, open-label phase 3 study investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line recurrent or metastatic HNSCC. 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 22.1) are updated accordingly

15.3.23. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/II/0017, Orphan

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.4, 4.5 and 4.6 of the SmPC in order to reflect available information of co-administration of pitolisant with cytochrome P450 3A4 (CYP3A4) substrates based on the results from the following studies: 1) study R-B478-2.649: a drug-drug interaction in-vitro study of CYP450 3A induction: effect of BF2.649 (pitolisant), BP2.951 (pitolisant metabolite), BP1.8054(pitolisant metabolite) and BP1.4787 (modafinil); 2) study R.BF2.649-SK-005: evaluation of the induction potential of CYP3A4 by BF2.649, P2.951 and BP1.8054 gene expression analysis in human primary hepatocytes; 3) study R-B472-1.11413: quantification of 4β-hydroxycholesterol (BP1.11413) in human serum from a two-part, open label, one sequence, cross-over pharmacokinetic study to evaluate: study part I: at steady-state, the pitolisant (40 mg) interaction (as inducer) on both a single dose of midazolam and of bupropion in eighteen healthy male volunteers; study to assess the tolerance and pharmacokinetic profile of repeated 20 mg oral doses of BF2.649, in healthy elderly subjects and a young adult control group; a study to assess the potential impact of drug-drug interaction of rifampicin on the relative bioavailability of BF2.649 in healthy male subjects; B28-day repeated dose study, to evaluate pharmacokinetic parameters and accumulation rate of BF2.649, administered once a day, in six ambulatory healthy male volunteers. The MAH

took the opportunity to update section 5.2 of the SmPC to more accurately reflect information previously assessed during procedure II/0004/G finalised in 2017. The RMP (version 6.0) is updated accordingly. In addition, the MAH took the opportunity to clarify details on the manufacturers of the finished product in the package leaflet

15.3.24. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0027

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Cyramza (ramucirumab) as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alfa fetoprotein (AFP) of ≥ 400 ng/mL, after prior sorafenib therapy. 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 8.1) are updated accordingly

15.3.25. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/II/0035

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

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

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

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of final study reports from five mechanistic in vitro studies, namely: 1) 3083-N03-050: inhibition of multidrug resistance-associated protein 2 (MRP2) in vitro in membrane vesicles (PAM MEA 020); 2) 3083-N04-050: cell viability in 3D spheroid micro-tissues (PAM MEA 021); 3) 3083-N05-050: cell viability in 'sandwich' (PAM MEA 022); 4) 3083-N01-050: effects of ulipristal acetate (UPA) and its main metabolite PGL4002 on mitochondrial function and cell health markers in vitro in HepG2[43] cells (PAM REC), 4) 3083-N02-050: in vitro interaction studies of UPA and PGL4002 test articles with human bile salt export pump (BSEP), MRP3 (multidrug resistance-associated protein 3) and multidrug resistance-associated protein 4 (MRP4) efflux (ABC) transporters and with the human sodium/taurocholate co-transporting

[43] Human liver cancer cell line

polypeptide (NTCP) uptake transporter (PAM REC), as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMEA/H/A-20/1460). The RMP (version 16.1) is updated accordingly

15.3.27. Varenicline - CHAMPIX (CAP) - EMEA/H/C/000699/II/0074

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to reflect results of paediatric study A3051073 (MEA 047): a phase 4, twelve-week, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study with follow-up, evaluating the safety and efficacy of varenicline for smoking cessation in healthy adolescent smokers. The package leaflet and the RMP (version 11.0) are updated accordingly

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

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

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

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

16.1.1. Agalsidase alfa - REPLAGAL (CAP) - PSUSA/00000069/201808

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.2. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS (CAP) - PSUSA/00010530/201808

Applicant: MolMed S.p.A, ATMP[44]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[44] Advanced therapy medicinal product

16.1.3. Asenapine - SYCREST (CAP) - PSUSA/00000256/201808

Applicant: N.V. Organon

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.4. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/201808

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.5. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/201809

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.6. Burosumab - CRYSVITA (CAP) - PSUSA/00010669/201808

