



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

09 September 2021
EMA/PRAC/532676/2021
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC minutes on 11-14 January 2021

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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1. Introduction

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

The Chairperson opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19 outbreak), and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

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 revision 2 of the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.2](#)). All decisions taken at this meeting held under the conditions of an emergency situation, the Agency's BCP and in compliance with internal guidelines were made in the presence of a quorum of members (i.e. 18 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chair welcomed Panagiotis Psaras, replacing Helena Panayiotopoulou, as the new member for Cyprus at the plenary meeting on 11-14 January 2021. In addition, the Chair welcomed at the organisational matters (ORGAM) teleconference on 28 January 2021 Christina Sylvia Chrysostomou, as the new alternate for Cyprus, replacing Panagiotis Psaras, as well as Roxana Dondera, as the new member for Romania, replacing Roxana Stefania Stroe.

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

1.2. Agenda of the meeting on 11-14 January 2021

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 23-26 November 2020

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 23 – 26 November 2020 were published on the EMA website on 16 February 2021 ([EMA/PRAC/87359/2021](#)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures¹

None

3.5. Others

None

4. Signals assessment and prioritisation²

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

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

² Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Hydrocortisone – ALKINDI (CAP)

Applicant(s): Diurnal Europe BV

PRAC Rapporteur: Annika Folin

Scope: Signal of adrenal crisis

EPITT 19656 – New signal

Lead Member State(s): SE

Background

Hydrocortisone is a glucocorticoid indicated, as Alkindi, a centrally authorised product, for the replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old).

Alkindi (hydrocortisone) is estimated to have been used by more than 560 patients worldwide, in the period from 2018 to 2020.

Following a spontaneous case report reported with Alkindi (hydrocortisone), a signal of adrenal crisis was identified by the MAH in children switching from hydrocortisone formulations for children to Alkindi (hydrocortisone). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence, following assessment of the data and literature provided by the MAH for Alkindi (hydrocortisone), the PRAC agreed that the product information of Alkindi (hydrocortisone) needs to be updated in order to reflect the risk of acute adrenal insufficiency when switching from crushed or compounded oral hydrocortisone formulation(s) to Alkindi (hydrocortisone granules in capsules for opening) due to a potential risk of inaccurate dosing.

Summary of recommendation(s)

- The MAH for Alkindi (hydrocortisone) should submit to EMA, within 60 days, a variation to amend³ the product information.
- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.

For the full PRAC recommendation, see [EMA/PRAC/19647/2021](#) published on 08 February 2021 on the EMA website.

³ Update of SmPC sections 4.2 and 4.4. The package leaflet is to be updated accordingly

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab - AMGEVITA (CAP); AMSPARITY (CAP), HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP) - EMEA/H/C/000481/SDA/118.1; HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP)

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of abnormal weight gain

EPITT 19520 – Follow-up to July 2020

Background

For background information, see [PRAC minutes July 2020](#).

The MAH for Humira (adalimumab) replied to the request for information on the signal of abnormal weight gain and the responses were assessed by the Rapporteur.

Discussion

Based on the assessment of the available evidence in EudraVigilance and literature, together with the cumulative review provided by the MAH for Humira (adalimumab) that includes data from clinical trials, the PRAC considered that there is a reasonable possibility for a causal relationship between adalimumab and abnormal weight gain. Therefore, the PRAC agreed that an update of the product information is warranted to add weight increased as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAH(s) for adalimumab-containing products should submit to EMA, within 60 days, a variation to amend⁴ the product information.

For the full PRAC recommendation, see [EMA/PRAC/19647/2021](#) published on 08 February 2021 on the EMA website.

4.3.2. Anastrozole (NAP)

Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of depressed mood disorders

EPITT 19592 – Follow-up to September 2020

Background

For background information, see [PRAC minutes September 2020](#).

The MAH for the originator anastrozole-medicinal product(s) replied to the request for information on the signal of depressed mood disorders and the responses were assessed by

⁴ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

the Rapporteur.

Discussion

Having considered the available evidence from case reports in EudraVigilance and Lareb⁵ databases, literature and cumulative reviews, including clinical trial data, provided by the MAH of the originator anastrozole-medicinal product(s), as taking into account the plausible biological mechanism of action, the PRAC considered that there is sufficient evidence for an association between anastrozole and mood depression. Therefore, the PRAC agreed that an update of the product information is warranted to add depression as an undesirable effect with a frequency 'very common'.

Summary of recommendation(s)

- The MAH(s) for anastrozole-containing medicinal product(s) should submit to EMA, within 60 days, a variation to amend⁶ the product information.

For the full PRAC recommendation, see [EMA/PRAC/19647/2021](#) published on 08 February 2021 on the EMA website.

4.3.3. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/027

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Signal of systemic scleroderma

EPITT 19591 – Follow-up to September 2020

Background

For background information, see [PRAC minutes September 2020](#).

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

Discussion

Having considered the available evidence and the cumulative review provided by the MAH of Keytruda (pembrolizumab), the PRAC considered that there is insufficient evidence at present to establish a causal association between systemic scleroderma and pembrolizumab. Therefore, the PRAC concluded that no regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for Keytruda (pembrolizumab) should continue to monitor cases of systemic scleroderma as part of routine safety surveillance. Should new cases arise, the MAH should include in the next PSUR a discussion regarding the possibility that pembrolizumab may increase symptomatic manifestation of a pre-existing autoimmune scleroderma/sclerodermic condition.

For the full PRAC recommendation, see [EMA/PRAC/19647/2021](#) published on 08 February 2021 on the EMA website.

⁵ Netherlands Pharmacovigilance Centre

⁶ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Autologous glioma tumour cells (inactivated), autologous glioma tumour cell lysates (inactivated), allogeneic glioma tumour cells (inactivated), allogeneic glioma tumour cell lysates (inactivated) - EMEA/H/C/003693, Orphan

Applicant: Epitopoietic Research Corporation-Belgium (E.R.C.), ATMP⁷

Scope: Treatment of glioma

5.1.2. Coronavirus (COVID-19) vaccine (Ad26.COVS-S, recombinant) - EMEA/H/C/005737

Scope: Active immunisation for prevention of coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults ≥18 years old

5.1.3. Coronavirus (COVID-19) mRNA⁸ vaccine (nucleoside-modified) - EMEA/H/C/005791

Scope: Active immunisation for prevention of coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults aged 18 years and older

At an extraordinary meeting convened remotely on 04 January 2021, the PRAC reviewed the proposed RMP in the context of an initial marketing authorisation application procedure. The PRAC is responsible for providing advice to the CHMP.

5.1.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - EMEA/H/C/005675

Scope: Active immunisation for prevention of coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

At an extraordinary meeting convened remotely on 22 January 2021, the PRAC reviewed the proposed RMP in the context of an initial marketing authorisation application procedure. The PRAC is responsible for providing advice to the CHMP.

⁷ Advanced therapy medicinal product

⁸ Messenger ribonucleic acid

5.1.5. Dexamethasone phosphate - EMEA/H/C/005740

Scope: Treatment for cerebral oedema, post-traumatic shock-lung syndrome, asthma, skin diseases, autoimmune diseases, rheumatoid arthritis, prophylaxis and treatment of post-operative or cytostatic-induced vomiting, treatment of coronavirus (COVID-19), eye inflammation and infection

See [PRAC minutes October 2020](#)⁹.

5.1.6. Elivaldogene autotemcel - EMEA/H/C/003690, Orphan

Applicant: bluebird bio (Netherlands) B.V, ATMP¹⁰

Scope (accelerated assessment): Treatment of adenosine triphosphate (ATP) binding cassette subfamily D member 1 (ABCD1) genetic mutation and cerebral adrenoleukodystrophy

5.1.7. Ponesimod - EMEA/H/C/005163

Scope: Treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features of demyelination

5.1.8. Pralsetinib - EMEA/H/C/005413

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

5.1.9. Relugolix, estradiol, norethisterone acetate - EMEA/H/C/005267

Scope: Treatment of uterine fibroids

5.1.10. Salmeterol xinafoate, fluticasone propionate - EMEA/H/C/005591

Scope: Treatment of asthma

See [PRAC minutes October 2020](#)¹¹.

5.1.11. Salmeterol xinafoate, fluticasone propionate - EMEA/H/C/004881

Scope: Treatment of asthma

See [PRAC minutes October 2020](#)¹².

5.1.12. Tanezumab - EMEA/H/C/005189

Scope: Treatment of moderate to severe chronic pain associated with osteoarthritis (OA) in adult patients for whom treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and/or an opioid is ineffective, not tolerated or inappropriate

⁹ Held 28 September – 01 October 2020

¹⁰ Advanced therapy medicinal product

¹¹ Held 28 September – 01 October 2020

¹² Held 28 September – 01 October 2020

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

See also Annex I 15.2.

5.2.1. Sildenafil - REVATIO (CAP) - EMEA/H/C/000638/II/0091

Applicant: Upjohn EESV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 7.0) in line with revision 2 of GVP module V on 'Risk management systems'. Consequently, the educational programme for the risk of hypotension is proposed to be terminated

Background

Sildenafil is a cyclic guanosine monophosphate (cGMP) inhibitor indicated, as Revatio, for the treatment of adult patients with pulmonary arterial hypertension (PAH), classified as WHO¹³ functional class II and III, to improve exercise capacity. It is also indicated for the treatment of paediatric patients aged 1 year to 17 years old with PAH.

The PRAC is evaluating a type II variation procedure for Revatio, a centrally authorised medicine containing sildenafil, to update the RMP to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to propose the termination of the existing educational programme on the risk of hypotension. 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.

Summary of advice

- The RMP for Revatio (sildenafil) in the context of the variation procedure under evaluation by the PRAC could be considered acceptable provided that an update to RMP version 7.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed with the update of the summary of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and/or these are sufficiently characterised over the post-marketing experience years. However, the PRAC considered that bleeding events should remain as an important identified risk in the RMP. The PRAC also agreed with the proposed removal of additional pharmacovigilance activity associated with the safety concern on hypotension. Nevertheless, hypotension should remain as an important potential risk in the PSUR safety specification. The PRAC supported the removal of the information to healthcare professionals (HCPs) and associated controlled distribution system designed to facilitate the reporting of events of hypotension as additional risk minimisations. As a consequence, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is to be updated accordingly.

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

See Annex I 15.3.

¹³ World Health Organization

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. Apixaban - ELIQUIS (CAP) - PSUSA/00000226/202005

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Apixaban is a factor Xa inhibitor direct oral anticoagulant (DOAC) indicated, as Eliquis, for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery for the prevention of stroke and systemic embolism (SE) in adult patients with non-valvular atrial fibrillation (NVAf) with one or more risk factors. It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Eliquis, a centrally authorised medicine containing apixaban 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 Eliquis (apixaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include erythema multiforme as an undesirable effect with a frequency 'very rare' in the indication for the prevention of stroke and systemic embolism in adults with NVAf, and a frequency 'not known' in the indication for the treatment of DVT and PE, and prevention of recurrent DVT and PE. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁴.
- In the next PSUR, the MAH should provide cumulative reviews of cases of agranulocytosis and peripheral oedema and propose an update of the product information as warranted. The MAH should also provide a causality assessment for cases of arthralgia.

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

6.1.2. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/202005

Applicant: Roche Registration GmbH

¹⁴ 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

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

Background

Atezolizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death-ligand 1 (PD-L1). It is indicated, as Tecentriq, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC), subject to certain conditions, and for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. It is also indicated, in combination with nab-paclitaxel, for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression $\geq 1\%$ and who have not received prior chemotherapy for metastatic disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tecentriq, a centrally authorised medicine containing atezolizumab 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 Tecentriq (atezolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add pemphigoid as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁵.
- In the next PSUR, the MAH should provide a cumulative review of cases of immune-related myocarditis along with a discussion on whether the current warning adequately addresses the updated data on this undesirable effect. The MAH should provide detailed reviews of cases of gastrointestinal perforations, of haemophagocytic lymphohistiocytosis (HLH) and of cases of haemolytic anaemia and autoimmune haemolytic anaemia. For all reviews, the MAH should propose an update of the product information as warranted. Finally, the MAH should provide further discussion on the possible relationship between atezolizumab/immune checkpoint inhibitors and arthritis and whether an update of the product information is warranted.

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

6.1.3. Avatrombopag - DOPTELET (CAP) - PSUSA/00010779/202005

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

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

Avatrombopag is a small molecule thrombopoietin (TPO) receptor agonist indicated, as Doptelet, for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Doptelet, a centrally authorised medicine containing avatrombopag 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 Doptelet (avatrombopag) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypersensitivity as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁶.
- In the next PSUR, the MAH should include a discussion and a causality assessment on the need for more detailed information on and the need for additional related terms to hypersensitivity reactions. The MAH should also propose an update of the product information as warranted.

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

6.1.4. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/202006

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Blinatumomab is a bispecific T-cell engager molecule indicated, as Blincyto, in monotherapy for the treatment of adults with Philadelphia chromosome negative CD¹⁷19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL), for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% and for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

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

Summary of recommendation(s) and conclusions

¹⁶ 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

¹⁷ Cluster of differentiation

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Blincyto (blinatumomab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on CD19-negative B-precursor ALL reported in relapsed patients and a warning on lineage switch from ALL to acute myeloid leukaemia (AML) reported in relapsed patients who received blinatumomab treatment. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH should include a review of cases of thromboembolic events (TE) including data from clinical trials and from post-marketing and assess whether there is a possible causal relationship between TE cases and blinatumomab treatment.

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

6.1.5. Decitabine - DACOGEN (CAP) - PSUSA/00009118/202005

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Decitabine is a cytidine deoxynucleoside analogue indicated, as Dacogen, for the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML) according to the WHO¹⁹ classification, who are not candidates for standard induction chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dacogen, a centrally authorised medicine containing decitabine 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 Dacogen (decitabine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add differentiation syndrome as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁰.
- The MAH should submit to EMA, within 90 days, reviews on the need for pregnancy tests, on the time period for breastfeeding after the last dose of decitabine, as well as the duration of contraception following the end of treatment with decitabine taking into account the Safety Working Party ([SWP](#)) response document dated February 2020 on questions from CMDh on 'recommendations on the duration of contraception following

¹⁸ Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

¹⁹ World Health Organization

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

the end of treatment with a genotoxic drug'. The MAH should propose an update of the product information as warranted.

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

6.1.6. Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/202005

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Dolutegravir is a human immunodeficiency virus (HIV) integrase inhibitor and rilpivirine a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. In combination dolutegravir/rilpivirine is indicated, as Juluca, for the treatment of HIV-1 infection in adults who are virologically-suppressed on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any NNRTI or integrase inhibitor.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Juluca, a centrally authorised medicine containing dolutegravir/rilpivirine 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 Juluca (dolutegravir/rilpivirine) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a variation to amend the product information to reflect the transfer of dolutegravir into breast milk in small quantities in line with other dolutegravir-containing products.

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

6.1.7. Hydroxycarbamide²¹ - SIKLOS (CAP); XROMI (CAP) - PSUSA/00001692/202006

Applicant(s): Addmedica S.A.S. (Siklos), Nova Laboratories Ireland Limited (Xromi)

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Hydroxycarbamide is a hydroxylated analogue of urea indicated, as Siklos, for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults,

²¹ Centrally authorised product(s) only

adolescents and children older than 2 years suffering from symptomatic Sickle cell syndrome. It is also indicated, as Xromi, for the prevention of vaso-occlusive complications of Sickle cell disease (SCD) in patients over 2 years of age.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Siklos and Xromi, centrally authorised medicines containing hydroxycarbamide 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 Siklos and Xromi (hydroxycarbamide) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) for Siklos (hydroxycarbamide) should be maintained.
- Nevertheless, based on the results of the ESCORT-HU²² study, the product information for Xromi (hydroxycarbamide) should be updated to amend the intervals for blood cells monitoring at initiation of treatment and the toxic ranges for neutrophils counts and to remove the requirement to follow-up the growth of treated children and adolescents. In addition, the undesirable effect of parvovirus B19 infection should be removed and information regarding the time period for monitoring blood counts after overdose should be included. Therefore, the current terms of the marketing authorisation(s) should be varied²³.
- The MAHs should submit to EMA, within 60 days, a detailed review of all available data in children < 2 years of age together with a proposal to update the product information as warranted. In addition, the MAHs should submit a detailed review of all available data in pregnancy with a proposal to update the product information as warranted.
- The MAH for Xromi (hydroxycarbamide) should submit to EMA, an updated RMP to reflect the final study results of study ESCORT-HU within the next regulatory opportunity and/or within six months at the latest.
- In the next PSUR, the MAHs should provide a cumulative review of cases of myelosuppression in the context of overdose, female fertility impairment and medication errors.

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

6.1.8. Levodopa - INBRIJA (CAP) - PSUSA/00107800/202006

Applicant: Acorda Therapeutics Ireland Limited

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

²² ESCORT-HU (European Sickle Cell Disease Cohort-Hydroxyurea): an observational prospective cohort study to measure the occurrence of adverse events and serious adverse events

²³ Update of SmPC sections 4.2, 4.4, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Levodopa is a precursor of dopamine indicated, as Inbrija, for the intermittent treatment of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson's disease (PD) treated with a levodopa/dopa-decarboxylase inhibitor.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Inbrija, a centrally authorised medicine containing levodopa 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 Inbrija (levodopa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated by including an additional cleaning step of the inhaler mouthpiece and providing more detailed instructions for use (IFU) on this step, in order to mitigate usage complaints regarding clogged devices. Therefore, the current terms of the marketing authorisation(s) should be varied²⁴.
- In the next PSUR, the MAH should provide a detailed analysis of cases of dyspnoea/wheezing/asthma together with a causality assessment.

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

6.1.9. Mitotane - LYSODREN (CAP) - PSUSA/00002075/202004

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Mitotane is an adrenal cytotoxic indicated, as Lysodren, for the symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma (ACC).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lysodren, a centrally authorised medicine containing mitotane 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 Lysodren (mitotane) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypogonadism as an undesirable effect with a frequency 'not known' and to add etoposide under substances metabolised through cytochrome P450 in order to reflect the interaction with mitotane. Therefore, the current terms of the marketing authorisation(s) should be varied²⁵.

²⁴ Update of SmPC section 4.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁵ Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

6.1.10. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - PSUSA/00010848/202005

Applicant: Novartis Gene Therapies EU Limited, ATMP²⁶

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Onasemnogene abeparvovec is a gene therapy substance indicated, as Zolgensma, for the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zolgensma, a centrally authorised medicine containing onasemnogene abeparvovec 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 Zolgensma (onasemnogene abeparvovec) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warnings on immunogenicity and hepatotoxicity to include details on liver injury and acute liver failure, also added as undesirable effects with a frequency 'not known' with relevant details. In addition, further instructions on the use of corticosteroids in the initial period after administration of Zolgensma (onasemnogene abeparvovec) are added. Therefore, the current terms of the marketing authorisation(s) should be varied²⁷.
- In the next PSUR, the MAH should provide detailed reviews of cases of thrombotic microangiopathy (TMA) and of medication errors.

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

6.1.11. Pegvaliase - PALYNZIQ (CAP) - PSUSA/00010761/202005

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

²⁶ Advanced therapy medicinal product

²⁷ Update of SmPC sections 4.2, 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

Pegvaliase is a PEGylated recombinant phenylalanine ammonia lyase enzyme indicated, as Palynziq, for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/L) despite prior management with available treatment options.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Palynziq, a centrally authorised medicine containing pegvaliase 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 Palynziq (pegvaliase) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on hypersensitivity reaction with anaphylaxis and to add anaphylaxis as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.
- In the next PSUR, the MAH should provide a detailed review of cases of dyspnoea.

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

6.1.12. Semaglutide - OZEMPIC (CAP); RYBELSUS (CAP) - PSUSA/00010671/202005

Applicant(s): Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue indicated, as Ozempic and Rybelsus, for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (TD2M) as monotherapy when metformin is considered inappropriate due to intolerance or contraindications or in combination with other medicinal products for the treatment of diabetes.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ozempic and Rybelsus, centrally authorised medicines containing semaglutide 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 Ozempic and Rybelsus (semaglutide) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) for Rybelsus (semaglutide for oral use) should be maintained.

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

- Nevertheless, the product information for Ozempic (semaglutide for subcutaneous use) should be updated to include angioedema as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.

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

6.1.13. Tedizolid phosphate - SIVEXTRO (CAP) - PSUSA/00010369/202006

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Tedizolid phosphate is an antibacterial prodrug indicated, as Sivextro, for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and adolescents 12 years of age and older.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sivextro, a centrally authorised medicine containing tedizolid phosphate 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 Sivextro (tedizolid phosphate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include thrombocytopenia as an undesirable effect with a frequency 'not known' and add a warning to patients at a higher risk of developing this undesirable effect, as well as a recommendation to minimise the risk. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH closely monitor cases of serotonin syndrome.

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

6.1.14. Tolvaptan³¹ - JINARC (CAP) - PSUSA/00010395/202005

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

²⁹ 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

³⁰ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³¹ Indicated for adults with autosomal dominant polycystic kidney disease (ADPKD)

Background

Tolvaptan is a vasopressin antagonist indicated, as Jinarc, to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jinarc, a centrally authorised medicine containing tolvaptan 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 Jinarc (tolvaptan) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include dysgeusia, syncope, dry skin, urticaria, arthralgia, myalgia and weight increase as undesirable effects with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied³².
- In the next PSUR, the MAH should closely monitor cases of hepatic toxicity caused by the association of amoxicillin/clavulanic acid and tolvaptan, cases of rhabdomyolysis and cases of creatine phosphokinase (CPK) increase. Glaucoma and ocular hypertension alongside skin neoplasms (basal cell carcinoma) should continue to be monitored. The MAH should also provide a further discussion on the inclusion of chest pain in the product information as applicable.
- The MAH should submit to EMA, within 60 days, cumulative reviews of cases of rapid correction of hyponatremia and neurological sequelae with a proposal for updating the product information as appropriate.

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

6.1.15. Vedolizumab - ENTYVIO (CAP) - PSUSA/00010186/202005

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Vedolizumab is a humanised monoclonal antibody indicated, as Entyvio, for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alfa (TNF α) antagonist. It is also indicated in Crohn's disease.

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Entyvio, a centrally authorised medicine containing vedolizumab 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 Entyvio (vedolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include interstitial lung disease as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³³.
- In the next PSUR, the MAH should provide a cumulative review of cases of psoriasis with a proposal for updating the product information as appropriate.

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

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

See also Annex I 16.2.

6.2.1. Fentanyl³⁴ - EFFENTORA (CAP); INSTANYL (CAP); PECFENT (CAP); NAP - PSUSA/00001369/202004

Applicant(s): Kyowa Kirin Holdings B.V. (PecFent), Takeda Pharma A/S (Instanyl), Teva B.V. (Effentora), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Fentanyl is an opioid indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Effentora, Instanyl and Pecfent, centrally authorised medicines containing fentanyl, and nationally authorised medicine(s) containing fentanyl for transmucosal use 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 fentanyl-containing medicinal products³⁵ in the approved indication(s) remains unchanged.

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

³⁴ Transmucosal route of administration only

³⁵ Transmucosal route of administration only

- Nevertheless, the product information should be updated to add sleep-related breathing disorders as a warning and opioid use disorder as a new or refined warning as applicable. In addition, Cheynes Stokes respiration should be added as a case of fentanyl overdose. Moreover, the product information for Actiq (fentanyl) should be also updated to add that regular dental visits are advised and to add bleeding at the site of application as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied³⁶.
- In the next PSUR, the MAHs should provide detailed reviews of cases of central sleep apnoea, rashes, eruptions and exanthems; drug abuse, dependence and withdrawal; overdose; off-label use and medication errors as well as a review of opioid use and increased risk of pulmonary infections. In addition, the MAHs should closely monitor cases of leukoencephalopathy, encephalopathy and cases of hypoglycaemia. The MAHs of fentanyl nasal sprays should provide an analysis of cases of accidental exposure following product appearance confusion. Moreover, the MAHs should provide a detailed analysis on the effectiveness of the implemented risk minimisation measures with a proposal for additional measures, as appropriate.

In light of the concerns raised regarding off-label use, misuse and accidental exposure, the PRAC considered that MAHs should perform a thorough review of their current labelling to ensure these risks are appropriately mitigated and should propose corrective actions as appropriate. Further consideration should be given at the level of CHMP and CMDh.

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

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

See also Annex I 16.3.

6.3.1. **Amfepramone (NAP) - PSUSA/00000138/202006**

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Amfepramone is a sympathomimetic agent with indirect action, belonging to the group of anorexigens, indicated as an adjunctive therapy to diet, in patients with obesity and a body mass index (BMI) of 30 kg/m² or higher who have not responded to an appropriate weight-reducing regimen alone.

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

Summary of recommendation(s) and conclusions

³⁶ Update of SmPC sections 4.4, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

Twenty-five members voted in favour of this recommendation whilst three members³⁷ had divergent views. The Icelandic and Norwegian PRAC members supported the majority.

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.

Considering the reported cases of cardiac-related adverse drug reactions, off-label use, the mechanism of action of amfepramone, safety concerns related to this therapeutic class and taking into account the benefits of amfepramone in the context of the current knowledge on the treatment of obesity, the PRAC considered that a thorough review is needed to assess the impact of these concerns on the benefit-risk balance of amfepramone.

6.3.2. Azithromycin³⁸ (NAP) - PSUSA/00010491/202004

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Azithromycin is a macrolide antibiotic indicated for systemic use for the treatment of infections caused by susceptible organisms, including respiratory tract infections, acute otitis media, odonto-stomatological infections, skin and soft tissue infections and genital infections under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing azithromycin for systemic use 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 azithromycin-containing product(s) for systemic use in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, MAH(s) should continue to closely monitor the concomitant use of azithromycin and ivabradine and any relevant cases as part of routine pharmacovigilance.

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.

³⁷ Adrien Inoubli, Martin Huber, Amelia Cupelli

³⁸ Formulation(s) for systemic use only

6.3.3. Ciprofloxacin hydrochloride, dexamethasone acetate³⁹ (NAP) - PSUSA/00010012/202004

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Ciprofloxacin is a fluoroquinolone (FQ) and dexamethasone a corticosteroid. In combination, ciprofloxacin hydrochloride/dexamethasone acetate is indicated for the treatment of acute otitis media in patients with tympanostomy tubes (AOMT) and acute otitis externa (AOE).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ciprofloxacin hydrochloride/dexamethasone acetate as ear drops, suspension 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 ciprofloxacin hydrochloride/dexamethasone acetate-containing product(s) ear drops, suspension in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should add tympanic membrane perforation (TMP) and delayed healing of TMP to the list of PSUR safety concerns. In addition, MAH(s) should provide a review on the information regarding special populations, based on the information on frequency of administration in paediatric population and elderly patients.

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. Clotiazepam (NAP) - PSUSA/00000827/202005

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Clotiazepam is a benzodiazepine indicated for the treatment of anxiety disorders, insomnia and prevention and treatment of delirium tremens and other manifestations of alcohol withdrawal.

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

Summary of recommendation(s) and conclusions

³⁹ Ear drops, suspension only

- Based on the review of the data on safety and efficacy, the benefit-risk balance of clotiazepam-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the risk of fall in elderly patients. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁰.
- In the next PSUR, MAH(s) should provide a literature search of new relevant safety information for both clotiazepam and benzodiazepines in general and propose an update of the product information as warranted.

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

6.3.5. Gadobenic acid (NAP) - PSUSA/00001500/202004

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gadobenic acid is a linear gadolinium-based contrast agent (GdCA) indicated for use in diagnostic magnetic resonance imaging (MRI) of the liver, only when diagnostic information is essential and not available with unenhanced MRI and when delayed phase imaging is required.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadobenic acid 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 gadobenic acid-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a cumulative review of all available data on gadolinium retention in the body after exposure to GdCA that have become available since the completion of the referral procedure under Article 31 of Directive 2001/83/EC in 2017 (EMA/H/A-31/1437), including data from spontaneous reports, non-clinical and clinical studies and literature. The review should also include cases in which laboratory tests are performed to assess gadolinium levels in blood and urine and cases where patients are treated with chelating or other treatment for gadolinium retention or gadolinium deposition disease. The MAH(s) should propose to update the product information and/or RMP as warranted. Finally, the MAH(s) should include a detailed overview of all ongoing and planned studies (non-clinical and clinical).

The frequency of PSUR submission should be revised from five-yearly to yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. Submission of

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

PSUR(s) for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended are required. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.6. Gadobutrol (NAP) - PSUSA/00001502/202004

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gadobutrol is a macrocyclic gadolinium-based contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, including cranial and spinal MRI, head and neck, thoracic space, breast, abdomen, pelvis, retroperitoneal space, musculoskeletal system, magnetic resonance angiography and cardiac MRI.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadobutrol 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 gadobutrol-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a cumulative review of all available data on gadolinium retention in the body after exposure to GdCA that have become available since the completion of the referral procedure under Article 31 of Directive 2001/83/EC in 2017 (EMA/H/A-31/1437), including data from spontaneous reports, non-clinical and clinical studies and literature. The review should also include cases in which laboratory tests are performed to assess gadolinium levels in blood and urine and cases where patients are treated with chelating or other treatment for gadolinium retention or gadolinium deposition disease. The MAH(s) should propose to update the product information and/or RMP as warranted. Finally, the MAH(s) should include a detailed overview of all ongoing and planned studies (non-clinical and clinical).

The frequency of PSUR submission should be revised from five-yearly to yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. Submission of PSUR(s) for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended are required. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.7. Gadodiamide (NAP) - PSUSA/00001503/202004

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Gadodiamide is a linear non-ionic chelate of gadolinium-contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, cranial and spinal MRI, as well as cardiac MRI.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadodiamide 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 gadodiamide-containing product(s) remains unchanged.
- The current status of the marketing authorisation(s) should be maintained⁴¹.

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

6.3.8. Gadopentetic acid (NAP) - PSUSA/00001504/202004

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Gadopentetic acid is a linear gadolinium-contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, as well as cranial and spinal MRI. It is also indicated for contrast enhancement in magnetic resonance arthrography and for the demonstration and demarcation of the digestive tract from adjacent normal and pathological tissue structures in MRI, under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadopentetic acid 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 gadopentetic acid-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a cumulative review of all available data on gadolinium retention in the body after exposure to GdCA that have become available since the completion of the referral procedure under Article 31 of Directive 2001/83/EC in 2017 (EMA/H/A-31/1437), including data from spontaneous reports, non-clinical and clinical studies and literature. The review should also include cases in which laboratory tests are performed to assess gadolinium levels in blood and urine and cases where patients are treated with chelating or other treatment for gadolinium retention or

⁴¹ Currently suspended following the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC in 2017 (EMA/H/A-31/1437)

gadolinium deposition disease. The MAH(s) should propose to update the product information and/or RMP as warranted. Finally, the MAH(s) should include a detailed overview of all ongoing and planned studies (non-clinical and clinical).