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.7. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/201808

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.8. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/201808

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.9. Cobicistat - TYBOST (CAP) - PSUSA/00010081/201808

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.10. Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - PSUSA/00010082/201808

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.11. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/201808

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.12. Copper (^{64}Cu) chloride - CUPRYMINA (CAP) - PSUSA/00010040/201808

Applicant: Sparkle S.r.l.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.13. Deferiprone - FERRIPROX (CAP) - PSUSA/00000940/201808

Applicant: Apotex Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.14. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) - VAXELIS (CAP) - PSUSA/00010469/201808

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.15. Eliglustat - CERDELGA (CAP) - PSUSA/00010351/201808

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.16. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/201808

Applicant: Chiesi Farmaceutici S.p.A., ATMP[45]

[45] Advanced therapy medicinal product

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.17. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/201808

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.18. Fluticasone, salmeterol[46] - AERIVIO SPIROMAX (CAP); AIREXAR SPIROMAX (CAP) - PSUSA/00010531/201808

Applicant: Teva B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.19. Human alpha$_1$-proteinase inhibitor[47]- RESPREEZA (CAP) - PSUSA/00010410/201808

Applicant: CSL Behring GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.20. Human coagulation factor VIII, human von Willebrand factor[48] - VONCENTO (CAP) - PSUSA/00010102/201808

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.21. Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/201808

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.22. Interferon beta-1b - BETAFERON (CAP); EXTAVIA (CAP) - PSUSA/00001759/201807

Applicant(s): Bayer AG (Betaferon), Novartis Europharm Limited (Extavia)

PRAC Rapporteur: Julie Williams

[46] Centrally authorised product(s) only
[47] Centrally Authorised Product(s) only
[48] Centrally Authorised Product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.23. Linaclotide - CONSTELLA (CAP) - PSUSA/00010025/201808

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.24. Loxapine[49] - ADASUVE (CAP) - PSUSA/00010113/201808

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.25. Maraviroc - CELSENTRI (CAP) - PSUSA/00001934/201808

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.26. Mecasermin - INCRELEX (CAP) - PSUSA/00001942/201808

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.27. Nonacog alfa - BENEFIX (CAP) - PSUSA/00002183/201808

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.28. Pandemic influenza vaccine (H5N1) (whole virion, vero cell derived, inactivated) - PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP); prepandemic influenza vaccine (H5N1) (whole virion, vero cell derived, inactivated) - VEPACEL (CAP) - PSUSA/00002282/201808

Applicant: Ology Bioservices Ireland Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[49] Pre-dispensed inhalation powder only

16.1.29. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/201808

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.30. Pyronaridine, artesunate - PYRAMAX (Art 58[50]) - EMEA/H/W/002319/PSUV/0020

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUR procedure

16.1.31. Reslizumab - CINQAERO (CAP) - PSUSA/00010523/201808

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.32. Rolapitant - VARUBY (CAP) - PSUSA/00010592/201808

Applicant: Tesaro UK Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.33. Safinamide - XADAGO (CAP) - PSUSA/00010356/201808

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.34. Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/201808

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.35. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/201808

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

[50] 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)

16.1.36. Telotristat ethyl - XERMELO (CAP) - PSUSA/00010639/201808

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.37. Tivozanib - FOTIVDA (CAP) - PSUSA/00010636/201808

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.38. Vemurafenib - ZELBORAF (CAP) - PSUSA/00009329/201808

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

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. Eflornithine - VANIQA (CAP), NAP - PSUSA/00001202/201807

Applicants: Almirall S.A (Vaniqa), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.2.2. Human protein c - CEPROTIN (CAP); NAP - PSUSA/00002563/201807

Applicants: Baxter AG (Ceprotin), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Amlodipine, rosuvastatin (NAP) - PSUSA/00010434/201807

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.2. Benperidol (NAP) - PSUSA/00000329/201807

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.3. Budesonide, salmeterol (NAP) - PSUSA/00010511/201807

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.4. Fluticasone propionate, formoterol fumarate dihydrate (NAP) - PSUSA/00010339/201807