The frequency of PSUR submission should be revised from five-yearly to yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. Submission of PSUR(s) for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended are required. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.9. Gadoteric acid⁴² (NAP) - PSUSA/00001506/202004

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Gadoteric acid is a macrocyclic gadolinium-based contrast agent (GdCA) indicated as intravenous (IV) and intravascular formulations for intensification of the contrast in magnetic resonance imaging (MRI) for a better visualisation/delineation of lesions of the brain, spine, and surrounding tissues, lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast, and musculoskeletal system in adults and paediatrics. It is also indicated for a better visualisation/delineation of lesions or stenoses of the non-coronary arteries in adults.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadoteric acid⁴³ 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 gadoteric acid-containing product(s) as IV and intravascular formulations in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a cumulative review of all available data on gadolinium retention in the body after exposure to GdCA that have become available since the completion of the referral procedure under Article 31 of Directive 2001/83/EC in 2017 (EMA/H/A-31/1437), including data from spontaneous reports, non-clinical and clinical studies and literature. The review should also include cases in which laboratory tests are performed to assess gadolinium levels in blood and urine and cases where patients are treated with chelating or other treatment for gadolinium retention or gadolinium deposition disease. The MAH(s) should propose to update the product information and/or RMP as warranted. In addition, the MAH(s) are requested to discuss all cases of throat irritation. Finally, the MAH(s) should include a detailed overview of all ongoing and planned studies (non-clinical and clinical).

The frequency of PSUR submission should be revised from five-yearly to yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union

⁴² Intravenous (IV) and intravascular formulation(s) only

⁴³ IV and intravascular formulation(s) only

reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.10. Gadoteridol (NAP) - PSUSA/00001507/202004

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Gadoteridol is a macrocyclic gadolinium-contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the whole body, including head, neck, liver, breast, musculoskeletal system and soft tissue pathologies, as well as cranial and spinal MRI.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadoteridol 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 gadoteridol-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a cumulative review of all available data on gadolinium retention in the body after exposure to GdCA that have become available since the completion of the referral procedure under Article 31 of Directive 2001/83/EC in 2017 (EMA/H/A-31/1437), including data from spontaneous reports, non-clinical and clinical studies and literature. The review should also include cases in which laboratory tests are performed to assess gadolinium levels in blood and urine and cases where patients are treated with chelating or other treatment for gadolinium retention or gadolinium deposition disease. The MAH(s) should propose to update the product information and/or RMP as warranted. Finally, the MAH(s) should include a detailed overview of all ongoing and planned studies (non-clinical and clinical).

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

6.3.11. Gadoxetic acid disodium (NAP) - PSUSA/00001509/202004

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Gadoxetic acid disodium is a linear gadolinium-based contrast agent (GdCA) indicated for diagnostic magnetic resonance imaging (MRI) of the liver.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gadoxetic acid disodium 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 gadoxetic acid disodium-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a cumulative review of all available data on gadolinium retention in the body after exposure to GdCA that have become available since the completion of the referral procedure under Article 31 of Directive 2001/83/EC in 2017 (EMA/H/A-31/1437), including data from spontaneous reports, non-clinical and clinical studies and literature. The review should also include cases in which laboratory tests are performed to assess gadolinium levels in blood and urine and cases where patients are treated with chelating or other treatment for gadolinium retention or gadolinium deposition disease. The MAH(s) should propose to update the product information and/or RMP as warranted. Finally, the MAH(s) should include a detailed overview of all ongoing and planned studies (non-clinical and clinical).

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

6.3.12. Iomeprol (NAP) - PSUSA/00001769/202004

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Background

Iomeprol is a non-ionic iodinated contrast medium indicated for angiography, phlebography, angiocardiology, head and body computed tomography (CT), urography, endoscopic retrograde cholangiopancreatography (ERCP), cholangiography, cavernosography, fistulography, myelography, discography, arthrography, dacrocystography, sialography, hysterosalpingography and galactography.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing iomeprol 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 iomeprol-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add encephalopathy as an undesirable effect with a frequency 'not known', as well as a warning on contrast

induced encephalopathy. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁴.

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 MAH(s) should be requested to provide a detailed review on hypothyroidism mainly in newborns and on hyperthyroidism, along with a causality assessment. In addition, the MAH(s) should provide a cumulative review of cases of drug reaction with eosinophilia and systemic symptoms (DRESS). Further consideration will be given at the level of CMDh.

6.3.13. Irinotecan⁴⁵ (NAP) - PSUSA/00001783/202005

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Irinotecan is a topoisomerase I inhibitor indicated for the treatment of patients with advanced/metastatic colorectal cancer either as a single agent or in combination subject to certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing irinotecan (all formulations except liposomal) 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 irinotecan-containing product(s)⁴⁶ in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on concomitant use of irinotecan with other medicinal products by including apalutamide to the list of strong inducers of CYP3A4⁴⁷ and to include the interaction of irinotecan with other antineoplastic agents, including flucytosine. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁸.
- In the next PSUR, the MAHs should discuss the *Mashimo K, et al*⁴⁹ publication and assess whether an update of the product information is warranted. In addition, the MAHs should provide cumulative reviews of cases of blood creatine phosphokinase (CPK)

⁴⁴ 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

⁴⁵ All formulation(s) except liposomal

⁴⁶ All formulation(s) except liposomal

⁴⁷ Cytochrome P450 3A4

⁴⁸ Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁴⁹ Mashimo K, Fujiwara D, Hoshida T, Morimoto N, Noda A, Takeda T, Tsubaki M, Nishida S, Sakaguchi K. Three cases of augmented chemotherapy-induced peripheral neuropathy after changing from modified FOLFOX6 mFOLFOX6 to FOLFIRI therapy in patients with colorectal cancer. *Gan To Kagaku Ryoho*. 2020 Jun;47(6):993-995. Japanese. PMID: 32541182

increased and rhabdomyolysis. Finally, MAHs should further monitor adverse events reported in patients with reduced UGT1A1⁵⁰ activity.

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 MAHs should provide further analyses relating to irinotecan starting dose in patients with reduced UGT1A1 activity are necessary to assess the possible need for additional risk minimisation measures. Further consideration will be given at the level of CMDh.

6.3.14. Mifepristone (NAP) - PSUSA/00002060/202005

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Mifepristone is a synthetic steroid indicated for medical termination of a developing intra-uterine pregnancy in sequential combination with a prostaglandin analogue up to 63 days of amenorrhea, softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester, preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons and labour induction in foetal death in utero, subject to certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing mifepristone 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 mifepristone-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include acute generalised exanthematous pustulosis (AGEP) as an undesirable effect with a frequency 'not known' and to add a warning on severe cutaneous adverse reactions. Therefore, the current terms of the marketing authorisation(s) should be varied⁵¹.
- In the next PSUR, MAHs Nordic Group and Linepharma should closely monitor severe cutaneous adverse reactions, including data from the literature. The MAHs should provide a discussion on new cases, including a causality assessment and propose to update the product information as warranted. The MAH Linepharma should also provide a causality assessment for cases of foetal malformations and propose to update the product information as warranted.

⁵⁰ Uridine diphosphate glucuronosyltransferase

⁵¹ 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

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 the risk of AGEF is also relevant to mifepristone/misoprostol-containing products as a fixed dose combination (FDC). Further consideration will be given at the level of CMDh.

6.3.15. Tamoxifen (NAP) - PSUSA/00002846/202004

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Tamoxifen is a selective oestrogen receptor modulator indicated for the treatment of breast cancer, endometrial cancer and anovulatory infertility, as well as for the prevention of breast cancer in women at moderate to high risk.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tamoxifen 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 tamoxifen-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add toxic epidermal necrolysis (TEN) as an undesirable effect with a frequency 'rare' and to include a warning on the risk of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and TEN. In addition, the product information should be updated to add exacerbation of hereditary angioedema as an undesirable effect with a frequency 'not known' and as a warning. Moreover, the warning on the use of tamoxifen in breastfeeding should be amended to reflect available data on the excretion and accumulation of tamoxifen and its active metabolites in breastmilk. Therefore, the current terms of the marketing authorisation(s) should be varied⁵².
- In the next PSUR, the MAHs should provide a detailed analysis on the potential association between tamoxifen and reduced bone mineral density, osteoporosis, osteopenia and related terms in pre-menopausal women being treated for breast cancer and propose to update the product information as warranted. In addition, the MAHs should include embryo-foetal toxicity as an important potential risk and use in breastfeeding as an area of missing information in their PSUR summary of safety concerns.

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.

⁵² 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

The PRAC considered that MAHs should review their product information taking into account the Safety Working Party ([SWP](#)) response document dated February 2020 on questions from CMDh on 'recommendations on the duration of contraception following the end of treatment with a genotoxic drug'. Further consideration will be given at the level of CMDh.

6.3.16. **Tramadol (NAP) - PSUSA/00003002/202005**

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tramadol 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 tramadol-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include warnings on sleep-related breathing disorders and on adrenal insufficiency respectively and to add hiccups as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵³.
- In the next PSUR, the MAH(s) should provide cumulative reviews of cases of hyperacusis, of drug interaction between nefopam and tramadol leading to serotonin syndrome, of opioid use disorder (OUD), of hyponatremia/syndrome of inappropriate antidiuretic hormone secretion (SIADH), cases of genetic polymorphism affecting pharmacokinetic (PK) of tramadol, cases related to deficiencies in the hypothalamic-pituitary-adrenal or -gonadal axes and make proposals to update the product information as warranted. In addition, MAH(s) should provide a detailed analysis of cases of suicidal ideation/behaviour. Moreover, MAH(s) should closely monitor cases of adrenal insufficiency, cases of central sleep apnoea, fatal cases occurring in the context of unintentional overdose or drug interaction, the risk of medication errors with liquid formulations along with the risk of medication errors in children and provide a detailed analysis of these cases. Furthermore, MAH(s) should include analyses of cases of abuse/diversion and of available information on testicular effects and sexual hormonal data from repeat dose toxicology studies, including the impact on male and female fertility, including a literature review, and discuss the need for an update of the product information as warranted.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. Submission of PSUR(s) for products referred to in Articles 10(1), 10a, 14, 16a

⁵³ 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

of Directive 2001/83/EC as amended are not required any longer. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.17. Xylometazoline (NAP) - PSUSA/00003134/202005

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Xylometazoline is a sympathomimetic agent indicated for the symptomatic relief of nasal congestion, perennial and allergic rhinitis (including hay fever), and sinusitis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing xylometazoline 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 xylometazoline-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include epistaxis as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵⁴.
- In the next PSUR, the MAH(s) should provide a detailed discussion on the use of xylometazoline during pregnancy and a proposal to update the product information as warranted.

The frequency of PSUR submission should be revised from eight-yearly to three-yearly and the next PSUR should be submitted to 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.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Methotrexate - JYLAMVO (CAP) - EMEA/H/C/003756/LEG 002

Applicant: Therakind (Europe) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Comprehensive review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002014/201910) adopted in May 2020

⁵⁴ 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

Background

Methotrexate is a folic acid antagonist indicated, as Jylamvo a centrally authorised product, for the treatment of active rheumatoid arthritis, juvenile idiopathic arthritis (JIA), psoriasis and severe psoriatic arthritis, under certain conditions. It is also indicated in oncology, as maintenance treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the PRAC requested the MAH to submit a review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications. For further background, see [PRAC minutes May 2020](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the product information should be updated to reflect that liver biopsy should no longer be recommended as a diagnostic tool for routine monitoring of methotrexate hepatotoxicity, but only be considered for diagnostic purposes on an individual patient level after careful consideration.
- In view of amending the product information to revise the existing warning on the need for a liver biopsy to monitor hepatotoxicity for methotrexate-containing products for non-oncologic indication(s), the MAH is requested to provide further responses to a request for supplementary information (RSI).

6.4.2. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/LEG 003

Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: Comprehensive review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002014/201910) adopted in May 2020

Background

Methotrexate is a folic acid antagonist indicated, as Nordimet a centrally authorised product, for the treatment of active rheumatoid arthritis, juvenile idiopathic arthritis (JIA), psoriasis and severe psoriatic arthritis, under certain conditions.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the PRAC requested the MAH to submit a review of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications. For further background, see [PRAC minutes May 2020](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the product information should be updated to reflect that liver biopsy should no longer be recommended as a diagnostic tool for routine monitoring of methotrexate

hepatotoxicity, but only be considered for diagnostic purposes on an individual patient level after careful consideration.

- In view of amending the product information to revise the existing warning on the need for a liver biopsy to monitor hepatotoxicity for methotrexate-containing products for non-oncologic indication(s), the MAH is requested to provide further responses to a request for supplementary information (RSI).

6.5. Variation procedure(s) resulting from PSUSA evaluation

See Annex I 16.5.

6.6. Expedited summary safety reviews⁵⁵

6.6.1. Coronavirus (COVID-19) mRNA⁵⁶ vaccine (nucleoside-modified) BNT162b1 - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: First expedited monthly summary safety report (MSSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) during the coronavirus disease (COVID-19) pandemic

Background

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Comirnaty, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people aged 16 years and older.

The PRAC assessed the first monthly summary safety report (MSSR) for Comirnaty ((COVID-19) mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the organisational, regulatory and methodological matters (ORGAM) meeting on 28 January 2021, the PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- The MAH should submit to EMA a cumulative review with a causality assessment of all cases reporting serious hypersensitivity and/or reactions suggestive of anaphylaxis.
- In the next MSSR, the MAH should review case reports of diarrhoea and vomiting and discuss whether a causal relationship can be established. The MAH should also provide cumulative overviews of eye pains, eye swelling, paraesthesias and dysaesthesias.

6.6.2. Coronavirus (COVID-19) mRNA vaccine (nucleoside-modified) BNT162b1 - COMIRNATY (CAP) - EMEA/H/C/005735/LEG 019

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review of reports of deaths (overall and in frail elderly subjects) from

⁵⁵ Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

⁵⁶ Messenger ribonucleic acid

EudraVigilance and reports from Norway

Background

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Comirnaty, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people aged 16 years and older.

The PRAC assessed cumulative review of reports of deaths (overall and in frail elderly subjects) from EudraVigilance and reports from Norway for Comirnaty ((COVID-19) mRNA vaccine (nucleoside-modified)). At the organisational, regulatory and methodological matters (ORGAM) meeting on 28 January 2021, the PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- The information provided in the fatal case reports of individuals ≤65 years of age and >65 years of age does not raise any safety concerns, and therefore, did not support a safety signal. In the next MSSR, the MAH should continue thoroughly reviewing all reports with fatal outcome (without excluding any age groups, or patient populations).

6.6.3. Coronavirus (COVID-19) mRNA vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/LEG 002

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Review of cases of serious allergic reactions in the US

Background

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as COVID-19 Vaccine Moderna, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults.

The PRAC assessed a review of cases of serious allergic reactions in the US for COVID-19 Vaccine Moderna ((COVID-19) mRNA vaccine (nucleoside-modified)). At the organisational, regulatory and methodological matters (ORGAM) meeting on 28 January 2021, the PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- In the first monthly summary safety report (MSSR), the MAH should provide detailed reviews of cases of anaphylaxis, including follow-up information and specify lot numbers as part of routine case handling.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁵⁷

See Annex I 17.1.

⁵⁷ In accordance with Article 107n of Directive 2001/83/EC

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁵⁸

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)⁵⁹

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁶⁰

See also Annex I 17.4.

7.4.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/II/0068

Applicant: Bayer AG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final study report of the study evaluating physician knowledge of safety and safe use information for aflibercept in Europe (listed as a category 3 study in the RMP): a follow-up physician survey. The RMP (version 27.1) is updated accordingly

Background

Aflibercept is a recombinant fusion protein indicated, as Eylea a centrally authorised product, for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DME), as well as for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV).

In 2017, the MAH for Eylea (aflibercept) submitted the results of a non-imposed non-interventional PASS (study 16526 – variation II/0039) to evaluate the physician and patient knowledge of safety and safe use information for aflibercept in Europe as stated in the EU educational material for Eylea (aflibercept) (wave 1 survey). As agreed in 2018 and as stated in the RMP of Eylea (aflibercept), the MAH revised the prescriber guide and conducted a follow-up survey (wave 2 survey) to evaluate the effectiveness of the risk minimisation measures following revision and redistribution of the materials. The Rapporteur assessed the MAH's final study report.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC considered that the MAH should be requested to submit to EMA within 30 days responses to a request for supplementary information (RSI).
- The MAH should provide an update of the educational material for healthcare professionals (HCPs), with a focus on the key handling and safety elements for the vial and prefilled syringe (PFS) formulations, taking also into account the root cause analysis of intraocular pressure (IOP) increase. In addition, the MAH should provide a draft direct healthcare professional communication (DHPC) and communication plan regarding IOP

⁵⁸ 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

⁵⁹ In accordance with Article 107p-q of Directive 2001/83/EC

⁶⁰ 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

increase, its surveillance and management.

7.4.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0048

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of the results of study WO41486 evaluating the effectiveness of the healthcare professional (HCP) brochure designed to mitigate important immune-related risks in patients receiving atezolizumab in the European Union. As a consequence, section 4.4 of the SmPC and Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' are updated. The RMP (version 17.0) is updated accordingly. In addition, a delay until 31 August 2021 in the due date for the submission of the final clinical safety report (CSR) for IMvigor210: a phase 2, multicentre, single-arm study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer, is introduced

Background

Atezolizumab is a programmed death-ligand 1 (PD-L1) inhibitor antibody indicated, as Tecentriq a centrally authorised product, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) under certain conditions, as well as for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. In combination with nab-paclitaxel, it is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression $\geq 1\%$ and who have not received prior chemotherapy for metastatic disease.

As stated in the RMP of Tecentriq (atezolizumab), the MAH conducted a study to evaluate the effectiveness of the healthcare professional (HCP) brochure designed to mitigate important immune-related risks in patients receiving atezolizumab in the European Union. The Rapporteur assessed the MAH's final study report together with the MAH's responses to the request for supplementary information (RSI). For further background, see [PRAC minutes October 2020](#)⁶¹.

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report can be advised for approval. Based on the evaluation of the study results and fulfilment of the study objectives, the PRAC agreed with removing the guide for HCPs as an additional risk minimisation measure as the knowledge and handling of immune-related adverse reactions (irARs) is well known amongst HCPs. The patient card should be maintained as it is still considered as a valid tool to raise patients' awareness on irADRs and when to seek medical assistance. As a result, Annex II-D and the RMP (version 17.1) are updated.

⁶¹ Held 28 September – 01 October 2020

7.4.3. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS1810/0061; dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS1810/0082; dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS1810/0028

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report for study 201177 (EuroSIDA) (listed as a category 3 study in the RMP): a prospective observational cohort study to monitor and compare the occurrence of hypersensitivity reactions (HSR) and hepatotoxicity in patients receiving dolutegravir (with or without abacavir) and other integrase inhibitors (with or without abacavir)

Background

Dolutegravir is a human immunodeficiency virus (HIV) integrase inhibitor indicated, as Tivicay, for the treatment of HIV infection in adults, adolescents and children above 6 years of age. It is also indicated in combination with abacavir and lamivudine, nucleoside reverse transcriptase inhibitors, as Triumeq, for the treatment of HIV infection in adults and adolescents above 12 years of age weighing at least 40 kg, under certain conditions. In addition, it is indicated in combination with rilpivirine, a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI), as Juluca, for the treatment of HIV-1 infection in adults, under certain conditions.

As stated in the RMP of Tivicay (dolutegravir), Triumeq (abacavir/lamivudine) and Juluca (dolutegravir/rilpivirine), the MAH conducted an observational study to monitor and compare the occurrence of hypersensitivity reactions (HSR) and hepatotoxicity in patients receiving dolutegravir and other integrase inhibitors. The Rapporteur assessed the MAH's final study report together with the MAH's responses to the request for supplementary information (RSI). For further background, see [PRAC minutes September 2020](#)⁶².

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report can be advised for approval. Based on the evaluation of the study results, the PRAC confirmed that the product information should include alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations as an undesirable effect with a frequency common, and increased bilirubin in combination with increased transaminase with a frequency rare.

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.

⁶² Held 31 August – 03 September 2020

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See 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 EMA

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Ethinylestradiol; ethinylestradiol, levonorgestrel (NAP) - FR/H/0516/001/II/016

Applicant(s): Theramex Ireland Limited (Seasonique)

PRAC Lead: Adrien Inoubli

Scope: PRAC consultation on a national procedure evaluating results of an imposed PASS: a retrospective longitudinal cohort study to assess the risk of venous thromboembolic events (VTE) in women exposed to Seasonique conducted in the USA and results of a drug utilisation study (DUS) conducted in Europe: France, Italy and Belgium, on request of France

Background

Ethinylestradiol (EE) is an oestrogen and levonorgestrel (LNG) a progestogen. Used in combination alternating with EE alone, it is indicated, as Seasonique, as a 91-day extended combined oral contraceptive (COC).

In the context of an ongoing decentralised type II variation procedure evaluating the results of a PASS as a retrospective longitudinal cohort study exploring the risk of cardiovascular and breast cancer associated with the use of Seasonique (EE/LNG, EE) during standard clinical practice as well as the results of a drug utilisation study (DUS) assessing the pattern of use of Seasonique (EE/LNG, EE), France as reference Member State (RMS) for the medicinal product, requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and evidence, the PRAC agreed that the risks of arterial thromboembolism (ATE) and venous thromboembolic events (VTE) associated with Seasonique (EE/LNG, EE) cannot be considered as similar to traditional 28-days COC containing-LNG, based on the results of the PASS. It was considered that although the overall risk is not statistically significant, the sensitivity analysis performed by the MAH of Seasonique (EE/LNG, EE) showed that the medicinal product presented a higher risk of VTE, which might be higher in some particular sub-groups. Based on PRAC comments, the Committee supported to update the product information to amend the existing warnings on the risks of ATE and VTE.

11.2. Other requests

11.2.1. Methotrexate⁶³ (NAP) - DE/H/PSUFU/00002014/201910

Applicant(s): Addenda Pharma, Especialidades Farmacéuticas Centrum S.A., Gebro Pharma, medac, Morningside Healthcare Limited, Mylan, Nordic Group, Orion Pharma, Pfizer, Remedica, Rompharm, Sandoz, Teva

PRAC Lead: Martin Huber

Scope: PRAC consultation on a PSUR follow-up (PSU FU) procedure evaluating comprehensive reviews of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indications, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00002014/201910) concluded in May 2020, on request of Germany

Background

Methotrexate is a folic acid antagonist indicated for the treatment of autoimmune disease such as active rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriasis and severe psoriatic arthritis, as well as in the treatment of cancer such as lymphoblastic leukaemia (ALL), subject to certain conditions.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for methotrexate (PSUSA/00002014/201910) concluded in May 2020, the PRAC considered that reviews of the value of performing liver biopsies as a diagnostic tool to monitor hepatotoxicity of methotrexate in non-oncologic indication(s) should be further assessed. For further background, see to [PRAC minutes May 2020](#).

On request of the CMDh, MAH(s) for nationally approved methotrexate-containing product(s) submitted the requested safety reviews for evaluation within a worksharing periodic safety update follow-up (PSU FU) procedure. In the context of the ongoing evaluation of the PSU FU procedure (DE/H/PSUFU/00002014/201910), Germany, as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information and evidence, the PRAC supported the LMS assessment that the product information should be updated to reflect that liver biopsy should no longer be recommended as a diagnostic tool for routine monitoring of methotrexate hepatotoxicity, but only be considered for diagnostic purposes on an individual patient level after careful consideration. Non-invasive diagnostic options

⁶³ In non-oncology indication(s)

should be considered for monitoring of liver condition in accordance with local clinical guidance and availability of techniques. Further consideration will be given in the context of the ongoing procedure.

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. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated the PRAC on the activities of the [COVID-19 EMA pandemic Task Force](#) (ETF), including an overview of ongoing clinical trials and epidemiological studies and initiatives, as well as a summary of medicines in development and medicines authorised for other indications, as potential treatments for COVID-19, and their safety surveillance. The EMA Secretariat also updated the PRAC on COVID-19-observational research initiatives. Finally, the PRAC was given an overview of EMA COVID-19 vaccine safety monitoring plans, EC-funded-, EMA-procured- COVID-19 vaccine safety studies for 2021/2022. The update also included information on the joint ECDC⁶⁴/EMA COVID-19 vaccine monitoring programme and a call for interest to PRAC (as well to ETF and CHMP) to join its advisory board.

Post-meeting note: Daniel Morales was nominated amongst PRAC to be part of the joint ECDC/EMA COVID-19 vaccine monitoring programme advisory board.

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

⁶⁴ European Centre for Disease Prevention and Control

12.7. PRAC work plan

12.7.1. PRAC work plan 2021

PRAC lead: Sabine Straus, Martin Huber

The EMA Secretariat presented to the PRAC the draft final PRAC work plan 2021, further to previous discussion and comments received (see [PRAC minutes December 2020](#)⁶⁵).

Post-meeting note: At the organisational, regulatory and methodological matters (ORGAM) meeting on 28 January 2021, the PRAC adopted the work plan 2021. It was published on the EMA website ([EMA/PRAC/610324/2020](#)) on 23 August 2021.

12.8. Planning and reporting

12.8.1. EMA Executive Director - introduction to PRAC

The PRAC welcomed Emer Cooke as the new EMA Executive Director who started her first renewable five-year mandate on 16 November 2020.

12.8.2. Marketing authorisation applications (MAA) forecast for 2021 - initial MAA submissions with eligibility request to the centralised procedure (CP) – planning update dated Q4 2020

At the organisational, regulatory and methodological matters (ORGAM) meeting on 28 January 2021, the EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline') in 2021.

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

⁶⁵ Held 23-26 November 2020

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 Granularity and Periodicity Advisory Group (GPAG) focussing on harmonising and streamlining the EURD list and noted the GPAG progress highlights. The PRAC also reviewed and adopted the GPAG work plan 2021.

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list, version January 2021, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of January 2021, the updated EURD list was adopted by the CHMP and CMDh at their January 2021 meetings and published on the EMA website on 03/02/2021, 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 EMA Secretariat provided PRAC with an update from the Signal Management Review Technical (SMART) working group work stream on 'Methods' consisting in an overview on vaccine preparedness for COVID-19. This covers adverse events of special interest (AESI) and the mapping to vaccine targeted medical events (vTMEs), tools and processes supporting intensive review as well as methodologies supporting effective monitoring.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 28/01/2021, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.13.2. EU individual case safety report (ICSR) implementation guide – revision 2

The EMA Secretariat presented to PRAC the draft revised EU individual case safety report (ICSR) implementation guide that describes the additional EU specific requirements to generate a valid ICSR and message acknowledgment in accordance with ICH E2B(R3)⁶⁶ as well as operational aspects in EU for post-authorisation and clinical trials ICSRs. This further revision includes the mandatory use of the ISO⁶⁷ ICSR/ICH E2B(R3) format by June 2022 as announced by the EMA Management Board (MB) in December 2019 taking into account previous PRAC recommendation. It also includes the mandatory use by June 2022 of the ISO terminology on pharmaceutical dose forms and routes of administration referred to in Article 25(1)(f) of Commission Implementing Regulation (EU) No 520/2012. At the organisational, regulatory and methodological matters (ORGAM) meeting on 28 January 2021, the PRAC adopted revision 2 of the EU ICSR implementation guide. As next steps, the revised document is due for agreement by the EU Network Pharmacovigilance Oversight Group ([EU-POG](#)) in line with the EU pharmacovigilance governance structure.

Post-meeting note: On 07 April 2021, EU ICSR implementation guide revision 2 ([EMA/51938/2013 Rev 2*](#)) was published on the EMA website.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

⁶⁶ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E2B (R3) on electronic transmission of ICSRs - data elements and message specification - implementation guide

⁶⁷ International Organization for Standardization

12.14.3. EU RMP Annex 1 tool update - suspension of submission

The EMA Secretariat informed the PRAC of the suspension of MAHs' submissions to EMA of electronic structured data RMP Annex 1 updates (as .xml files) after each RMP approval/update for centrally authorised products. This was agreed by EMA as part of the Agency's business continuity planning (BCP) relating to the current COVID-19 pandemic.

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

PRAC lead: Sabine Straus

As a follow-up to the October 2020 discussion (for background, see [PRAC minutes October 2020](#)⁶⁸) and in line with the [PRAC work plan 2021](#), the EMA Secretariat updated PRAC on revision 3 of GVP module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' and Addendum II on 'methods for effectiveness evaluation' following other Committees and Working Groups consultation, the European Commission (EC) review as well as the agreement by the EU Network Pharmacovigilance Oversight Group ([EU-POG](#)) in line with the EU pharmacovigilance governance structure. On 22 January 2021, the PRAC adopted by written procedure the documents following minor updates.

Post-meeting note: On 03 February 2021, GVP module XVI on 'Risk minimisation measures: selection of tools and 5 effectiveness indicators' (Rev 3) ([EMA/204715/2012 Rev 3*](#)) and Addendum II on 'Methods for effectiveness evaluation' ([EMA/419982/2019](#)) were published on the EMA website for a public consultation lasting until 28 April 2021.

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

⁶⁸ Held 28 September – 01 October 2020

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.18.3. Safety updates for COVID-19 vaccines - publication

At the organisational, regulatory and methodological matters (ORGAM) meeting on 28 January 2021, the EMA Secretariat presented to PRAC the format and content of safety updates for COVID-19 vaccines for publication.

Post-meeting note: on 29 January 2021, the first safety updates for Comirnaty ((COVID-19) mRNA vaccine (nucleoside-modified)) was published on the EMA website ([Safety update COVID-19 vaccine - Comirnaty](#)).

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. EMA policy on handling of competing interests for scientific committees' members and experts – revision of policy 0044

At the organisational, regulatory and methodological matters (ORGAM) meeting on 28 January 2021, the EMA Secretariat presented to PRAC the revision of the 'EMA policy 0044 on handling of competing interests of scientific committees' members and experts' that came into force on 01 January 2021 ([EMA/MB/89351/2020](#)) together with the revised declaration of interests and confidentiality undertaking form (e-DoI version 4).

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁶⁹

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 timetables⁷⁰.