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.5. Inosine dimepranol acedoben (NAP) - PSUSA/00010425/201808

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

16.3.6. Landiolol (NAP) - PSUSA/00010570/201808

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.7. Magnesium sulfate, sodium sulfate, potassium sulfate (NAP) - PSUSA/00010239/201808

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

16.3.8. Miglitol (NAP) - PSUSA/00002061/201808

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.9. Opium (NAP) - PSUSA/00010670/201808

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.10. Paracetamol, tramadol (NAP) - PSUSA/00002310/201808

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.3.11. Poliovirus type 1, poliovirus type 3 (oral, live, attenuated) vaccine (NAP) - PSUSA/00010642/201807

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.12. Tiapride (NAP) - PSUSA/00002944/201807

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/LEG 057

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Detailed analysis of cases of hypofibrinogenaemia and whether these cases observed in tocilizumab-exposed patients are related to a disorder of liver protein synthesis performance, as requested in the conclusions of PSUSA/00002980/201804 adopted at the November 2018 PRAC

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[51]

17.1.1. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/PSP/S/0063.2

Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to PSP/S/0063.1 [protocol for study 190-504 (replacing study 190-501): a non-interventional PASS (observational drug study) in order to evaluate the long-term safety of cerliponase alfa, including the occurrence of serious hypersensitivity reactions and anaphylaxis in patients with neuronal ceroid lipofuscinosis type 2 (CLN2)] as per the request for supplementary information (RSI) adopted at the November 2018 PRAC

17.1.2. Umeclidinium bromide – INCRUSE ELLIPTA (CAP), ROLUFTA ELLIPTA (CAP); umeclidinium bromide, vilanterol – ANORO ELLIPTA (CAP), LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/PSA/S/0032.1

Applicant: Glaxo Group Limited

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to PSA/S/0032 [amendment to a protocol initially endorsed by PRAC in March 2015 (EMEA/H/C/PSP/J/003.1) for study 201038: a post-authorisation safety (PAS) observational cohort study to quantify the incidence of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients using inhaled umeclidinium bromide/vilanterol (UMEC/VI) combination, inhaled UMEC, or tiotropium] as per the request for supplementary information (RSI) adopted in October 2018

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[52]

17.2.1. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 011.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 011.2 [revised statistical analysis plan (SAP) and submission of protocol for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection

[51] In accordance with Article 107n of Directive 2001/83/EC
[52] 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

fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in October 2018

17.2.2. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 003.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 003.2 [revised statistical analysis plan (SAP) and submission of protocol for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in October 2018

17.2.3. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 007.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 007.2 [revised statistical analysis plan (SAP) and submission of protocol for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI

including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in October 2018

17.2.4. Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/MEA 002

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023] (from initial opinion/MA)

17.2.5. Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/MEA 002

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023] (from initial opinion/MA)

17.2.6. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/MEA 002

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study 8835-062/000: a PASS to assess the risk of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents [final study report due date: December 2023] (from initial opinion/MA)

17.2.7. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002.2

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to MEA 002.1 [protocol for study 3000-04-001: a non-interventional PASS to evaluate the risks of myelodysplastic syndrome/acute myeloid leukaemia and secondary primary malignancies in adult patients with relapsed ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula (niraparib)] as per the request for supplementary information (RSI) adopted in October 2018

17.2.8. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.1 [PASS protocol for a safety surveillance programme using existing EU rheumatoid arthritis (RA) registries conducted in four countries: Germany (German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (OBS15180)), Spain (Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER) (6R88-RA-1720)), Sweden (Register for Antirheumatic Therapies in Sweden (ARTIS) (OBS15220)) and UK (British Society for Rheumatology Biologicals Register (BSRBR) (6R88-RA-1634)) (from initial MAA/opinion)] as per the request for supplementary information (RSI) adopted in September 2018

17.2.9. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/MEA 008.1

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 008 [protocol for a study to evaluate the effectiveness of risk minimisation measures (RMM): a survey among healthcare professionals to assess their knowledge on dosing and administration of Obizur (susoctocog alfa) in six European countries] as per the request for supplementary information (RSI) adopted in September 2018