14.1.1. Eliglustat – CERDELGA (CAP)

Applicant(s): Genzyme Europe BV
PRAC Rapporteur: Eva Segovia
Scope: Signal of erectile dysfunction
EPITT 19644 – New signal
Lead Member State(s): ES

14.1.2. Labetalol (NAP)

Applicant(s): various
PRAC Rapporteur: Pernille Harg
Scope: Signal of nipple pain and suppressed lactation
EPITT 19639 – New signal
Lead Member State(s): NO

14.1.3. Rituximab – MABTHERA (CAP)

Applicant(s): Roche Registration GmbH
PRAC Rapporteur: Hans Christian Siersted
Scope: Signal of sarcoidosis
EPITT 19642 – New signal
Lead Member State(s): DK

14.1.4. Romosozumab – EVENITY (CAP)

Applicant(s): UCB Pharma S.A.
PRAC Rapporteur: Adrien Inoubli
Scope: Signal of cardiac arrhythmia

⁶⁹ ⁶⁹ 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

⁷⁰ 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

EPITT 19629 – New signal

Lead Member State(s): FR

14.1.5. Secukinumab – COSENTYX (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Signal of Henoch-Schonlein purpura

EPITT 19640 – New signal

Lead Member State(s): ES

14.1.6. Secukinumab – COSENTYX (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Signal of facial paralysis

EPITT 19653 – New signal

Lead Member State(s): ES

14.1.7. Sulfamethoxazole, trimethoprim (co-trimoxazole) (NAP)

Applicant(s): various

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of acute respiratory distress syndrome

EPITT 19625 – New signal

Lead Member State(s): HR

14.1.8. Sulfamethoxazole, trimethoprim (co-trimoxazole) (NAP)

Applicant(s): various

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of haemophagocytic lymphohistiocytosis (HLH)

EPITT 19655 – New signal

Lead Member State(s): HR

14.1.9. Tramadol (NAP)

Applicant(s): various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Signal of serotonin syndrome

EPITT 19635 – New signal

Lead Member State(s): FR

14.1.10. Warfarin (NAP)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of anticoagulant-related nephropathy

EPITT 19652 – New signal

Lead Member State(s): DK

14.2. New signals detected from other sources

14.2.1. Alemtuzumab – LEMTRADA (CAP)

Applicant(s): Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of sarcoidosis

EPITT 19638 – New signal

Lead Member State(s): DK

14.2.2. Clindamycin (NAP)

Applicant(s): various

PRAC Rapporteur: Sonja Hrabcik

Scope: Signal of acute renal failure

EPITT 19647 – New signal

Lead Member State(s): AT

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. Hydrocortisone - EMEA/H/C/005105, Orphan

Applicant: Diurnal Europe BV

Scope: Replacement therapy for congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and 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. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/II/0054

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 4.4) to include several updated study milestones and to bring it in line with revision 2 of GVP module V on 'Risk management systems'

15.2.2. Cetorelix - CETROTIDE (CAP) - EMEA/H/C/000233/II/0075

Applicant: Merck Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 5.2) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' including the consequential removal of a number of important identified risks and important potential risk of congenital anomalies, as well as the removal of missing information on infertile premenopausal women. The MAH also revised the RMP based on the most recent data and post-marketing exposure

15.2.3. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0015

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of an updated RMP (version 1.4) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to include long-term safety data from the completed PREMIERE registry: a prospective observational long-term safety registry of multiple sclerosis patients who have participated in cladribine clinical studies; and to remove it from the pharmacovigilance plan. Furthermore, the status of the post-approval safety study MS 700568-0002: a long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine (CLARION); and study MS 700568-0004: pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study (CLEAR). Finally, the RMP is updated in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010634/201907) adopted in January 2020

15.2.4. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/II/0034, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 5) in order to update the safety

specifications and the pharmacovigilance plan, and to add healthcare provider educational materials and process indicator to evaluate the distribution of the educational materials. The RMP is also brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

15.2.5. Influenza vaccine (surface antigen, inactivated, adjuvanted) - FLUAD TETRA (CAP) - EMEA/H/C/004993/II/0008

Applicant: Seqirus Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of an updated RMP (version 1.9) in order to provide a consolidated RMP for adjuvanted trivalent influenza vaccine (aTIV) and adjuvanted quadrivalent influenza vaccine (aQIV), including an alignment of safety concerns for aTIV and aQIV

15.2.6. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/001252/II/0042, Orphan

Applicant: Pharmaxis Europe Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 9.0) brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to review the safety information and proposed to reclassify 'cough' from an important potential risk to an important identified risk; to remove the important identified risks of 'bronchospasm during and after the initiation dose assessment' and 'bronchospasm during long term use'; to remove the important potential risk of 'cough-related sequelae', 'off label use in non-cystic fibrosis (CF) bronchiectasis', 'off label use in paediatric/adolescent CF patients (aged 6-17 years)', 'administration of Bronchitol via the wrong inhaler device' and 'starting Bronchitol treatment without completing the full Bronchitol initiation dose assessment (BIDA) dose'; to remove the missing information of 'patients requiring home oxygen or needing assisted ventilation', 'children <6 years of age', 'pregnancy and lactation', 'risks associated with long-term use' from the list of safety concerns; to add 'increased risk of respiratory or systemic infection' as an important potential risk replacing 'pulmonary abscess on continued use', 'septicaemia on continued use', 'increased risk of bacteria sputum identified or infections with extended use of Bronchitol' and 'microbial infection via a contaminated inhaler device' previously classified as important potential risks. In addition, the pharmacovigilance plan is updated with completed studies. Finally, the RMP is updated as requested as per the conclusions of the periodic safety update report single assessment (PSUSA) procedure (PSUSA/00009226/201904) adopted at the November 2019 PRAC meeting

15.2.7. Melatonin - CIRCADIN (CAP) - EMEA/H/C/000695/II/0061

Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 7.0) to remove the following risks from the list of potential risks: drug interaction with levothyroxine, panic attacks, potential interaction with warfarin, sperm motility decreased/spermatozoa morphology abnormal and withdrawal. Furthermore, the MAH took the opportunity to introduce minor corrections

throughout the RMP

15.2.8. Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/WS1975/0051; saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/WS1975/0049

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 15.1 for Onglyza; version 16.1 for Komboglyze) in order to change the milestones to Q1 2021 of the final study report for study D1680C00016 (MEASURE-HF) (listed as a category 3 study in the RMP): a 24-week, multicentre, randomised, double-blind, parallel group, placebo-controlled study to investigate the effects of saxagliptin and sitagliptin in patients with type 2 diabetes mellitus (T2DM) and heart failure. The MAH took the opportunity to introduce minor changes throughout the RMP

15.2.9. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/II/0029

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 14.4) to include dehydration and the pregnancy prevention programme as additional risk minimisation measures (aRMM) in order to align the RMP with Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'

15.2.10. Vildagliptin - GALVUS (CAP) - EMEA/H/C/000771/WS1970/0067; JALRA (CAP) - EMEA/H/C/001048/WS1970/0069; XILIRX (CAP) - EMEA/H/C/001051/WS1970/0067; vildagliptin, metformin hydrochloride - EUCREAS (CAP) - EMEA/H/C/000807/WS1970/0081; ICANDRA (CAP) - EMEA/H/C/001050/WS1970/0084; ZOMARIST (CAP) - EMEA/H/C/001049/WS1970/0083

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 15.0) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and aligned with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00003113/201802) adopted in October 2018. In addition, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' of the product information is updated to remove the statement on submission of an RMP update every 3 years

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. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/II/0009

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 5.3 of the SmPC in order to include non-clinical information based on final results from a 26-week study TOX13540 (listed as a category 3 study in the RMP): a carcinogenicity study of JNJ-56021927-AAA (apalutamide) by oral gavage in CByB6F1/TgrasH2 hemizygous mice. The RMP (version 3.2) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest quality review of (QRD) template (version 10.1)

15.3.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0080

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of lupus nephritis. 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 38) are updated in accordance

15.3.3. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0038, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the use of blinatumomab as monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor acute lymphoblastic leukaemia (ALL) as consolidation 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 13.0) are updated in accordance

15.3.4. Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/II/0005, Orphan

Applicant: GW Pharma (International) B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 1 year of age and older. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated accordingly. The MAH took the opportunity to correct typographic errors in the product information, to introduce editorial updates and to implement the updated ethanol statement in compliance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.5. Cholera vaccine (recombinant, live, oral) - VAXCHORA (CAP) - EMEA/H/C/003876/II/0003/G

Applicant: Emergent Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Grouped variations consisting of: 1) extension of indication for the active immunisation against disease caused by *Vibrio cholerae* serogroup O1, from the currently approved age range 'adults and children aged 6 years and older' to 'adults and children aged 2 years and older'. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 2.0) are updated in accordance; 2) update section 5.1 of the SmPC to include long-term immunogenicity data supporting Vaxchora (cholera vaccine (recombinant, live, oral)) effectiveness at generating a protective immune response that persists for 2 years following vaccination; based on the final results from study PXVX-VC-200-006: a randomised, double-blind, placebo-controlled trial aimed to assess the safety and immunogenicity of Vaxchora (cholera vaccine (recombinant, live, oral)) in children 2 to <18 years of age. The MAH took the opportunity to include editorial changes throughout the SmPC and Annex II

15.3.6. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0075

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of the product information to remove discrepancies between SmPC and package leaflet in sections dedicated to pregnancy and breastfeeding. In addition, the product information is updated in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and in line with the latest quality review of documents (QRD) template (version 10.1). The MAH took the opportunity to update the list of update the details of local representatives in Estonia, Latvia and the Netherlands. The RMP (version 18.0) is updated to remove the important identified risk of 'severe cutaneous adverse reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms)', to change the milestone for study C1CL670E2422 (listed as a category 1 in Annex II of the product information): an observational, multicentre study to evaluate the safety of deferasirox in the treatment of paediatric non transfusion dependant-thalassaemia (NTDT) patients over 10 years old for whom deferoxamine is contraindicated or inadequate; to change to RMP commitment deliverable and milestone for study C1CL670F2202 (listed as category 3 in the RMP): a randomized, open-label, multicentre, two arm, phase 2 study to evaluate treatment compliance, efficacy and safety of an improved deferasirox formulation (granules) in paediatric patients with iron overload; and to remove study C1CL670F2429 (category 1): a single-arm interventional phase iv, post-authorisation study evaluating the safety of paediatric patients with transfusional hemosiderosis treated with deferasirox crushed film coated tablets, due to fulfilment of the corresponding post-authorisation measure. Finally, the RMP is updated to remove the expedited reporting requirement for the serious adverse drug reactions (ADRs), 'increase in hepatic enzymes >10 x upper limit of normal (ULN)', 'serious rise in creatinine', 'results of renal biopsies', 'cataracts' and 'hearing loss' and 'gallstones as agreed in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000939/201910) adopted in May 2020. Annex II of the product information is updated accordingly

15.3.7. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0069/G

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC in order to add rhinorrhoea to the list of adverse drug reactions (ADRs) with frequency not known based on a systematic review of information from clinical and non-clinical studies, post-marketing data and scientific literature. The package leaflet has been updated accordingly; 2) update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study 109MS303 (ENDORSE) (listed as a category 3 study in the RMP): a dose-blind, multicentre, extension study to determine the long-term safety and efficacy of two doses of BG00012 (dimethyl fumarate) monotherapy in subjects with relapsing-remitting multiple sclerosis. The RMP (version 11.1) is updated accordingly

15.3.8. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA⁷¹), poliomyelitis (inactivated) and haemophilus type B conjugate vaccine (adsorbed) - HEXACIMA (CAP) - EMEA/H/C/002702/WS1965/0110/G; HEXYON (CAP) - EMEA/H/C/002796/WS1965/0114/G

Applicant: Sanofi Pasteur

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Grouped variations consisting of: 1) update of section 5.1 of the SmPC in order to describe the persistence of anti-surface antigens of the hepatitis B virus (HBs) antibodies in subjects 6 years of age having received a hexavalent vaccine based on the final results from study A3L00052: a phase 4, open-label, multicentre study in children previously vaccinated in study A3L38a with 3 doses of either Hexacima/Hexyon (group 1) or Infanrix Hexa (group 2); 2) update of sections 4.4 and 5.1 of the SmPC in order to reword safety and immunogenicity information regarding individuals with immunodeficiency based on the final results from study A3L44: a phase 3, single centre, open-label, two-arm study including human immunodeficiency virus (HIV)-exposed infected and uninfected infants vaccinated with a 3-dose infant primary series (at 6, 10, and 14 weeks of age) and a booster dose (at 15 to 18 months of age) with Hexacima/Hexyon in Republic of South Africa; 3) update of section 4.4 of the SmPC in order to include syncope within the precautions for use. The package leaflet and the RMP (version 13.0) are updated accordingly. In addition, the MAH/Scientific Opinion holder (SOH) took the opportunity to update the list of local representatives in the package leaflet

15.3.9. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0063

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.2, 4.8 and 5.2 of SmPC to clarify dosing recommendations to ensure accurate treatment of patients of 'East-/Southeast-Asian' ancestry and to correct the adverse drug reactions (ADR) list based on currently available data, which was previously submitted and reviewed. In addition, section 4.4 of the SmPC is updated in line with the 'Excipients in the labelling and package leaflet of medicinal products for human use'. The

⁷¹ Ribosomal deoxyribonucleic acid

package leaflet is updated accordingly. The RMP (version 53) is also updated accordingly and to reflect the updated date for the provision of the primary study report of CETB115E2201 (listed as a category 3 study in the RMP): a phase 2 dose-escalation study characterising the pharmacokinetic (PK) of eltrombopag in paediatric patients with previously untreated or relapsed severe aplastic anaemia or recurrent aplastic anaemia as well as to update it in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001205/201809) adopted in April 2019

15.3.10. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0055

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of adult patients with heart failure and reduced ejection fraction. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9 and 5.1 of the SmPC are updated based on final results from study EMPEROR-Reduced: 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 reduced ejection fraction (HFrEF). The package leaflet, labelling and the RMP (version 15.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.11. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/II/0001

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of active ulcerative colitis in adult patients. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, the package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the MAH took the opportunity to include minor updates to Annex II and to implement minor editorial changes throughout the product information

15.3.12. Follitropin delta - REKOVELLE (CAP) - EMEA/H/C/003994/II/0022

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.2 of the SmPC in order to introduce a new anti-Müllerian hormone (AMH) assay to determine the dose of follitropin delta, following an agreed recommendation. The RMP (version 5.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'. The MAH took the opportunity to amend section 4.4 of the SmPC to introduce traceability information. Finally, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.13. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/II/0032

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.8 and 5.1 of the SmPC following the interim data from the primary vaccination phase (stage 1) of study B1971057: a phase 3, randomised, active-controlled, observer-blinded study to assess the immunogenicity, safety and tolerability of bivalent rLP2086 vaccine (Trumenba (meningococcal group B vaccine)) when administered as a 2-dose regimen and a first-in-human study to describe the immunogenicity, safety and tolerability of a bivalent rLP2086 containing pentavalent vaccine (MenABCWY) in healthy subjects ≥ 10 to < 26 years of age. The RMP (version 5.0) is updated accordingly. The MAH took the opportunity to implement some editorial changes in section 4.4 of the SmPC and in the package leaflet to introduce information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.14. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0035

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include chronic rhinosinusitis with nasal polyps (CRSwNP). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7) are updated in accordance. In addition, the MAH took the opportunity to update the local representative for Italy in the package leaflet

15.3.15. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0036/G

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) extension of indication to include eosinophilic granulomatosis with polyangiitis (EGPA). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 7) are updated in accordance. In addition, the MAH took the opportunity to update the local representative for Italy in the package leaflet; 2) addition of a new pack size of 9x100mg/mL multipack for pre-filled pens 100 mg/mL solution for injection and another pack size of 9x100mg/mL multipack for pre-filled syringes 100 mg/mL solution for injection. As a consequence, sections 6.5 and 8 of the SmPC and the package leaflet are updated accordingly. Annex III-A on 'labelling' is also updated to include information relating to the new pack sizes

15.3.16. Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0037

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include hypereosinophilic syndrome (HES). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 6.6 of the SmPC for the powder for solution for injection presentations is updated. The package leaflet and the RMP (version 7) are updated in accordance. The MAH took the opportunity to update the local representative for Italy in the package leaflet

15.3.17. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/X/0116

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension application to introduce a new pharmaceutical form (solution for injection), associated with a new strength (150 mg) and a new route of administration (subcutaneous use). The RMP (version 26.1) is updated accordingly

15.3.18. Netupitant, palonosetron - AKYNZEO (CAP) - EMEA/H/C/003728/X/0031

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension application to introduce a new pharmaceutical form (concentrate for solution for infusion). The RMP (version 2.8) is updated accordingly

15.3.19. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0107

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the 5 year data including data on late relapses from the ongoing studies: 1) study CAMN107I2201 (ENESTfreedom): a phase 2, single-arm, open-label, multicentre nilotinib treatment-free remission (TFR) study in patients with breakpoint cluster region gene/Abelson proto-oncogene 1 (BCR-ABL1) positive chronic myeloid leukaemia in chronic phase (CML-CP), who had achieved durable minimal residual disease (MRD) status on first-line nilotinib treatment; 2) study CAMN107A2408 (ENESTop): a phase 2, single-arm, open-label, multicentre study, evaluating TFR in patients with BCR-ABL1-positive CML-CP who achieved a sustained molecular response of MR4.5 on nilotinib treatment after switching from imatinib to nilotinib. The RMP (version 23.0) is updated accordingly

15.3.20. Nintedanib - VARGATEF (CAP) - EMEA/H/C/002569/II/0035/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: Grouped variations consisting of: 1) update of sections 4.5, 4.6 and 5.2 of the SmPC to reflect the results of study 1199-0340 conducted in female patients with systemic sclerosis associated interstitial lung disease (SSc-ILD) to investigate a potential interaction between nintedanib and a combined oral contraceptive (COC) containing ethinylestradiol/levonorgestrel; 2) update of sections 4.3 and 4.6 of the SmPC to introduce a new contraindication of pregnancy. This follows the update for Ofev (nintedanib) on SSc-ILD introduced in the context of variation II/0026 finalised in February 2020 and as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010318/201910) adopted in May 2020. The package leaflet and the RMP (version 7.0) are updated accordingly

15.3.21. Nintedanib - VARGATEF (CAP) - EMEA/H/C/002569/II/0037

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: Submission of the final report from study LUME BioNIS (listed as an obligation in the Annex II of the product information): a non-interventional study in patients eligible for treatment with Vargatef (nintedanib) to explore whether genetic or genomic markers (alone or combined with clinical covariates) could be used to predict overall survival. Annex II and the RMP (version 8.0) are updated accordingly

15.3.22. Pegvisomant - SOMAVERT (CAP) - EMEA/H/C/000409/II/0098/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Grouped variations consisting of: 1) update of section 4.4 of the SmPC to remove the warning on growth hormone secreting tumours, consequential to the removal of pituitary tumour growth as a potential risk from the RMP. The package leaflet is updated accordingly; 2) update of the RMP (version 2.0) to reflect the evaluation of the final results of study A6291010 (ACROSTUDY) (listed as a category 3 study in the RMP): an open-label, global, multicentre, non-interventional PASS performed to monitor the long-term safety and outcomes of pegvisomant treatment in clinical practice as per the conclusions of variation II/0089 adopted in July 2019. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems'

15.3.23. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/II/0054

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final report from study MO28047 (PERUSE) (listed as an obligation in Annex II): a multicentre, open-label, single-arm study of pertuzumab in combination with trastuzumab and taxane in first line treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive advanced (metastatic or locally recurrent) breast cancer. The RMP (version 13.0) is updated accordingly

15.3.24. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/II/0023/G, Orphan

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of an update of sections 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC based on new clinical data from: 1) study P09-10 (HARMONY III): an open-label naturalistic pragmatic study to assess the long-term safety of pitolisant in the treatment of excessive daytime sleepiness (EDS) (with or without cataplexy) in narcolepsy; 2) study P16-02: a randomised, double-blind, active- and placebo-controlled, single-dummy, 4-way crossover study to determine the abuse potential of pitolisant compared to phentermine and placebo, in healthy, non-dependent recreational stimulant users. The proposed update also includes results of a post approval network meta-analysis which compares efficacy and

safety of multiple treatments, multi-arm studies, and multi-criteria treatment decisions. The package leaflet and the RMP (version 6.0) are updated accordingly

15.3.25. Pyronaridine, artesunate - PYRAMAX (Art 58⁷²) - EMEA/H/W/002319/II/0023/G

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Adrien Inoubli

Scope: Grouped variations consisting of the submission of the final clinical study reports (CSR) of two completed studies: 1) study SP-C-021-15 (listed as a category 3 study in the RMP): a phase 3b/4 cohort event monitoring study conducted in Central Africa to evaluate the safety in patients after the local registration of Pyramax (pyronaridine/artesunate) (CANTAM study); 2) study SP-C-026-18: a randomized open-label exploratory study to determine the efficacy of different treatment regimens of Pyramax (pyronaridine/artesunate) in asymptomatic carriers of *Plasmodium falciparum* mono-infections. This non-imposed study was conducted in Gambia and Zambia and compared asymptomatic subjects with parasitaemia dosed according to the approved label of 3-day dosing with 2-day and 1-day dosing. As a consequence, sections 4.2, 4.4, 4.6, 4.8 and 5.1 are updated. The package leaflet is updated in accordance. The RMP (version 17) is also updated accordingly and in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

15.3.26. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0093

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Update of section 4.6 of the SmPC in order to update safety information following pregnancy outcome data for raltegravir 400 mg film-coated tablet from prospective reports of pregnancy data with known outcome and time of raltegravir exposure. The RMP (version 15.1) is updated accordingly. In addition, the MAH took the opportunity to introduce some minor changes agreed in previous procedures in the product information and to update the list of local representatives for Germany. Finally, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.27. Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/004195/II/0017

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.8 and 5.1 of the SmPC to provide results from the further analysis of the continuation study 261302: a phase 3b, prospective, open label, multicentre continuation study of safety and efficacy of BAX 855 (rurioctocog alfa pegol) in the prophylaxis of bleeding; and the pharmacokinetics (PK)-guided dosing study 261303: a phase 3, prospective, randomised, multicentre clinical study comparing the safety and efficacy of rurioctocog alfa pegol following PK-guided prophylaxis targeting two different factor VIII (FVIII) trough levels in subjects with severe haemophilia A. The package leaflet

⁷² 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)

and the RMP (version 2.0) are updated accordingly. The MAH took the opportunity to update the product information to introduce information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

15.3.28. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0050

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.2 and 5.1 of the SmPC to include the final results of study CINC424A2201 (EXPAND study) (listed as a category 3 study in the RMP): a phase 1b open-label, dose-finding study intended to establish the maximum safe starting dose (MSSD) of ruxolitinib tablets administered orally to patients with myelofibrosis (MF) in previous unstudied population of patients who had baseline platelet counts $\geq 50 \times 10^9/L$ and $< 100 \times 10^9/L$. The package leaflet and the RMP (version 12.0) are updated accordingly. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems' and in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010015/202002) adopted in October 2020

15.3.29. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/II/0031

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to reflect new data based on final results from study D1693C00001 (DECLARE): a multicentre, randomised, double-blind, placebo-controlled study to evaluate the effect of dapagliflozin on cardiovascular (CV) and renal outcomes in patients with type 2 diabetes mellitus (T2DM) with or without established CV disease. The labelling, package leaflet and the RMP (version 5.1) are updated accordingly. The MAH took the opportunity to introduce additional editorial changes to the product information

15.3.30. Tegafur, gimeracil, oteracil - TEYSUNO (CAP) - EMEA/H/C/001242/II/0045

Applicant: Nordic Group B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of metastatic colorectal cancer in adult patients where it is not possible to initiate or continue treatment with another fluoropyrimidine. As a consequence, sections 4.1, 4.2, 4.3, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 10.0) are updated in accordance

15.3.31. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/II/0049

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include, in co-administration with acetylsalicylic acid (ASA), the prevention of stroke in adult patients with acute ischaemic stroke or transient

ischaemic attack (TIA), based on the final results of study D5134C00003 (THALES): a phase 3, international, multicentre, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of ticagrelor and ASA compared with ASA in the prevention of stroke and death in patients with acute ischaemic stroke or transient ischaemic attack. 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 13.0) are updated in accordance

15.3.32. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0028

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report on Biospecimen testing study (listed as a category 3 study in the RMP): an exploratory study to assess biomarkers related to venous thromboembolism (VTE) events in study A3921133 (a phase 3b/4 randomised safety endpoint study of 2 doses of tofacitinib in comparison to a tumour necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis). The RMP (version 14.1) is updated accordingly

15.3.33. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0081/G

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of: 1) update of section 4.2 of the SmPC solution for injection presentations in order to change posology recommendations for patients with ulcerative colitis, and section 5.1 of the SmPC to update efficacy information based on 2-year results from study 3001 (listed as a category 3 study in the RMP): a phase 3, randomized, double blind, placebo controlled, parallel-group, multicentre protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis; 2) update of section 5.1 of the SmPC in order to update efficacy information based on 5-year results from study 3003 (listed as a category 3 study in the RMP): a phase 3, randomized, double blind, placebo controlled, parallel-group, multicentre trial to evaluate the safety and efficacy of ustekinumab maintenance therapy in adult patients with moderately to severely active Crohn's disease. The RMP (version 18.1) is updated accordingly

15.3.34. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0030

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication in combination with hypomethylating agents (HMAs) or low dose cytarabine (LDAC) for the treatment of adult patients with newly-diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. As a consequence, sections 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and RMP (version 6.1) 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. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/202006

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.2. Angiotensin II - GIAPREZA (CAP) - PSUSA/00010785/202006

Applicant: La Jolla Pharmaceutical II B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Betibeglogene autotemcel - ZYNTEGLO (CAP) - PSUSA/00010769/202005

Applicant: bluebird bio (Netherlands) B.V, ATMP⁷³

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.4. Binimetinib - MEKTOVI (CAP) - PSUSA/00010717/202006

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.5. Buprenorphine⁷⁴ - SIXMO (CAP) - PSUSA/00010778/202005

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

⁷³ Advanced therapy medicinal product

⁷⁴ Implant(s) only

PRAC Rapporteur: Adam Przybylkowski
Scope: Evaluation of a PSUSA procedure

16.1.6. Cannabidiol⁷⁵ - EPIDYOLEX (CAP) - PSUSA/00010798/202006

Applicant: GW Pharma (International) B.V.
PRAC Rapporteur: Ana Sofia Diniz Martins
Scope: Evaluation of a PSUSA procedure

16.1.7. Chlorhexidine - UMBIPRO (Art 58⁷⁶) - EMEA/H/W/003799/PSUV/0006

Applicant: GlaxoSmithKline Trading Services Limited
PRAC Rapporteur: Rugile Pilviniene
Scope: Evaluation of a PSUR procedure

16.1.8. Cholera vaccine (inactivated, oral) - DUKORAL (CAP) - PSUSA/00000730/202004

Applicant: Valneva Sweden AB
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

16.1.9. Cholera vaccine (oral, live) - VAXCHORA (CAP) - PSUSA/00010862/202006

Applicant: Emergent Netherlands B.V.
PRAC Rapporteur: Jean-Michel Dogné
Scope: Evaluation of a PSUSA procedure

16.1.10. Crisaborole - STAQUIS (CAP) - PSUSA/00010842/202006

Applicant: Pfizer Europe MA EEIG
PRAC Rapporteur: Eva Segovia
Scope: Evaluation of a PSUSA procedure

16.1.11. Darunavir, cobicistat - REZOLSTA (CAP) - PSUSA/00010315/202005

Applicant: Janssen-Cilag International NV
PRAC Rapporteur: Ilaria Baldelli
Scope: Evaluation of a PSUSA procedure

⁷⁵ Centrally authorised product(s) only

⁷⁶ 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)

16.1.12. Dasatinib - SPRYCEL (CAP) - PSUSA/00000935/202006

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.13. Delafloxacin - QUOFENIX (CAP) - PSUSA/00010822/202006

Applicant: A. Menarini Industrie Farmaceutiche Riunite s.r.l.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.14. Dengue tetravalent vaccine (live, attenuated) - DENGVAXIA (CAP) - PSUSA/00010740/202006

Applicant: Sanofi Pasteur

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.15. Dimethyl fumarate⁷⁷ - SKILARENCE (CAP) - PSUSA/00010647/202006

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.16. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/202006

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.17. Emedastine - EMADINE (CAP) - PSUSA/00001207/202005

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.18. Emicizumab - HEMLIBRA (CAP) - PSUSA/00010668/202005

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

⁷⁷ Indicated for the treatment of psoriasis

16.1.19. Encorafenib - BRAFTOVI (CAP) - PSUSA/00010719/202006

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.1.20. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/202005

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.21. Fidaxomicin - DIFICLIR (CAP) - PSUSA/00001390/202005

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.22. Fluciclovine (¹⁸F) - AXUMIN (CAP) - PSUSA/00010594/202005

Applicant: Blue Earth Diagnostics Ireland Limited

PRAC Rapporteur: Rugile Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.1.23. Follitropin beta - PUREGON (CAP) - PSUSA/00001465/202005

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.24. Fulvestrant - FASLODEX (CAP) - PSUSA/00001489/202004

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.25. Galsulfase - NAGLAZYME (CAP) - PSUSA/00001515/202005

Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.26. Gemtuzumab ozogamicin - MYLOTARG (CAP) - PSUSA/00010688/202005

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.27. Givosiran - GIVLAARI (CAP) - PSUSA/00010839/202005

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.28. Glibenclamide⁷⁸ - AMGLIDIA (CAP) - PSUSA/00010690/202005

Applicant: Ammtek

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.29. Human fibrinogen, human thrombin - EVICEL (CAP); TACHOSIL (CAP); VERASEAL (CAP) - PSUSA/00010297/202006

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.30. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/202006

Applicant: MSD Vaccins

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.31. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/202005

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.32. Larotrectinib - VITRAKVI (CAP) - PSUSA/00010799/202005

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

⁷⁸ Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.33. Lumacaftor, ivacaftor - ORKAMBI (CAP) - PSUSA/00010455/202005

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.34. Lutetium (¹⁷⁷Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/202006

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.35. Methylthioninium chloride - METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP) - PSUSA/00002029/202005

Applicant: Provepharm SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.36. Mexiletine⁷⁹ - NAMUSCLA (CAP) - PSUSA/00010738/202006

Applicant: Lupin Europe GmbH

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.37. Migalastat - GALAFOLD (CAP) - PSUSA/00010507/202005

Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.38. Netarsudil - RHOKIINSA (CAP) - PSUSA/00107812/202006

Applicant: Aerie Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.39. Nonacog beta pegol - REFIXIA (CAP) - PSUSA/00010608/202005

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

⁷⁹ Centrally authorised product(s) only

Scope: Evaluation of a PSUSA procedure

16.1.40. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/202006

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.41. Nusinersen - SPINRAZA (CAP) - PSUSA/00010595/202005

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.42. Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/202005

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.43. Opicapone - ONGENTYS (CAP) - PSUSA/00010516/202006

Applicant: Bial - Portela & C^a, S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.44. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - PSUSA/00010501/202005

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.45. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP); prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - PREPANDRIX⁸⁰ - PSUSA/00002281/202005

Applicant(s): GlaxoSmithKline Biologicals SA

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

⁸⁰ European Commission (EC) Decision dated 17 December 2020 on the withdrawal of the marketing authorisation(s)

16.1.46. Pentosan polysulfate sodium⁸¹ - ELMIRON (CAP) - PSUSA/00010614/202006

Applicant: Bene-Arzneimittel GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.47. Pertuzumab - PERJETA (CAP) - PSUSA/00010125/202006

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.1.48. Polatuzumab vedotin - POLIVY (CAP) - PSUSA/00010817/202006

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.49. Prasterone⁸² - INTRAROSA (CAP) - PSUSA/00010672/202005

Applicant: Endoceutics S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.50. Ravulizumab - ULTOMIRIS (CAP) - PSUSA/00010787/202006

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.51. Rucaparib - RUBRACA (CAP) - PSUSA/00010694/202006

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.52. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/202006

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

⁸¹ Centrally authorised product(s) only

⁸² Pessary, vaginal use only

16.1.53. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/202006

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.54. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/202005

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.55. Tilmanocept - LYMPHOSEEK (CAP) - PSUSA/00010313/202005

Applicant: Navidea Biopharmaceuticals Europe Ltd.