17.3. Results of PASS imposed in the marketing authorisation(s)[53]

17.3.1. Valproate (NAP) - EMEA/H/N/PSI/J/0003

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSI/J/0003 [third interim result report for a joint drug utilisation study (DUS) of valproate and related substances conducted in Europe aiming at describing the prescribing practices before and after the dissemination of risk minimisation measures (RMM) (i.e. educational materials and direct healthcare professional communication (DHPC)) and assessing the effectiveness of these measures using databases, as requested in the outcome of the referral procedure on valproate and related substances (EMEA/H/A-31/1387) concluded in 2014] as per the request for supplementary information (RSI) adopted at the November 2018 PRAC

17.4. Results of PASS non-imposed in the marketing authorisation(s)[54]

17.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0124/G

Applicant: Bristol-Myers Squibb Pharma EEIG

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

Scope: Grouped variations consisting of: 1) submission of the final reports from studies (listed as category 3 studies in the RMP), namely: study IM101125: a nationwide post-marketing study on the safety of abatacept treatment in Sweden Using the 'Antirheumatic Therapies in Sweden (ARTIS)' register, study IM101127: a long-term observation of treatment with biologics in rheumatoid arthritis (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)), study IM101211: a multinational surveillance of abatacept-treated patients during disease registries, study IM101213: a post-marketing observational study assessing the long-term safety of abatacept using a population-based cohort of rheumatoid arthritis patients in the province of British Columbia, Canada, as well as the interim report from study IM101121: Abatacept Pregnancy Exposure Registry 'Organization of Teratology Information Specialists (OTIS)' autoimmune diseases in pregnancy project an extension study. These are biologic registries and pharmacoepidemiology studies to assess the risk associated with the use of abatacept during post-marketing in geographically diverse populations and subgroups; 2) submission of the final study report from study IM101488: a retrospective cohort study assessing the long-term safety of abatacept; 3) The deadline for submission of the final study report from study IM101121 (pregnancy registry) is proposed to be extended. The RMP (version 26) is updated accordingly and also include the addition of two epidemiological studies as category 3 studies in the RMP, namely: study IM101803: a nationwide post-marketing study on the safety of abatacept treatment in Denmark using the DANBIO[55] register and IM101W52: a nationwide post-marketing study on the safety of abatacept treatment in Sweden using the ARTIS register. In addition, the RMP is updated to remove the following missing information: combination therapy, including biologic therapy, and elderly patients

17.4.2. Aflibercept - ZALTRAP (CAP) - EMEA/H/C/002532/II/0051

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from study OBS13597 (OZONE) (listed as a category 3 study in the RMP): a prospective international observational cohort non-comparative study describing the safety and effectiveness of Zaltrap (aflibercept) administered in combination with folinic acid, fluorouracil and irinotecan (FOLFIRI) for the treatment of patients with metastatic colorectal cancer in current clinical practice. The RMP (version 4.0) is updated accordingly and 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)

17.4.3. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/II/0020, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study ELIGLC06912 (listed as a category 3 study in the RMP) (MEA006): a drug utilisation study (DUS) of eliglustat in the United

[55] A nationwide registry of biological therapies in Denmark

States (US) population using MarketScan database and the International Collaborative Gaucher Group Registry. The RMP (version 6) is updated accordingly and 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)

17.4.4. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1526/0223; LIFMIOR (CAP) - EMEA/H/C/004167/WS1526/0018

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report from study Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) register cohort 2 (listed as a category 3 study in the RMP): a prospective, non-interventional, observational, long-term cohort Germanic biologics register to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor (TNF)-inhibitor therapies in the treatment of rheumatoid arthritis (RA) in comparison to cohorts of RA patients treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic (b)DMARDs

17.4.5. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 006.6

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 006.4 [submission of the final results for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase 4 study based on data collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients were followed-up for a total of five years (one year in the SCN study and four years within the registry)] as per the request for supplementary information (RSI) adopted in October 2018