PRAC Rapporteur: Rugile Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.1.56. Tolvaptan⁸³ - SAMSCA (CAP) - PSUSA/00002994/202005

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.57. Trametinib - MEKINIST (CAP) - PSUSA/00010262/202005

Applicant: Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.58. Treosulfan⁸⁴ - TRECONDI (CAP) - PSUSA/00010777/202006

Applicant: medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.1.59. Turoctocog alfa pegol - ESPEROCT (CAP) - PSUSA/00010782/202006

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

⁸³ Indicated for adults with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)

⁸⁴ Centrally authorised product(s) only

16.1.60. Varenicline - CHAMPIX (CAP) - PSUSA/00003099/202005

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.61. Vonicog alfa - VEYVONDI (CAP) - PSUSA/00010714/202006

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Human normal immunoglobulin (IgG) - FLEBOGAMMA DIF (CAP); HIZENTRA (CAP); HYQVIA (CAP); KIOVIG (CAP); PRIVIGEN (CAP); NAP - PSUSA/00001633/202005

Applicant(s): Baxalta Innovations GmbH (HyQvia), CSL Behring GmbH (Hizentra, Privigen), Instituto Grifols, S.A. (Flebogamma DIF), Takeda Manufacturing Austria AG (Kiovig), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.2.2. Ivabradine - CORLENTOR (CAP); IVABRADINE ANPHARM (CAP); PROCORALAN (CAP); NAP - PSUSA/00001799/202004

Applicant(s): Anpharm Przedsiębiorstwo Farmaceutyczne S.A. (Ivabradine Anpharm), Les Laboratoires Servier (Corlentor, Procoralan), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.2.3. Topotecan - HYCAMTIN (CAP); TOPOTECAN HOSPIRA (CAP); NAP - PSUSA/00002997/202005

Applicant(s): Novartis Europharm Limited (Hycamtin), Pfizer Europe MA EEIG (Topotecan Hospira), various

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.2.4. Treprostinil - TREPULMIX (CAP); NAP - PSUSA/00003013/202005

Applicant(s): SciPharm Sarl, various

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Azithromycin⁸⁵ (NAP) - PSUSA/00010492/202004

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.3.2. Chlorpromazine (NAP) - PSUSA/00000715/202005

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.3. Cidofovir (NAP) - PSUSA/00010558/202006

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.4. Clevidipine (NAP) - PSUSA/00010288/202005

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.5. Cyproterone, ethinylestradiol (NAP) - PSUSA/00000906/202005

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.6. Dexpanthenol, xylometazoline (NAP) - PSUSA/00010030/202005

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

⁸⁵ Formulation(s) for ocular use only

16.3.7. Diphtheria vaccine (adsorbed) (NAP); diphtheria, tetanus vaccine (adsorbed) (NAP)
- PSUSA/00001128/202005

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.8. Fluorescein⁸⁶ (NAP) - PSUSA/00009153/202004

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.9. Formoterol (NAP) - PSUSA/00001469/202005

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.10. Gadoteric acid⁸⁷ (NAP) – PSUSA/00001505/202004

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.11. Human hemin (NAP) - PSUSA/00001629/202005

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.12. Indobufen (NAP) - PSUSA/00001736/202005

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.13. Iodixanol (NAP) - PSUSA/00001766/202004

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

⁸⁶ Systemic use only

⁸⁷ Intra-articular formulation(s) only

16.3.14. Ivabradine, metoprolol (NAP) - PSUSA/00010381/202004

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.15. Ketobemidone (NAP) - PSUSA/00001807/202005

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.16. Lanreotide (NAP) - PSUSA/00001826/202005

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.17. Methoxyflurane (NAP) - PSUSA/00010484/202005

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.18. Mifepristone, misoprostol (NAP) - PSUSA/00010378/202005

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.19. Misoprostol⁸⁸ (NAP) - PSUSA/00010291/202006

Applicant(s): various

PRAC Lead: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

16.3.20. Misoprostol⁸⁹ (NAP) - PSUSA/00010353/202005

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

⁸⁸ Gastrointestinal indication(s) only

⁸⁹ Gynaecological indication(s) only - labour induction

16.3.21. Misoprostol⁹⁰ (NAP) - PSUSA/00010354/202005

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3.22. Mometasone (NAP) - PSUSA/00002085/202005

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.23. Nicergoline (NAP) - PSUSA/00002150/202005

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.24. Ozenoxacin (NAP) - PSUSA/00010651/202005

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.25. Peppermint oil (NAP) - PSUSA/00010436/202005

Applicant(s): various

PRAC Lead: Gudrun Stefansdottir

Scope: Evaluation of a PSUSA procedure

16.3.26. Solifenacin (NAP) - PSUSA/00002769/202006

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.27. Ticlopidine (NAP) - PSUSA/00002952/202005

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

⁹⁰ Gynaecological indication(s) only - termination of pregnancy

16.3.28. Valsartan (NAP); hydrochlorothiazide, valsartan (NAP) - PSUSA/00010396/202004

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/LEG 066

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Cumulative review of cases of pancreatitis as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000013/201912) adopted in September 2020

16.4.2. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/LEG 031

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Cumulative review of cases of acute pancreatitis as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00009204/202001) adopted in September 2020

16.4.3. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/LEG 049

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Cumulative review of cases of major adverse cardiovascular events (MACE), including fatal cases, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00003085/201912) adopted in July 2020

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/II/0055

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Update of sections 4.4 and 5.2 of the SmPC in order to include information on the use of ceftaroline in patients with cystic fibrosis, based on a pooled population pharmacokinetic (pop PK) analysis that included data from cystic fibrosis patients treated with ceftaroline fosamil as requested in the conclusions of LEG 016 adopted in June 2020, initially requested in the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00010013/201810) adopted in May 2019. The MAH took the opportunity to make minor editorial changes in the product information

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)⁹¹

17.1.1. Betibeglogene autotemcel – ZYNTÉGLO (CAP) - EMEA/H/C/PSA/S/0059.1

Applicant: Bluebird bio (Netherlands) B.V, ATMP⁹²

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0059 [substantial amendment to a protocol previously agreed in the framework of the initial marketing authorisation(s) for a non-interventional PASS to collect longitudinal data on clinical outcomes of patients with transfusion-dependent β -thalassaemia (TDT) who have received treatment with Zynteglo (betibeglogene autotemcel) in the post-marketing setting] as per the request for supplementary information (RSI) adopted in November 2020⁹³

17.1.2. Blinatumomab – BLINCYTO (CAP) - EMEA/H/C/PSA/S/0057.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: MAH's response to PSA/S/0057 [substantial amendment to a protocol previously agreed in February 2020 for study 20180130: an observational PASS to describe the long-term safety profile of first-relapse B-precursor acute lymphocytic leukaemia (ALL) paediatric patients who have been treated with blinatumomab or chemotherapy prior to undergoing haematopoietic stem cell transplant (HSCT)] as per the request for supplementary information (RSI) adopted in September 2020

17.1.3. Elosulfase alfa – VIMIZIM (CAP) - EMEA/H/C/PSA/S/0062

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Substantial amendment to a protocol previously agreed in the framework of the initial marketing authorisation(s) for a multicentre, multinational, observational Morquio A Registry Study (MARS) to characterise and describe the mucopolysaccharidosis IV type A (MPS IVA) population as a whole, including the heterogeneity, progression, and natural history of MPS IVA and to track the safety and clinical outcomes of patients with MPS IVA patients treated with Vimizim (elosulfase alfa)

⁹¹ In accordance with Article 107n of Directive 2001/83/EC

⁹² Advanced therapy medicinal product

⁹³ Held 26-29 October 2020

17.1.4. Turoctocog alfa pegol – ESPEROCT (CAP) - EMEA/H/C/PSA/S/0061

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment to a protocol previously agreed in April 2020 for a multinational, prospective, open labelled, non-controlled, non-interventional post-authorisation study to investigate the long-term safety of turoctocog alfa pegol (N8-GP) including the polyethylene glycol (PEG) moiety of the substance during routine prophylaxis in patients with haemophilia A

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁹⁴

17.2.1. Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/MEA 002.2

Applicant: Evolus Pharma Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 002.1 [protocol for study EV-010: a non-interventional post-authorisation safety study of Nuceiva (botulinum toxin type A) for the treatment of moderate-to-severe glabellar lines] as per the request for supplementary information (RSI) adopted in September 2020

17.2.2. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 003.2

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to MEA 003.1 [protocol for observational cohort study TV48125-MH-50038: a pregnancy database study assessing pregnancy outcomes in patients treated with Ajovy (fremanezumab)] as per the request for supplementary information (RSI) adopted in March 2020

17.2.3. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 033.4

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Substantial amendment to a protocol previously agreed in December 2017 for study MK-8259-050 (version 2.0) (listed as a category 3 study in the RMP): an observational PASS for golimumab in the treatment of poly-articular juvenile idiopathic arthritis (pJIA) using the German Biologics JIA registry (BiKeR)

17.2.4. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 020.2

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

⁹⁴ 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

Scope: MAH's response to MEA 020.1 [protocol for study CT-P13 4.8: an observational, prospective cohort study to evaluate the safety of Remsima (infliximab) subcutaneous in patients with rheumatoid arthritis (RA)] as per the request for supplementary information (RSI) adopted in September 2020

17.2.5. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/MEA 002

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Protocol for study VX20-445-120: a five year-registry based study to assess real-world effects and utilisation patterns of elexacaftor/tezacaftor/ivacaftor combination therapy (ELX/TEZ/IVA) in patients with cystic fibrosis (CF)

17.2.6. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/MEA 001.7

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 001.5 [substantial amendment to a protocol previously agreed in May 2018 for study AMDC-204-401: a post-authorisation observational study to evaluate the safety of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care] as per the request for supplementary information (RSI) adopted in July 2020

17.2.7. Lutetium (¹⁷⁷Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.5

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Progress report for study A-LUT-T-E02-402 (SALUS study) (listed as a category 3 study in the RMP): an international post-authorisation safety registry to assess the long-term safety of Lutathera (lutetium (¹⁷⁷Lu)) for unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) [final clinical study report (CSR) expected in December 2025]

17.2.8. Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/MEA 001.3

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 001.2 [protocol for an observational PASS of patients with chronic opioid use for non-cancer and cancer pain who have opioid-induced constipation (OIC) [final clinical study report (CSR) expected in January 2026]] as per the request for supplementary information (RSI) adopted in September 2020

17.2.9. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 004.6

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Substantial amendment to a protocol previously agreed in April 2018 for study NB-452: a cross-sectional survey to evaluate the effectiveness of the physician prescribing checklist (PPC) among physicians in the European Union (EU) as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010366/201909) adopted in April 2020

17.2.10. Patisiran - ONPATTRO (CAP) - EMEA/H/C/004699/MEA 003.1

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 003 [protocol for non-interventional study ALN-TTR02-010: patisiran-lipid nanoparticle (LNP) observational pregnancy surveillance programme] as per the request for supplementary information (RSI) adopted in September 2020

17.2.11. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁹⁵) - EMEA/H/W/002300/MEA 003.3

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Scientific Opinion Holder (SOH)'s response to MEA 003.2 [amended protocol previously agreed in May 2018 for study EPI-MAL-003 (listed as a category 3 study in the RMP): a phase 4 prospective observational study to evaluate the safety, effectiveness and impact of Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)) in young children in sub-Saharan Africa in order to estimate the incidence of potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with the vaccine] as per the request for supplementary information (RSI) adopted in September 2020

17.2.12. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 001.2 [protocol for study P19-633: a post-marketing registry-based prospective cohort study of long-term safety of risankizumab in real world setting in Denmark and Sweden [final study report expected in December 2031]] as per the request for supplementary information (RSI) adopted in September 2020

17.3. Results of PASS imposed in the marketing authorisation(s)⁹⁶

None

⁹⁵ 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)

⁹⁶ In accordance with Article 107p-q of Directive 2001/83/EC

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁹⁷

17.4.1. Agalsidase beta - FABRAZYME (CAP) - EMEA/H/C/000370/II/0120

Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final study report of the Fabry pregnancy sub-registry (listed as a category 3 study in the RMP): a multicentre, international, longitudinal, observational study on pregnancy outcomes for any pregnant woman enrolled in the MAH's Fabry registry who also consented to participate in the sub-registry, regardless of whether she was receiving disease therapy and irrespective of the commercial medicinal product with which she may have been be treated

17.4.2. Follitropin alfa - OVALEAP (CAP) - EMEA/H/C/002608/II/0034

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report for study SOFIA (listed as a category 3 study in the RMP): a phase 4, multi-national, comparative, prospective, non-interventional, observational cohort study evaluating the safety of Ovaleap (follitropin alfa) in infertile women undergoing superovulation for assisted reproductive technologies. The RMP (version 3.3) is updated accordingly

17.4.3. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/II/0032

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final clinical study report (CSR) for study AMDC-204-401: a post-authorisation observational study to evaluate the safety of Adasuve/Staccato (loxapine for inhalation) in agitated persons in routine clinical care (EU PASS). The RMP (version 9.3) 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 019.5

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Second interim report for drug utilisation survey OBS14697: a drug utilisation study to assess the effectiveness of dosing recommendation of Praluent (alirocumab) as per the product information to avoid very low-density lipoprotein (LDL)-C levels [final results expected in Q3 2021]

⁹⁷ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

17.5.2. Axicabtagene ciloleucel - YESCARTA (CAP) - EMEA/H/C/004480/ANX 002.1

Applicant: Kite Pharma EU B.V., ATMP⁹⁸

PRAC Rapporteur: Anette Kirstine Stark

Scope: First quarterly safety data report for study KT-EU-471-0117: a long-term non-interventional registry study of Yescarta (axicabtagene ciloleucel) to evaluate the incidence rate and severity of adverse drug reactions (ADRs) and further evaluate and characterise the identified risks, potential risks and missing information (from initial opinion/marketing authorisation)

17.5.3. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/MEA 024.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

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

17.5.4. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/ANX 002.7

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Third interim annual report for a prospective, multi-country, observational registry study to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole using the existing European registry on Cushing's syndrome (ERCUSYN) to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole

17.5.5. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 001.1

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study PUMA-NER-6201: an open-label study to characterize the incidence and severity of diarrhoea in patients with early stage human epidermal growth factor receptor 2 positive (HER2+) breast cancer treated with neratinib and intensive loperamide prophylaxis, with/without anti-inflammatory treatment (budesonide) and with/without a bile acid sequestrant (colestipol) [final study results expected in March 2021]

17.5.6. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/ANX 011.7

Applicant: Theramex Ireland Limited

⁹⁸ Advanced therapy medicinal product

PRAC Rapporteur: Adrien Inoubli

Scope: Fifth interim report for study P08291 (PRO-E2): a prospective observational controlled cohort study to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the VTE risk in users of combined oral contraceptives containing levonorgestrel

17.5.7. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/ANX 001.10

Applicant: Shionogi B.V.

PRAC Rapporteur: Kirsti Villikka

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

17.5.8. Rotavirus vaccine (live, oral) - ROTARIX (CAP) - EMEA/H/C/000639/MEA 094.2

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Second annual report for study EPI-ROTA-052 BOD EU SUPP (201433) (EuroRotaNet): an observational community-based strain surveillance study to monitor the potential emergence and spread of novel rotavirus strains throughout Europe [study extended until December 2020]

17.5.9. Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/ANX 001.4

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth interim report for study ALX-LALD-501: a non-interventional, multicentre, prospective disease and clinical outcome registry of patients with lysosomal acid lipase deficiency (LAL-D) to further understand the disease, its progression and any associated complication, and to evaluate the long-term efficacy and safety of Kanuma (sebelipase alfa)

17.5.10. Somatropin - OMNITROPE (CAP) - EMEA/H/C/000607/MEA 039

Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Second interim report for study EP00-502 – PATRO Adults: a non-interventional post-marketing surveillance in adult patients with growth hormone deficiency treated with Omnitrope (somatropin) within routine clinical practice in Europe

17.5.11. Tisagenlecleucel - KYMRIA[®] (CAP) - EMEA/H/C/004090/ANX 003.3

Applicant: Novartis Europharm Limited, ATMP⁹⁹

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Second 6-monthly interim report for a study based on disease registry CCTL019B2401 (listed as a category 1 study in Annex II and the RMP): a non-interventional PASS in acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL) patients in order to further characterise the safety, including long-term safety, of Kymriah (tisagenlecleucel). The procedure also includes the MAH's response to ANX 003.2 [final study report expected in December 2038]

17.6. Others

17.6.1. Apalutamide - ERLEADA (CAP) - EMEA/H/C/004452/MEA 004.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 004.1 [feasibility study for a prospective, observational safety study to characterise the risks of the use of apalutamide in non-metastatic castration-resistant prostate cancer (NM-CRPC) patients on androgen deprivation therapy (ADT) with clinically significant cardiovascular conditions [final report expected in 2023]] as per the request for supplementary information (RSI) adopted in February 2020

17.6.2. Avatrombopag - DOPTELET (CAP) - EMEA/H/C/004722/MEA 002.2

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.1 [feasibility assessment for study AVA-CLD-402: evaluation of the feasibility of conducting a PASS of Doptelet (avatrombopag) in patients with severe chronic liver disease (CLD) and of the use of potential European electronic health care databases] as per the request for supplementary information (RSI) adopted in July 2020

17.6.3. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/LEG 028.2

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Third six-monthly update on the development of the child-resistant multi-dose nasal spray DoseGuard as requested in the conclusions of procedure R/0049 finalised in April 2019

17.6.4. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/LEG 121.3

Applicant: AbbVie Deutschland GmbH & Co. KG

⁹⁹ Advanced therapy medicinal product

PRAC Rapporteur: Adrien Inoubli

Scope: Annual safety review of the PENTA - European Pregnancy and Paediatric human immunodeficiency virus (HIV) Cohort Collaboration (EPPICC) cohort study conducted in children from 14 days to 2 years of age as regards to chronic exposure to propylene glycol and ethanol and toxicity, medication errors and lack of efficacy/resistance in relation to potentially suboptimal pharmacokinetic (PK) parameters

17.6.5. Lusutrombopag - MUPLEO (CAP) - EMEA/H/C/004720/MEA 002.1

Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

17.6.6. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 064.1

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Interim report for study 101MS411 (listed as a category 3 study in the RMP): an observational cohort study utilising the Tysabri outreach unified commitment to health (TOUCH) prescribing programme and certain EU multiple sclerosis (MS) registries to estimate the risk of progressive multifocal leukoencephalopathy (PML) and other serious opportunistic infections among patients who were exposed to an MS disease modifying therapies prior to treatment with Tysabri (natalizumab) [final clinical study report expected in Q2 2024]

17.6.7. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/MEA 016

Applicant: Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Primary interim clinical study report (CSR) (report No. 1100510) for study BO28407 (KAITLIN): a randomised, multicentre, open-label, phase 3 trial comparing trastuzumab plus pertuzumab plus a taxane following anthracyclines versus trastuzumab emtansine plus pertuzumab following anthracyclines as adjuvant therapy in patients with operable human epidermal growth factor receptor 2 (HER2)-positive primary breast cancer

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0023 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Annual reassessment of the marketing authorisation

18.1.2. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0043 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.3. Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/S/0014 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.4. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/S/0039 (without RMP)

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Betibeglogene autotemcel - ZYNTEGLO (CAP) - EMEA/H/C/003691/R/0018 (without RMP)

Applicant: bluebird bio (Netherlands) B.V, ATMP¹⁰⁰

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.2. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0047 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Conditional renewal of the marketing authorisation

18.2.3. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/R/0011 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Conditional renewal of the marketing authorisation

18.2.4. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - EMEA/H/C/004750/R/0012 (without RMP)

Applicant: Novartis Gene Therapies EU Limited, ATMP¹⁰¹

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.5. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) - PANDEMIC INFLUENZA VACCINE H5N1 ASTRAZENECA (CAP) - EMEA/H/C/003963/R/0040 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Sonja Hrabcik

Scope: Conditional renewal of the marketing authorisation

18.2.6. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/R/0025 (without RMP)

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Conditional renewal of the marketing authorisation

¹⁰⁰ Advanced therapy medicinal product

¹⁰¹ Advanced therapy medicinal product

18.3. Renewals of the marketing authorisation

18.3.1. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/R/0018 (with RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.2. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/R/0026 (with RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.3. Human coagulation factor X - COAGADEX (CAP) - EMEA/H/C/003855/R/0031 (with RMP)

Applicant: BPL Bioproducts Laboratory GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.4. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/R/0055 (without RMP)

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

18.3.5. Saxagliptin, dapagliflozin - QTERN (CAP) - EMEA/H/C/004057/R/0030 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Ilaria Baldelli

Scope: 5-year renewal of the marketing authorisation

18.3.6. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/R/0054 (without RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

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 11-14 January 2021 meeting (marked as "a"), additionally for the 04 January 2021 extraordinary meeting (marked as "b"), for the 22 January 2021 extraordinary meeting (marked as "c"), and for the 28 January 2021 ORGAM teleconference (marked as "d").

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus ^{a, b, c, d}	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser ^{a, b, c, d}	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik ^{a, b, c}	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné ^{a, b, c}	Member	Belgium	No interests declared	Full involvement
Laurence de Fays ^{a, b, c}	Alternate	Belgium	No restrictions applicable to this meeting	Full involvement
Maria Popova-Kiradjieva ^{a, b, c, d}	Member	Bulgaria	No interests declared	Full involvement
Julian Eftimov ^{b, c}	Alternate	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce ^{a, b, c, d}	Member	Croatia	No interests declared	Full involvement
Panagiotis Psaras ^{a, b, c, d}	Member	Cyprus	No interests declared	Full involvement
Christina Sylvia Chrysostomou ^d	Alternate (from 20/01/2021)	Cyprus	No interests declared	Full involvement
Eva Jirsová ^{a, b, c, d}	Member	Czechia	No interests declared	Full involvement
Jana Lukacisinova ^{a, b, c, d}	Alternate	Czechia	No interests declared	Full involvement
Anette Kirstine Stark ^{a, b, c, d}	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted ^{a, b, c, d}	Alternate	Denmark	No participation in final deliberations and voting on:	15.3.14. Mepolizumab - NUCALA (CAP) - II/0035 15.3.15. Mepolizumab - NUCALA (CAP) - 0036/G 15.3.16. Mepolizumab - NUCALA (CAP) - II/0037
Maia Uusküla ^{a, b, c, d}	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka ^{a, b, c, d}	Member	Finland	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
Kimmo Jaakkola ^{a, b, c, d}	Alternate	Finland	No interests declared	Full involvement
Adrien Inoubli ^{a, b, c, d}	Member	France	No interests declared	Full involvement
Tiphaine Vaillant ^{a, b, c, d}	Alternate	France	No interests declared	Full involvement
Martin Huber ^{a, b, c, d}	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski ^{a, b, c}	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza ^{a, c}	Alternate	Greece	No interests declared	Full involvement
Julia Pallos ^{a, b, c}	Member	Hungary	No restrictions applicable to this meeting	Full involvement
Melinda Palfi ^{a, b, c, d}	Alternate	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir ^{a, b, c, d}	Member	Iceland	No participation in discussion, final deliberations and voting on:	4.3.1. Adalimumab - AMGEVITA (CAP); AMSPARITY (CAP), HALIMATOZ (CAP); HEFIYA (CAP); HULIO (CAP); HUMIRA (CAP) - SDA/118.1; HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP) 15.3.3. Blinatumomab - BLINCYTO (CAP) - II/0038 6.1.4. Blinatumomab - BLINCYTO (CAP) - PSUSA 6.1.21. Fidaxomicin - DIFICLIR (CAP) - PSUSA 17.1.2. Blinatumomab - BLINCYTO (CAP) - PSA/S/0057.1
Rhea Fitzgerald ^{a, b, c, d}	Member	Ireland	No interests declared	Full involvement
Ronan Grimes ^{a, b, c, d}	Alternate	Ireland	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
Amelia Cupelli ^{a, b, c, d}	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli ^{a, b, c, d}	Alternate	Italy	No interests declared	Full involvement
Zane Neikena ^{a, b, c, d}	Member	Latvia	No interests declared	Full involvement
Zane Stade ^b	Alternate	Latvia	No interests declared	Full involvement
Rugile Pilvinienė ^{a, b, c, d}	Member	Lithuania	No interests declared	Full involvement
Ruta Kerpauskienė ^a	Alternate	Lithuania	No interests declared	Full involvement
Nadine Petitpain ^{a, b, c}	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
Anne-Cécile Vuillemin ^{a, b, c, d}	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg ^{a, b, c}	Member	Malta	No interests declared	Full involvement
Menno van der Elst ^{a, b, c, d}	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan ^{a, b, c, d}	Alternate	Netherlands	No interests declared	Full involvement
David Olsen ^{a, b, c, d}	Member	Norway	No participation in final deliberations and voting on:	16.1.32. Larotrectinib - VITRAKVI (CAP) - PSUSA 6.3.6. Gadobutrol (NAP) - PSUSA 6.3.8. Gadopentetic acid (NAP) - PSUSA 6.3.9. Gadoteric acid (NAP) - PSUSA 6.3.11. Gadoxetic acid disodium (NAP) - PSUSA 7.4.1. Aflibercept - EYLEA (CAP) - II/0068
Karen Pernille Harg ^{a, b, c, d}	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski ^{a, b, c, d}	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska ^{a, b, c, d}	Alternate	Poland	No interests declared	Full involvement
Ana Sofia Diniz Martins ^{a, b, c, d}	Member	Portugal	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
Marcia Sofia Sanches de Castro Lopes Silva ^{a, b, c, d}	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe ^a	Member (until 25/01/2021)	Romania	No interests declared	Full involvement
Roxana Dondera ^d	Member (from 25/01/2021)	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni ^{a, b, c, d}	Alternate	Romania	No interests declared	Full involvement
Michal Radik ^{a, b, c, d}	Member	Slovakia	No interests declared	Full involvement
Marek Juracka ^{a, b, c, d}	Alternate	Slovakia	No interests declared	Full involvement
Gabriela Jazbec ^{a, b, c, d}	Member	Slovenia	No interests declared	Full involvement
Jasmina Klopčič ^d	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia ^{a, b, c, d}	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon ^{a, b, c, d}	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga ^{a, b, c, d}	Member	Sweden	No interests declared	Full involvement
Annika Folin ^{a, b, c}	Alternate	Sweden	No interests declared	Full involvement
Birgitta Grundmark ^{a, b, c}	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales ^{a, b, c}	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng ^a	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente ^{a, b}	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Milou Daniel Drici ^{a, b, c, d}	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stefan Weiler ^b	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson ^{a, b, c}	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini ^{a, b, c, d}	Alternate	Healthcare Professionals' Representative	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Cathalijne van Doorne ^{a, b, c, d}	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert ^{a, b, c}	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christian Gartner ^b	Expert - via telephone*	Austria	No restrictions applicable to this meeting	Full involvement
Andrea Laslop ^{b, c}	Expert - via telephone*	Austria	No interests declared	Full involvement
Christelle Bizimungu ^{a, b, c}	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani ^{a, b, c}	Expert - via telephone*	Belgium	No interests declared	Full involvement
Flora Musuamba Tshinanu ^a	Expert - via telephone*	Belgium	No interests declared	Full involvement
Martine Sabbe ^{a, b, c}	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume ^{a, b, c}	Expert - via telephone*	Belgium	No interests declared	Full involvement
Ivana Ljubičić ^a	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Petra Kaftanová ^{b, c}	Expert - via telephone*	Czechia	No interests declared	Full involvement
Kristýna Schneiderová ^b	Expert - via telephone*	Czechia	No interests declared	Full involvement
Karin Susanne Erneholm ^{b, c, d}	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Pernille Lynge Gammelgaard ^{a, d}	Expert - via telephone*	Denmark	No interests declared	Full involvement
Kirstine Moll Harboe ^b	Expert - via telephone*	Denmark	No interests declared	Full involvement
Anita Vibsig Neutzsky-Wulff ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Helle Gerda Olsen ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Anne Pastoft ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Peter Horskjær Rose ^a	Expert - via telephone*	Denmark	No interests declared	Full involvement
Bibi Fatima Syed Shah ^b	Expert - via telephone*	Denmark	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Josiane Uwera ^d	Expert - via telephone*	Denmark	No interests declared	Full involvement
Meera Varma ^b	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Päivi Susanna Worsøe ^{a, b, c, d}	Expert - via telephone*	Denmark	No interests declared	Full involvement
Krõõt Aab ^a	Expert - via telephone*	Estonia	No interests declared	Full involvement
Maija Kaukonen ^a	Expert - via telephone*	Finland	No restrictions applicable to this meeting	Full involvement
Outi Maki-Ikola ^b	Expert - via telephone*	Finland	No restrictions applicable to this meeting	Full involvement
Karima Adamo ^a	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Laura Andreoli ^a	Expert - via telephone*	France	No interests declared	Full involvement
Florent Arinal ^a	Expert - via telephone*	France	No interests declared	Full involvement
Pauline Dayani ^a	Expert - via telephone*	France	No interests declared	Full involvement
Emmanuel Doyen ^a	Expert - via telephone*	France	No interests declared	Full involvement
Alexis Jacquet ^{a, c}	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Alexandre Moreau ^{b, c}	Expert - via telephone*	France	No interests declared	Full involvement
Jean-Michel Race ^b	Expert - via telephone*	France	No interests declared	Full involvement
Maxim Frizler ^a	Expert - via telephone*	Germany	No interests declared	Full involvement
Dennis Lex ^{a, b, c, d}	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Tania Meier ^a	Expert - via telephone*	Germany	No interests declared	Full involvement
Jan Mueller-Berghaus ^b	Expert - via telephone*	Germany	No interests declared	Full involvement
Martina Schussler-Lenz ^a	Expert - via telephone*	Germany	No interests declared	Full involvement
Karin Seifert ^a	Expert - via telephone*	Germany	No interests declared	Full involvement
Agnes Gyurasics ^b	Expert - via telephone*	Hungary	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
Niamh Buckley ^a	Expert - via telephone*	Ireland	No interests declared	Full involvement
Eleanor Carey ^a	Expert - via telephone*	Ireland	No interests declared	Full involvement
Graine Kirwan ^b	Expert - via telephone*	Ireland	No interests declared	Full involvement
Martine Trauffler ^{b, c}	Expert - via telephone*	Luxembourg	No interests declared	Full involvement
Marcel Kwa ^d	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Petrus Luijsterburg ^d	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Bjorg Bolstad ^{b, c}	Expert - via telephone*	Norway	No restrictions applicable to this meeting	Full involvement
Ingrid Wang ^c	Expert - via telephone*	Norway	No restrictions applicable to this meeting	Full involvement
Ewa Balkowiec Iskra ^b	Expert - via telephone*	Poland	No interests declared	Full involvement
Sílvia Duarte ^a	Expert - via telephone*	Portugal	No interests declared	Full involvement
Bruno Sepodes ^{b, c}	Expert - via telephone*	Portugal	No restrictions applicable to this meeting	Full involvement
Roxana Dondera ^{a, c}	Expert - via telephone*	Romania	No interests declared	Full involvement
Raquel Granados Martín ^a	Expert - via telephone*	Spain	No interests declared	Full involvement
Francisco Javier López Perez ^a	Expert - via telephone*	Spain	No interests declared	Full involvement
Consuelo Mejías Pavón ^c	Expert - via telephone*	Spain	No interests declared	Full involvement
Mónica Martínez Redondo ^a	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Ana Sagredo ^c	Expert - via telephone*	Spain	No interests declared	Full involvement
Helena Back ^a	Expert - via telephone*	Sweden	No interests declared	Full involvement
Charlotte Backman ^{a, b, c, d}	Expert - via telephone*	Sweden	No interests declared	Full involvement
Lisbeth Barkholt ^a	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jessica Mwinyi ^a	Expert - via telephone*	Sweden	No interests declared	Full involvement
Monique Wakelkamp ^a	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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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:

<https://www.ema.europa.eu/en>