17.4.6. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 006.6

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 006.4 [submission of the final results for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase 4 study based on data collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients were followed-up for a total of five years (one year in the SCN study and four years within the registry)] as per the request for supplementary information (RSI) adopted in October 2018

17.4.7. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0046

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for study GS-EU-313-4226 (listed as a category 3 study in the RMP): a cross-sectional PASS to assess healthcare

provider awareness of risks associated with Zydelig (idelalisib) in the European Union. The study assesses the effectiveness of additional risk minimisation measures (RMM) by determining the level of knowledge of haematologists and oncologists on the infection risks associated with Zydelig (idelalisib) treatment and the corresponding recommendation to minimise these risks (fulfilment of post-authorisation measures (PAM) MEA 016)

17.4.8. Indacaterol, glycopyrronium - ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/WS1543/0029; ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/WS1543/0029; XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/WS1543/0033

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final study report for study CQVA149A2402 (listed as a category 1 study): a multinational database cohort study in Europe in chronic obstructive pulmonary disease (COPD) patients, to assess the incidence rates and hazard ratios of various safety outcomes in new users of indacaterol/glycopyrronium compared to new users of comparator drugs (at the drug-class level). The product information is updated to remove the black triangle and to amend Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' to remove the obligation to conduct the study. The RMP (version 5.0) is updated accordingly

17.4.9. Pegvisomant - SOMAVERT (CAP) - EMEA/H/C/000409/II/0089

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final clinical study report (CSR) from A6291010 (ACROSTUDY) (listed as a category 3 study in the RMP): an open-label, global, non-interventional PASS performed to monitor the long-term safety and outcomes of pegvisomant treatment in clinical practice (fulfilment of post-authorisation measures (PAM) MEA 059)

17.4.10. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/WS1557/0120; PROMETAX (CAP) - EMEA/H/C/000255/WS1557/0121

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final report for study CENA713D2409: a drug utilisation study (DUS) aimed to assess the extent of inappropriate use of Exelon/Prometax (rivastigmine) (fulfilment of post-authorisation measures (PAM) Exelon MEA 034 and Prometax MEA 035)

17.4.11. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/II/0078

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final clinical study report (CSR) for study NA0001: a PASS on

the effectiveness of the educational materials for Xyrem (sodium oxybate)

17.4.12. Vardenafil - LEVITRA (CAP) - EMEA/H/C/000475/WS1536/0064; VIVANZA (CAP) - EMEA/H/C/000488/WS1536/0060

Applicant: Bayer AG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final clinical study report (CSR) for study 12912: (listed as category 3 study in the RMP) a non-interventional PASS to investigate the risk of non-arteritic anterior ischemic optic neuropathy (NAION) associated with phosphodiesterase type 5 (PDE5) inhibitors. The RMP (version 6.0) 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. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017.3

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Second interim report for study ALIROC07997: a PASS using healthcare databases, in order to monitor the safety of Praluent (alirocumab) in patients affected with the human immunodeficiency virus (HIV) (from initial opinion/MA)

17.5.2. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 053.1

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Interim report for study M07-001: a prospective registry for an observational, multicentre, multinational study of patients with paroxysmal nocturnal haemoglobinuria (PNH)

17.5.3. Florbetaben (^{18}F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.8

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Martin Huber

Scope: Interim report for study FBB-01_03_13 (PASS 2): a non-interventional, prospective observational multicentre, multi-country registry to observe usage pattern, safety and tolerability of the diagnostic agent NeuraCeq (florbetaben (^{18}F)) in clinical practice [final clinical study report (CSR) expected in Q2/2020]

17.5.4. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 133.13

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Eleventh annual paediatric inflammatory bowel disease (IBD) registry (DEVELOP) report on long-term safety and efficacy of infliximab and other therapies, safety and

efficacy of variable infliximab dosing intervals, episodic therapy, monotherapy (initiated de novo or following discontinuation of concomitant immunomodulators), combined infliximab and immunomodulator therapy (azathioprine/6-mercaptopurine (AZA/6-MP) or methotrexate (MTX))

17.5.5. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 005.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Second annual progress report for a patient registry of lixisenatide use in adult patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and databases in Italy and Belgium [final report due date: December 2020] (from initial MAA/opinion)

17.5.6. Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/MEA 008.3

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Second annual progress report for a patient registry of lixisenatide use in adult patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and databases in Italy and Belgium [final report due date: December 2020] (from initial MAA/opinion)

17.5.7. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 001.7

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Interim results for study 178-CL-114: a non-imposed, non-interventional, safety long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (individual and composite outcomes) in patients administered mirabegron and other treatments for overactive bladder

17.5.8. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 009.2

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Annual progress study report for study D3820R00008: a US post-marketing, comparative, observational study in order to evaluate the cardiovascular safety of naloxegol in patients with non-cancer pain in comparison to other treatments for opioid

induced constipation [final study report: December 2023]

17.5.9. Voriconazole - VFEND (CAP) - EMEA/H/C/000387/MEA 091.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Interim report for study A1501103: a non-interventional PASS, an active safety surveillance programme to monitor selected events in patients with long-term voriconazole use

17.6. Others

17.6.1. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/LEG 087.6

Applicant: Roche Registration GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Sixth annual review on pregnancy cases

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. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0038 (with RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

18.1.2. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0047 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

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

Applicant: CTI Life Sciences Deutschland GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Canakinumab - ILARIS (CAP) - EMEA/H/C/001109/R/0062 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.2. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/R/0028

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: 5-year renewal of the marketing authorisation

18.3.3. Flutemetamol (^{18}F) - VIZAMYL (CAP) - EMEA/H/C/002557/R/0017 (without RMP)

Applicant: GE Healthcare AS

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.4. Insulin degludec, liraglutide - XULTOPHY (CAP) - EMEA/H/C/002647/R/0028 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.5. Insulin glargine - ABASAGLAR (CAP) - EMEA/H/C/002835/R/0023 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

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

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Ronan Grimes

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 12-15 March 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	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	
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	15.3.8. Eluxadoline - TRUBERZI (CAP)
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	17.5.7. Mirabegron - BETMIGA (CAP)
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Ruta Kerpauskiene	Alternate	Lithuania	No interests declared	Full involvement
Benjamin Micallef	Alternate	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	4.3.4. Paracetamol (NAP) 4.3.5. Paracetamol (NAP) 7.1.2. Radium (Ra223) dichloride - XOFIGO (CAP) 11.2.2. Levonorgestrel (NAP) 11.2.3. Levonorgestrel (NAP) 16.1.22. Interferon beta-1b - BETAFERON (CAP); EXTAVIA (CAP) 17.4.12. Vardenafil - LEVITRA (CAP); VIVANZA (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Alexandra-Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Sonja Beken	Expert - via telephone*	Belgium	No interests declared	Full involvement
Martin Zahle Larsen	Expert - in person*	Denmark	No interests declared	Full involvement
Ane Blicher Schelde	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Laura Andreoli	Expert - in person*	France	No interests declared	Full involvement
Tiphaine Vaillant	Expert - in person*	France	No interests declared	Full involvement
Nicole Bick	Expert - via telephone*	Germany	No interests declared	Full involvement
Jutta Dedorath	Expert - via telephone*	Germany	No interests declared	Full involvement
Nils Lilienthal	Expert - via telephone*	Germany	No interests declared	Full involvement
Kerstin Löschcke	Expert - via telephone*	Germany	No interests declared	Full involvement
Valerie Strassmann	Expert - in person*	Germany	No interests declared	Full involvement
Kate Browne	Expert - via telephone*	Ireland	No interests declared	Full involvement
Grainne Kirwan	Expert - in person*	Ireland	No interests declared	Full involvement
Anouk Neuteboom	Expert - in person*	Netherlands	No interests declared	Full involvement
Annette Jitske de Vries-van der Weij	Expert - in person*	Netherlands	No interests declared	Full involvement
Elizabeth van Vlijmen	Expert - in person*	Netherlands	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Inge Zomerdijk	Expert - in person*	Netherlands	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Jan Sjöberg	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/